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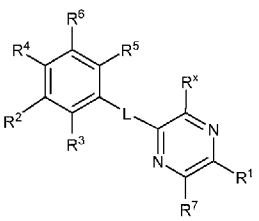
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(54) Title: KIF18A INHIBITORS

(57) Abstract: Compounds of formula (I): as defined herein, and synthetic intermediates thereof, which are capable of modulating KIF18A protein thereby influencing the process of cell cycle and cell proliferation to treat cancer and cancer-related diseases. The invention also includes pharmaceutical compositions, including the compounds, and methods of treating disease states related to the activity of KIF18A.



(I),

KIF18A INHIBITORS

[0001] The invention relates to the field of pharmaceutical agents and, more specifically, is directed to compounds and compositions useful for modulating KIF18A, and to uses and methods for managing cell proliferation and for treating cancer.

BACKGROUND OF THE INVENTION

[0002] Cancer is one of the most widespread diseases afflicting mankind and a major cause of death worldwide. In an effort to find an effective treatment or a cure for one or more of the many different cancers, over the last couple of decades, numerous groups have invested a tremendous amount of time, effort and financial resources. However, to date, of the available cancer treatments and therapies, only a few offer any considerable degree of success.

[0003] Cancer is often characterized by unregulated cell proliferation. Damage to one or more genes, responsible for the cellular pathways, which control progress of proliferation through the cell cycle and centrosome cycle, can cause the loss of normal regulation of cell proliferation. These deregulated genes can code for various tumor suppressor or oncogene proteins, which participate in a cascade of events, leading to unchecked cell-cycling progression and cell proliferation. Various kinase and kinesin proteins have been identified, which play key roles in cell cycle and mitotic regulation and progression of normal dividing cells and cancer cells.

[0004] Kinesins are molecular motors that play important roles in cell division and intracellular vesicle and organelle transport. Mitotic kinesin play roles in several aspects of spindle assembly, chromosome segregation, centrosome separation and dynamics (reviewed in O. Rath and F. Kozielski, *Nature Review Cancer,* 12:527-39, 2012). Human kinesins are categorized into 14 subfamilies based on sequence homology within the socalled "motor domain", this domains ATPase activity drives unidirectional movement along microtubules (MTs). The non-motor domain of these proteins is responsible for cargo attachment; a "cargo" can include any one of a variety of different membranous organelles, signal transduction scaffolding systems, and chromosomes. Kinesins use the energy of ATP hydrolysis to move cargo along polarized microtubules. Thus, kinesins are often called "plus-end" or "minus-end" directed motors.

[0005] *KIF18A* gene belongs to Kinesin-8 subfamily and is a plus-end-directed motor. KIF18A is believed to influence dynamics at the plus end of kinetochore microtubules to control correct chromosome positioning and spindle tension. Depletion of human KIF18A leads to longer spindles, increased chromosome oscillation at metaphase, and activation of the mitotic spindle assembly checkpoint in HeLa cervical cancer cells (MI Mayr et al , *Current Biology* 17, 488–98, 2007). KIF18A appears to be viable target for the treatment of cancer. KIF18A is overexpressed in various types of cancers, including but not limited to colon, breast, lung, pancreas, prostate, bladder, head, neck, cervix, and ovarian cancers. Further, genetic deletion or knockdown, or inhibition of KIF18A effects mitotic spindle apparatus in cancer cell lines. Particularly, inhibition of KIF18A has been found to induce mitotic cell arrest, a known vulnerability that can promote cell death in mitosis via apoptosis, mitotic catastrophe, or multipolarity

driven lethality or death after mitotic slippage in interphase. Accordingly, there has been a strong interest in finding inhibitors of KIF18A proteins.

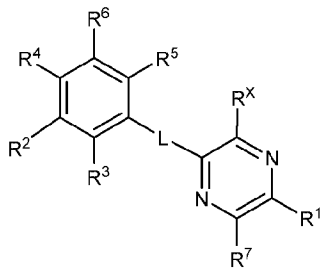
[0006] Thus, the inhibition of KIF18A ATPase activity is a promising approach for the development of novel anti-cancer agents.

SUMMARY OF THE INVENTION

[0007] An aspect of the present invention is a new class of compounds useful for modulating KIF18A protein alone or in a bound complex with microtubules for treating KIF18A-mediated conditions and/or diseases, including cancer, inflammation, or ciliopathologies.

[0008] The compounds provided by the invention have MT-based KIF18A modulatory activity and, in particular, KIF18A inhibitory activity. To this end, the invention also provides the use of these compounds, as well as pharmaceutically acceptable salts thereof, in the preparation and manufacture of a pharmaceutical composition or medicament for therapeutic, prophylactic, acute or chronic treatment of KIF18A mediated diseases and disorders, including without limitation, cancer. Thus, the compounds of the invention are useful in the manufacture of anti-cancer medicaments. The invention also provides processes for making compounds of Formula I, as well as intermediates useful in such processes.

[0009] In embodiment 1, the present invention provides a compound of Formula (I), A compound of formula I:



(I);

[0010] L is –(C=O)-NR^8- or -NR^8-(C=O)-;

[0011] R^1 is a group -Z-R^9; wherein Z is absent, -NR^{11}-, -$NR^{11}SO_2$-C_{1-4}alk-, -$NR^{11}SO_2NR^{11}$, -$NR^{11}SO_2NR^{11}$-C(=O)-O-, -N=S(=O)<, -SO_2NR^{11}-C_{0-4}alk-, C_{0-4}alk-S(=O)(=NH)-, C_{0-4}alk-S(=O)(=$N^+(CH_3)_2$)-, C_{1-4}alk-, C_{0-4}alk-S-, C_{0-4}alk-S(=O)-, C_{0-4}alk-SO_2-, -O-, -P-, -P(=O), -$P(=O)_2$, -(C=O)-, -(C=O)NR^{11}-, -C=N(OH)-, or -NR^{11}(C=O);

[0012] R^2 is a group –Y-R^{10}, wherein Y is absent, C_{0-4}alk-S-, C_{0-4}alk-S=O, C_{0-4}alk-$S(=O)_2$, -SO_2NR^{10c}-C_{0-4}alk-, -NR^{10c}-, -NR^{10c}-SO_2-C_{0-4}alk-, -C_{0-4}alk-S(=O)(=NH)-, -O-C_{0-4}alk-, -(C=O)-, -C_{0-4}alk-(C=O)-O-, or -N=S(=O)<;

[0013] R^3 is H, halo, C_{1-4}alk, or C_{1-4}haloalk;

[0014] R^4 is H, halo, C_{1-4}alk, or C_{1-4}haloalk;

[0015] R^5 is H, halo, C_{1-8}alk, or C_{1-4}haloalk;

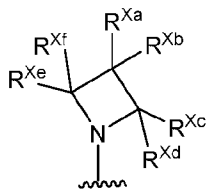
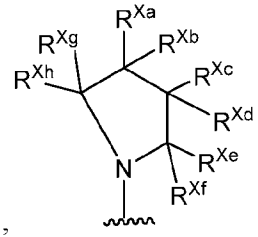
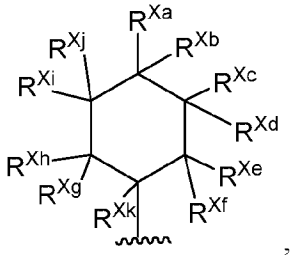
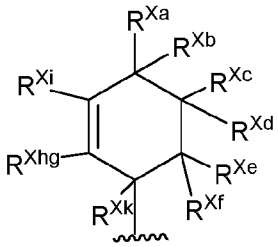
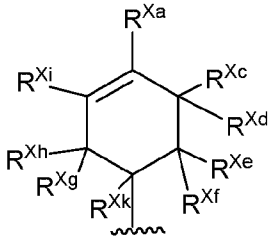
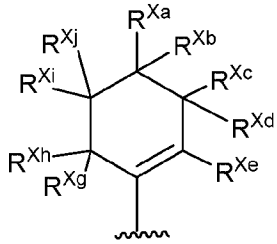
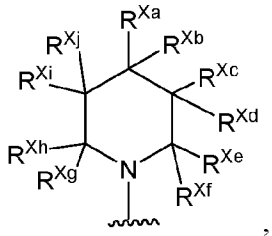
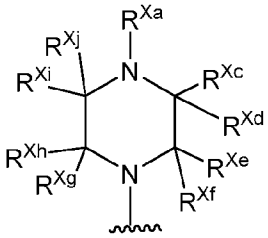
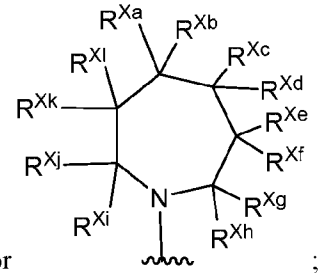
[0016] R^6 is H, halo, C_{1-8}alk, or C_{1-4}haloalk;

[0017] R^7 is H, halo, C_{1-4}alk, or C_{1-4}haloalk;

[0018] R^8 is H or C_{1-4}alk;

[0019] R^9 is H, R^{9a}, or R^{9b};

[0020] R^{10} is halo, R^{10a} or R^{10b};

[0021] R^X is selected from , , , , , , , , or ;

[0022] or R^X is an C_{2-8}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, $-CH_2F$, $-CHF_2$, $-CF_3$, $-C(=O)OR^a$, $-OR^a$, $-OC_{1-4}$haloalk, CN, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or R^{Xm};

[0023] or R^X is phenyl or unsaturated 5-membered monocyclic ring substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, $-C_{1-6}$alk, $-C_{1-6}$haloalk, $-C(=O)OR^a$, $-OR^a$, $-OC_{1-4}$haloalk, CN, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or R^{Xm}; wherein said 5-membered monocyclic ring contains 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S;

[0024] Each of R^{Xa}, R^{Xb}, R^{Xc}, R^{Xd}, R^{Xe}, R^{Xf}, R^{Xg}, R^{Xh}, R^{Xi}, R^{Xj}, R^{Xk}, and R^{Xl} is H, halo, R^{Xn}, or R^{Xo};

[0025] or alternatively, each of R^{Xa} and R^{Xb} pair, R^{Xc} and R^{Xd} pair, R^{Xe} and R^{Xf} pair, R^{Xg} and R^{Xh} pair, R^{Xi} and R^{Xj} pair, and R^{Xk} and R^{Xl} pair, independently, can combine with the carbon atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, 6-membered monocyclic ring spiro to the azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or azepanyl ring; wherein said 3-, 4-, 5-, 6-membered monocyclic ring contains 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, and further wherein said 3-, 4-, 5-, 6-membered monocyclic ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, $-OR^a$, $-OC_{1-4}$haloalk, CN, $-NR^aR^a$, or oxo;

[0026] Each R^{Xm} and R^{Xn} is independently, at each instance, selected from the group consisting of a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic or 8-, 9-, 10-, 11-, or 12-membered bicyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and

S, which is substituted by 0, 1, 2, 3, or 4 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, -OR^a, -OC_{1-4}haloalk, CN, -$C(=O)R^b$, -$C(=O)OR^a$, -$C(=O)NR^aR^a$, -$C(=NR^a)NR^aR^a$, -$OC(=O)R^b$, -$OC(=O)NR^aR^a$, -OC_{2-6}alkNR^aR^a, -OC_{2-6}alkOR^a, -SR^a, -$S(=O)R^b$, -$S(=O)_2R^b$, -$S(=O)_2NR^aR^a$, -NR^aR^a, -$N(R^a)C(=O)R^b$, -$N(R^a)C(=O)OR^b$,-$N(R^a)C(=O)NR^aR^a$, -$N(R^a)C(=NR^a)NR^aR^a$, -$N(R^a)S(=O)_2R^b$, -$N(R^a)S(=O)_2NR^aR^a$, -NR^aC_{2-6}alkNR^aR^a, -NR^aC_{2-6}alkOR^a, -C_{1-6}alkNR^aR^a, -C_{1-6}alkOR^a, -C_{1-6}alk$N(R^a)C(=O)R^b$, -C_{1-6}alk$OC(=O)R^b$, -C_{1-6}alk$C(=O)NR^aR^a$, -C_{1-6}alk$C(=O)OR^a$, and oxo;

[0027] R^{Xo} is independently, at each instance, selected from the group consisting of C_{1-8}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, -CH_2F, -CHF_2, -CF_3, -$C(=O)OR^a$, -OR^a, -OC_{1-4}haloalk, CN, NH_2, $NH(CH_3)$, or $N(CH_3)_2$;

[0028] R^{9a} and R^{10a} is independently, at each instance, selected from the group consisting of a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic or 8-, 9-, 10-, 11-, or 12-membered bicyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, which is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, -OR^a, -OC_{1-4}haloalk, CN, -$C(=O)R^b$, -$C(=O)OR^a$, -$C(=O)NR^aR^a$, -$C(=NR^a)NR^aR^a$, -$OC(=O)R^b$, -$OC(=O)NR^aR^a$, -OC_{2-6}alkNR^aR^a, -OC_{2-6}alkOR^a, -SR^a, -$S(=O)R^b$, -$S(=O)_2R^b$, -$S(=O)_2NR^aR^a$, -NR^aR^a, -$N(R^a)C(=O)R^b$, -$N(R^a)C(=O)OR^b$,-$N(R^a)C(=O)NR^aR^a$, -$N(R^a)C(=NR^a)NR^aR^a$, -$N(R^a)S(=O)_2R^b$, -$N(R^a)S(=O)_2NR^aR^a$, -NR^aC_{2-6}alkNR^aR^a, -NR^aC_{2-6}alkOR^a, -C_{1-6}alkNR^aR^a, -C_{1-6}alkOR^a, -C_{1-6}alk$N(R^a)C(=O)R^b$, -C_{1-6}alk$OC(=O)R^b$, -C_{1-6}alk$C(=O)NR^aR^a$, -C_{1-6}alk$C(=O)OR^a$, R^{11}, and oxo;

[0029] R^{9b} and R^{10b} is independently, at each instance, selected from the group consisting of C_{1-6}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, -CH_2F, -CHF_2, -CF_3, -$C(=O)OR^a$, -OR^a, -OC_{1-4}haloalk, CN, NH_2, $NH(CH_3)$, or $N(CH_3)_2$;

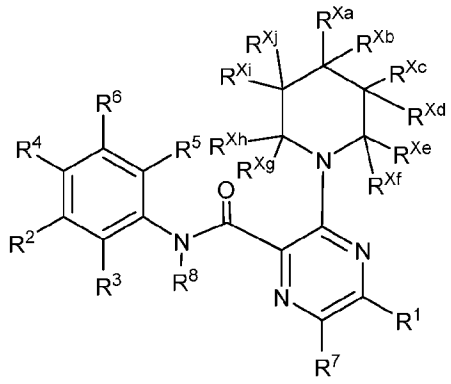
[0030] R^{10c} is H or C_{1-4}alk;

[0031] R^{11} is H or C_{1-8}alk;

[0032] R^a is independently, at each instance, H or R^b; and

[0033] R^b is independently, at each instance, C_{1-6}alk, phenyl, or benzyl, wherein the C_{1-6}alk is being substituted by 0, 1, 2 or 3 substituents selected from halo, -OH, -OC_{1-4}alk, -NH_2, -NHC_{1-4}alk, -$OC(=O)C_{1-4}$alk, or -$N(C_{1-4}$alk$)C_{1-4}$alk; and the phenyl or benzyl is being substituted by 0, 1, 2 or 3 substituents selected from halo, C_{1-4}alk, C_{1-3}haloalk, -OH, -OC_{1-4}alk, -NH_2, -NHC_{1-4}alk, -$OC(=O)C_{1-4}$alk, or -$N(C_{1-4}$alk$)C_{1-4}$alk.

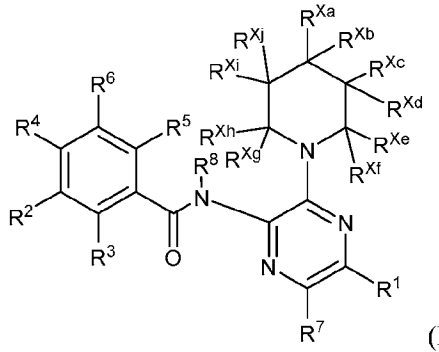
[0034] In embodiment 2, the present invention provides compounds wherein L is -NR^8-(C=O); having the formula (Ia):



(Ia);

[0035] wherein said R^{Xa} and R^{Xb} pair can combine with the carbon atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, 6-membered monocyclic ring spiro to the piperidinyl ring; wherein said 3-, 4-, 5-, 6-membered monocyclic ring contains 0 N, O, and S atoms, and further wherein said 3-, 4-, 5-, 6-membered monocyclic ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, -OR^a, -OC_{1-4}haloalk, CN, -NR^aR^a, or oxo.

[0036] In embodiment 3, the present invention provides compounds wherein L is –(C=O)-NR^8-; having the formula (Ib):



(Ib);

[0037] wherein said R^{Xa} and R^{Xb} pair can combine with the carbon atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, 6-membered monocyclic ring spiro to the piperidinyl ring; wherein said 3-, 4-, 5-, 6-membered monocyclic ring contains 0 N, O, and S atoms, and further wherein said 3-, 4-, 5-, 6-membered monocyclic ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, -OR^a, -OC_{1-4}haloalk, CN, -NR^aR^a, or oxo.

[0038] In embodiment 4, the present invention provides compounds wherein wherein R^8 is H or methyl.

[0039] In embodiment 5, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein each of R^{Xc}, R^{Xd}, R^{Xe}, R^{Xf}, R^{Xg}, R^{Xh}, R^{Xi}, R^{Xj}, R^{Xk}, and R^{Xl} is H, halo, C_{1-6}alk, or C_{1-4}haloalk; and each of R^{Xa} and R^{Xb} pair combine with the carbon atom attached to each of them form a saturated 3-, 4-, or 5-membered monocyclic ring spiro to the piperidinyl ring; wherein said ring contains 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S.

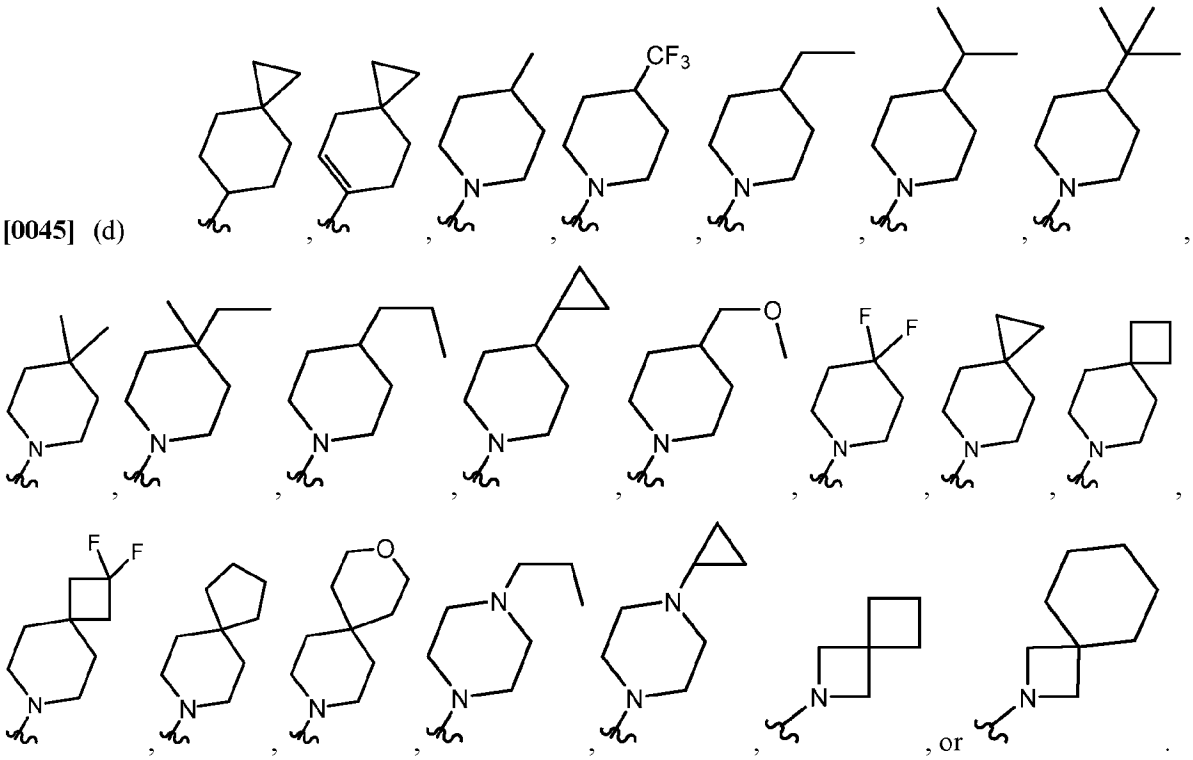
[0040] In embodiment 6, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein each of R^{Xc}, R^{Xd}, R^{Xe}, R^{Xf}, R^{Xg}, R^{Xh}, R^{Xi}, R^{Xj}, R^{Xk}, and R^{Xl} is H, methyl, or ethyl; and each of R^{Xa} and R^{Xb} pair combine with the carbon atom attached to each of them form a cyclopropyl, cyclobutyl, or cyclopentyl ring spiro to the piperidinyl ring.

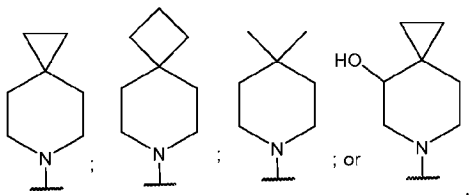
[0041] In embodiment 7, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^X is selected from

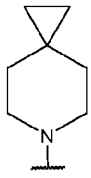
[0042] (a) ethynyl substituted by isobutyl or cyclopentyl;

[0043] (b) phenyl substituted by 0, 1, 2, or 3 F, Cl, CF_3, CH_2OCH_3, methyl, ethyl, propyl, isopropyl, *tert*-butyl, or cyclopropyl group(s);

[0044] (c) or pyrazolyl substituted by 0, 1, 2, or 3 F, Cl, CF_3, CH_2OCH_3, methyl, ethyl, propyl, isopropyl, *tert*-butyl, or cyclopropyl group(s);

[0045] (d) 

[0046] In embodiment 8, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^X is selected from: 

[0047] In embodiment 9, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^X is .

[0048] In embodiment 10, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein Z is absent, -NH-, $-NHSO_2-$, $-SO_2NH-$, or $-CH_2SO_2-$.

[0049] In embodiment 11, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, R^9 is selected from:

[0050] a) H;

[0051] (b) C_{1-6}alk substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, $-CF_3$, or -OH; or

[0052] (c) a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, which is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, ethyl, $-CF_3$, $-CH_2OH$, -OH, $-OCH_3$, $-NH_2$, or oxo.

[0053] In embodiment 12, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^9 is selected from cyclopropyl, cyclobutyl, cyclopentyl, oxetanyl, azetidinyl, diazirinyl, oxazolidinyl, isothiazolidinyl, pyrazolyl, or pyrrolidinyl.

[0054] In embodiment 13, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^1 is a group $-Z-R^{12}$, wherein R^1 is a group $-Z-R^9$, wherein Z is absent, -NH-, $-NHSO_2-$, $-SO_2NH-$, or $-CH_2SO_2-$; and R^9 is cyclopropyl or oxazolinyl substituted by 0, 1, 2 or 3 OH, $-CH_2OH$, methyl, or oxo group(s), or R^9 is C_{1-6}alk substituted by 0, 1, 2 or 3 OH or CF_3 group(s).

[0055] In embodiment 14, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^1 is a group $-Z-R^9$, wherein Z is $-NHSO_2-$ and R^9 is $-CH_2-CH_2-OH$.

[0056] In embodiment 15, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^2 is a group $-Y-R^{10}$, wherein Y is absent, -NH-, $-NHSO_2-$, SO_2NH-, or SO_2-; and

[0057] R^{10} is a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, which is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, ethyl, CF_3, CH_2OH, -OH, $-OCH_3$, $-NH_2$, $-NH(CH_3)$, and oxo; or;

[0058] R^{10} is C_{1-6}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, -OH, or $-CF_3$.

[0059] In embodiment 16, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^2 is morpholinyl, thiomorpholinyl, cyclobutyl, cyclopentyl, or piperidinyl ring, wherein each of said ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, CF_3, -OH, $-OCHF_2$, or oxo.

[0060] In embodiment 17, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, R^2 is morpholinyl or piperidinyl substituted by 0, 1, 2 or 3 selected from F or methyl.

[0061] In embodiment 18, the present invention provides compounds in accordance with embodiments 1-17, or pharmaceutically acceptable salts thereof, wherein R^3 is H or F.

[0062] In embodiment 19, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^4 is H.

[0063] In embodiment 20, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^5 is H.

[0064] In embodiment 21, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^6 is H, F, or methyl.

[0065] In embodiment 22, the present invention provides compounds in accordance with any of the above embodiments, or pharmaceutically acceptable salts thereof, wherein R^7 is H.

[0066] In embodiment 23, the present invention provides compounds in accordance with any of the above embodiments,, or any pharmaceutically-acceptable salt thereof, selected from the group consisting of:

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-methylpiperidin-1-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4,4-difluoropiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(trifluoromethyl)piperidin-1-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-ethylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4,4-dimethylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-isopropylpiperidin-1-yl)pyrazine-2-carboxamide;

3-(4-(*tert*-butyl)piperidin-1-yl)-*N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

3-(4-(*sec*-butyl)piperidin-1-yl)-*N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-propylpiperidin-1-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-cyclopropylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(methoxymethyl)piperidin-1-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(2-azaspiro[3.3]heptan-2-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(2-azaspiro[3.5]nonan-2-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(3-oxa-9-azaspiro[5.5]undecan-9-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(7-azaspiro[3.5]nonan-7-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(2,2-difluoro-7-azaspiro[3.5]nonan-7-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(8-azaspiro[4.5]decan-8-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-methylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)-N-(3-((1,1,1-trifluoro-2-methylpropan-2-yl)sulfonyl)phenyl)pyrazine-2-carboxamide;

N-(3-(*tert*-butylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-methylcyclobutyl)sulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)-5-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)-2-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(1,1-dioxidothiomorpholino)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-morpholinophenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-hydroxy-2-methylpropan-2-yl)amino)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

(*S*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

(*R*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(Cyclopentylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(cyclopentylsulfonyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((2-hydroxy-2-methylpropyl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-chlorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(trifluoromethyl)phenyl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-ethylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

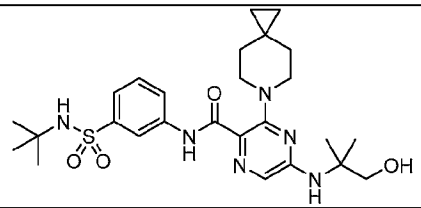
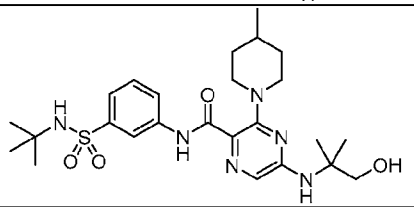
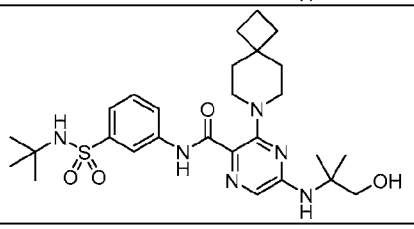
N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-isopropylphenyl)pyrazine-2-carboxamide;

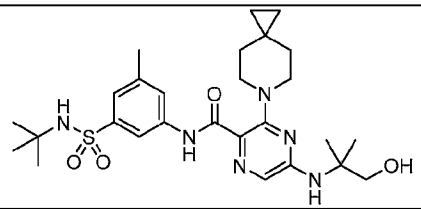
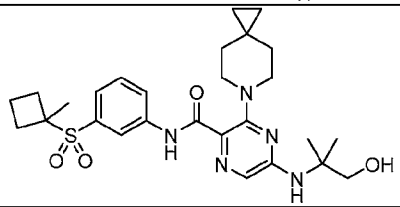
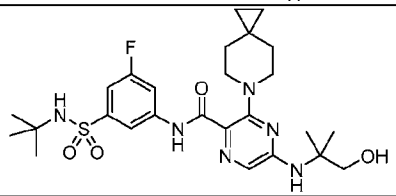
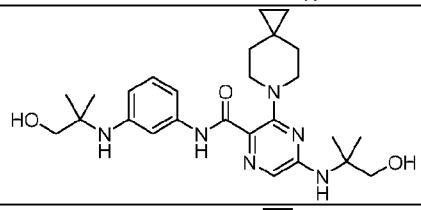
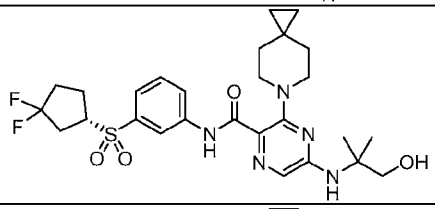
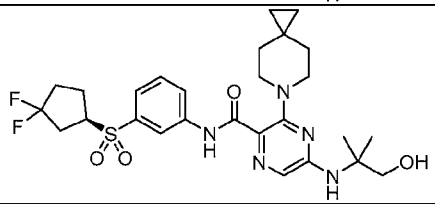
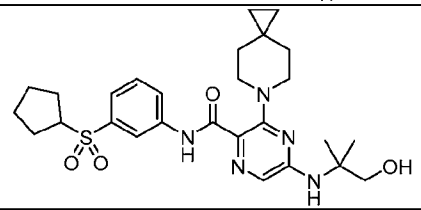
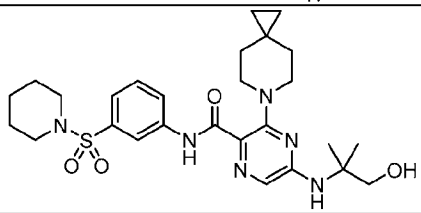
(*R*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide;

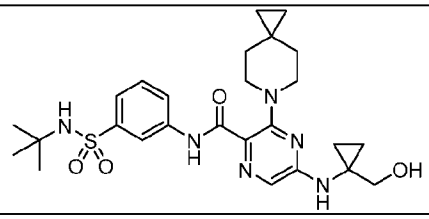
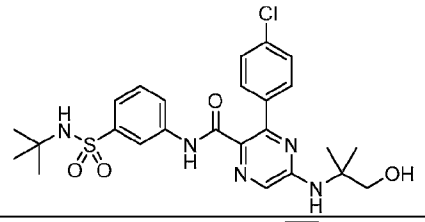
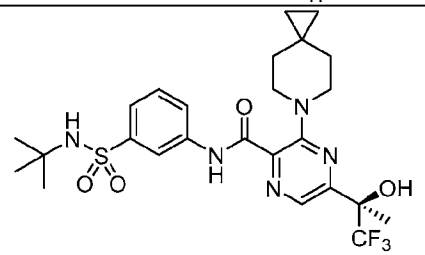
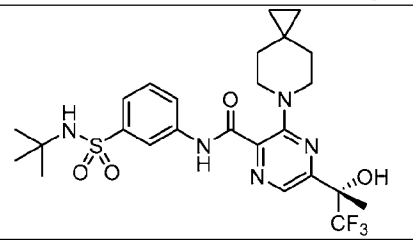
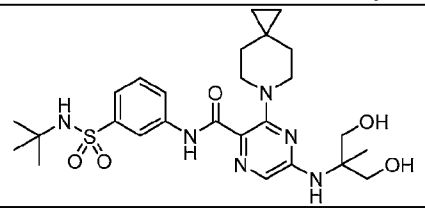
(*S*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide; or

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1,3-dihydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide.

[0067] In embodiment 24, the present invention provides a compound, or pharmaceutically acceptable salts thereof, selected from:

Example #	Chemical Structure	Name
100		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
100-1		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-methylpiperidin-1-yl)pyrazine-2-carboxamide
100-15		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(7-azaspiro[3.5]nonan-7-yl)pyrazine-2-carboxamide

Example #	Chemical Structure	Name
101		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-methylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
101-3		5-((1-Hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-methylcyclobutyl)sulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
101-4		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
101-8		5-((1-Hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-hydroxy-2-methylpropan-2-yl)amino)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
102-1		(*S*)-*N*-(3-((3,3-Difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
102-2		(*R*)-*N*-(3-((3,3-Difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
103		*N*-(3-(Cyclopentylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
103-1		5-((1-Hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide

Example #	Chemical Structure	Name
103-3		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
104		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-3-(4-chlorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide
105-1		(*R*)-*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide
105-2		(*S*)-*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide
106		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1,3-dihydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide

or any pharmaceutically-acceptable salt thereof.

[0068] Another aspect of the present invention is a pharmaceutical composition comprising a new class of compounds useful for modulating KIF18A protein alone or in a bound complex with microtubules or pharmaceutically acceptable salts thereof.

[0069] In embodiment 25, the present invention provides pharmaceutical compositions comprising a compound, or pharmaceutically acceptable salts thereof, in accordance with any one of embodiments 1-24, and a pharmaceutically acceptable diluent or carrier.

[0070] Yet another aspect of the present invention is a method of treating a condition that may be treated with KIF18a inhibitors, the method comprising administering to a patient in need thereof a therapeutically effective amount of a new class of compounds useful for modulating KIF18A protein alone or in a bound complex with microtubules or pharmaceutically acceptable salts thereof.

[0071] In embodiment 26, the present invention provides a method of treating a condition that may be treated with KIF18a inhibitors, the method comprising administering to a patient in need thereof a

therapeutically effective amount of the compound in accordance with embodiments 1-24, or the composition according to embodiment 25.

[0072] In embodiment 27, the present invention provides the method of embodiment 26, wherein said condition is cancer selected from the group consisting of (a) a solid or hematologically derived tumor selected from cancer of the cancer of the bladder, endometrial, lung squamous cell, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall-bladder, brain, head and neck, ovary, pancreas, stomach, cervix, thyroid, prostate and skin, (b) a hematopoietic tumor of lymphoid lineage selected from leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma, (c) a hematopoietic tumor of myeloid lineage selected from acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia (d) a tumor of mesenchymal origin selected from fibrosarcoma and rhabdomyosarcoma, (e) a tumor of the central and peripheral nervous system selected from astrocytoma, neuroblastoma, glioma and schwannoma, or (f) a melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer or Kaposi's sarcoma.

[0073] In a sub-embodiment 27a, the present invention provides the method of embodiment 26, wherein said condition is cancer selected from the group consisting of melanoma, prostate cancer, cervical cancer, breast cancer, colon cancer, sarcoma, or leukemia. See: Zhang C. et. al., "Kif18A is involved in human breast carcinogenesis", Carcinogenesis, 2010 Sep;31(9):1676-84. doi: 10.1093/carcin/bgq134. Epub 2010 Jul 1. See also: (1) https://www.proteinatlas.org/ENSG00000121621-KIF18A/pathology; (2) Nagahara, M. et. al., "Kinesin 18A expression: clinical relevance to colorectal cancer progression", Int. J. Cancer: 129, 2543–2552 (2011) VC 2011 UIC; and (3) Yu, Y. et. al., "The Role of Kinesin Family Proteins in Tumorigenesis and Progression - Potential Biomarkers and Molecular Targets for Cancer Therapy", Cancer 2010;116:5150–60. VC 2010 American Cancer Society.

[0074] In embodiment 28, the present invention provides a method of reducing the size of a solid tumor in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of the compound in accordance with embodiments 1-24, or the composition according to embodiment 25.

[0075] In embodiment 29, the present invention provides a method of treating a cell proliferation disorder in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of the compound in accordance with embodiments embodiments 1-24, or the composition according to embodiment 25.

[0076] In embodiment 30, the present invention provides a method of inhibiting KIF18A in a cell, comprising contacting the cell with a compound, or pharmaceutically acceptable salts thereof, in accordance with embodiments embodiments 1-24, or the composition according to embodiment 25.

[0077] Yet another aspect of the present invention is a method of preparing a new class of compounds useful for modulating KIF18A protein alone or in a bound complex with microtubules or pharmaceutically acceptable salts thereof.

[0078] In embodiment 31, the invention provides a method of preparing a compound of Formula (I) as described herein.

[0079] In embodiment 32, the invention provides an intermediate compound used in the method of preparing a compound of Formula (I) as described herein.

DETAILED DESCRIPTION OF THE INVENTION

[0080] The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of the present invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

[0081] Examples of isotopes suitable for inclusion in the compounds of the invention include, but are not limited to, isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{38}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

[0082] Certain isotopically-labelled compounds of the present invention, 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.

[0083] 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 may be preferred in some circumstances.

[0084] 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.

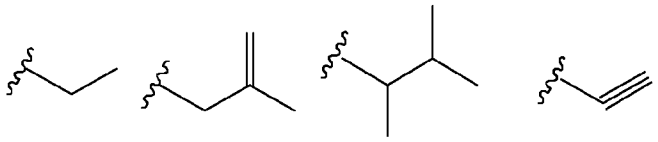
[0085] Isotopically-labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0086] Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

[0087] Specific embodiments of the present invention include the compounds exemplified in the Examples below and their pharmaceutically acceptable salts, complexes, solvates, polymorphs, stereoisomers, metabolites, prodrugs, and other derivatives thereof.

[0088] Unless otherwise specified, the following definitions apply to terms found in the specification and claims:

[0089] "$C_{\alpha-\beta}$alk" means an alkyl group comprising a minimum of α and a maximum of β carbon atoms in a branched or linear relationship or any combination of the three, wherein α and β represent integers. The alkyl groups described in this section may also contain one or two double or triple bonds. A designation of C_0alk indicates a direct bond. Examples of C_{1-6}alkyl include, but are not limited to the following:



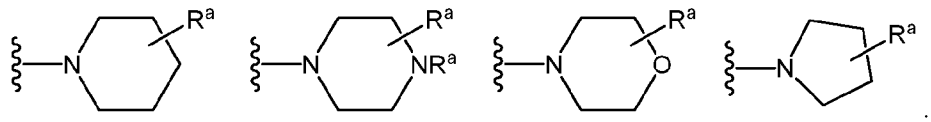
[0090] "Benzo group", alone or in combination, means the divalent radical C_4H_4=, one representation of which is -CH=CH-CH=CH-, that when vicinally attached to another ring forms a benzene-like ring--for example tetrahydronaphthylene, indole and the like.

[0091] The terms "oxo" and "thioxo" represent the groups =O (as in carbonyl) and =S (as in thiocarbonyl), respectively.

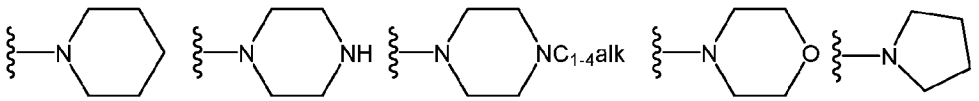
[0092] "Halo" or "halogen" means a halogen atom selected from F, Cl, Br and I.

[0093] "$C_{\alpha\text{-}\beta}$haloalk" means an alk group, as described above, wherein any number --at least one-- of the hydrogen atoms attached to the alk chain are replaced by F, Cl, Br or I.

[0094] The group $N(R^a)R^a$ and the like include substituents where the two R^a groups together form a ring, optionally including a N, O or S atom, and include groups such as:



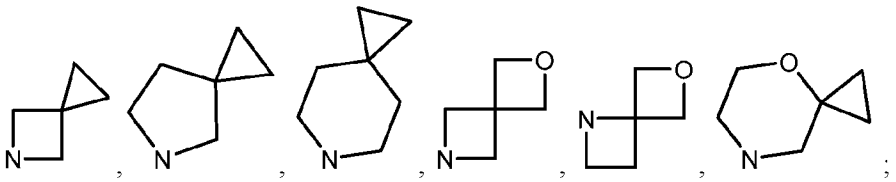
[0095] The group $N(C_{\alpha\text{-}\beta}alk)$ $C_{\alpha\text{-}\beta}alk$, wherein α and β are as defined above, include substituents where the two $C_{\alpha\text{-}\beta}alk$ groups together form a ring, optionally including a N, O or S atom, and include groups such as:



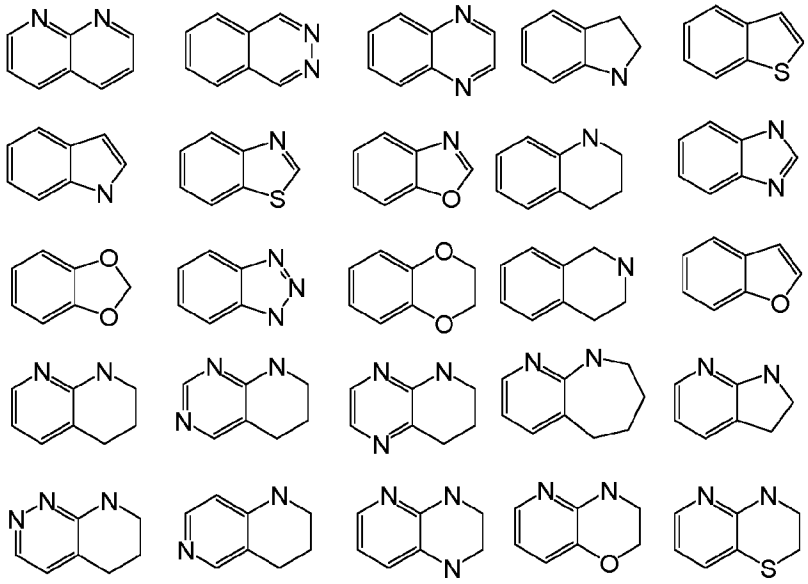
[0096] "Bicyclic ring" means a group that features two joined rings. A bicyclic ring can be carbocyclic (all of the ring atoms are carbons), or heterocyclic (the rings atoms consist, for example, 1, 2 or 3 heteroatoms, such as N, O, or S, in addition to carbon atoms). The two rings can both be aliphatic (*e.g.* decalin and norbornane), or can be aromatic (*e.g.*naphthalene), or a combination of aliphatic and aromatic (*e.g.* tetralin).

[0097] Bicyclic rings includes:

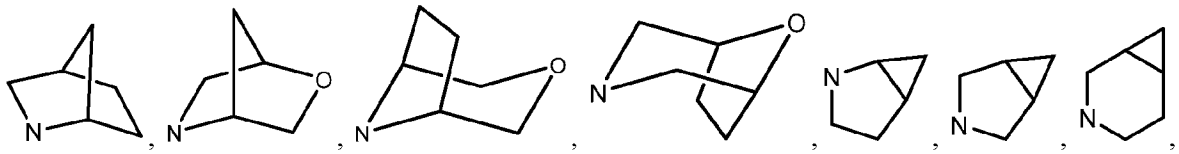
[0098] (a) spirocyclic compounds, wherein the two rings share only one single atom, the spiro atom, which is usually a quaternary carbon. Examples of spirocyclic compound include, but are not limited to:

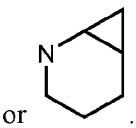


[0099] (b) fused bicyclic compounds, wherein two rings share two adjacent atoms. In other words, the rings share one covalent bond, *i.e.* the bridgehead atoms are directly connected (*e.g.* α-thujene and decalin). Examples of fused bicyclic rings include, but are not limited to:


; and

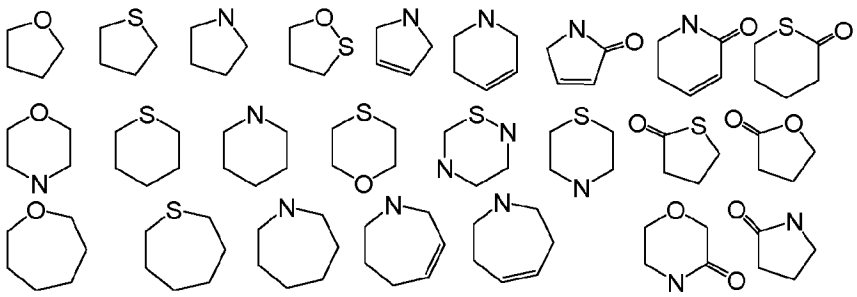
[0100] (c) bridged bicyclic compounds, wherein the two rings share three or more atoms, separating the two bridgehead atoms by a bridge containing at least one atom. For example, norbornane, also known as bicyclo[2.2.1]heptane, can be thought of as a pair of cyclopentane rings each sharing three of their five carbon atoms. Examples of bridged bicyclic rings include, but are not limited to:

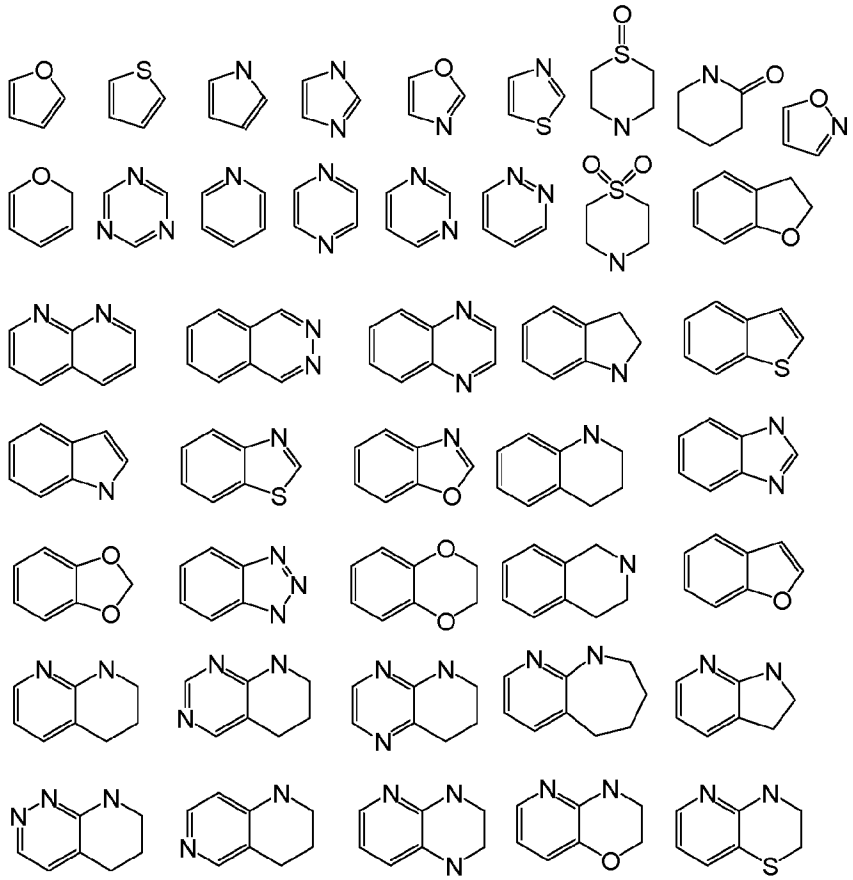

, , , , , , ,


or .

[0101] "Carbocycle" or "Carbocyclic" means a ring comprising by itself or in combination with other terms, represents, unless otherwise stated, cyclic version of "$C_{\alpha\text{-}\beta}$alk". Examples of carbocycle include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, cyclobutylene, cyclohexylene and the like.

[0102] "Heterocycle" or "Heterocyclic" means a ring comprising at least one carbon atom and at least one other atom selected from N, O and S. Examples of heterocycles that may be found in the claims include, but are not limited to, the following:





and  .

[0103] "Pharmaceutically-acceptable salt" means a salt prepared by conventional means, and are well known by those skilled in the art. The "pharmacologically acceptable salts" include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, malic acid, acetic acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," *see infra* and Berge et al., J. Pharm. Sci. 66:1 (1977).

[0104] "Saturated, partially-saturated or unsaturated" includes substituents saturated with hydrogens, substituents completely unsaturated with hydrogens and substituents partially saturated with hydrogens.

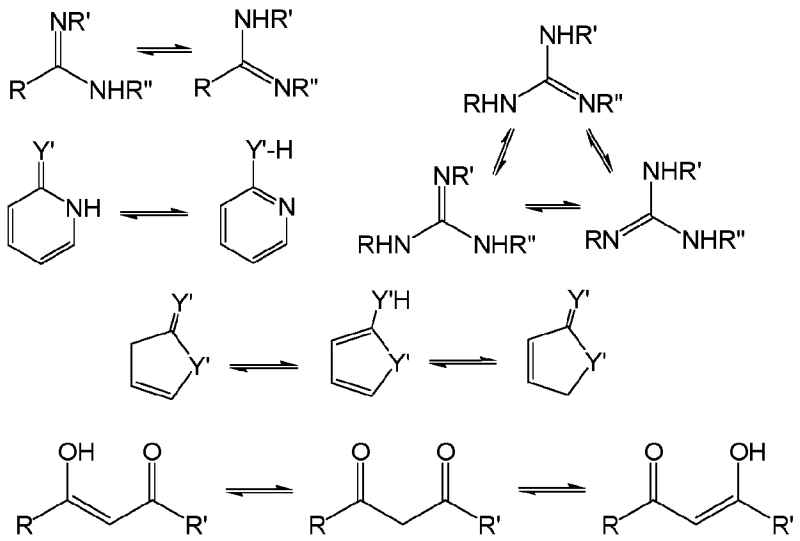
[0105] "Leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

[0106] "Protecting group" generally refers to groups well known in the art which are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the like. Preferred protecting groups are indicated herein where appropriate. Examples of amino protecting groups include, but are not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenyl alkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl, silyl and the like. Examples of aralkyl include, but are not limited to, benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl, alkoxy, hydroxy, nitro, acylamino, acyl and the like, and salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthyl, indanyl, anthracenyl, 9-(9-phenylfluorenyl), phenanthrenyl, durenyl and the like. Examples of cycloalkenylalkyl or substituted cycloalkylenylalkyl radicals, preferably have 6-10 carbon atoms, include, but are not limited to, cyclohexenyl methyl and the like. Suitable acyl, alkoxycarbonyl and aralkoxycarbonyl groups include benzyloxycarbonyl, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, trifluoroacetyl, trichloro acetyl, phthaloyl and the like. A mixture of protecting groups can be used to protect the same amino group, such as a primary amino group can be protected by both an aralkyl group and an aralkoxycarbonyl group. Amino protecting groups can also form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, such as nitrophthalimidyl. Amino groups may also be protected against undesired reactions, such as oxidation, through the formation of an addition salt, such as hydrochloride, toluenesulfonic acid, trifluoroacetic acid and the like. Many of the amino protecting groups are also suitable for protecting carboxy, hydroxy and mercapto groups. For example, aralkyl groups. Alkyl groups are also suitable groups for protecting hydroxy and mercapto groups, such as tert-butyl.

[0107] Silyl protecting groups are silicon atoms optionally substituted by one or more alkyl, aryl and aralkyl groups. Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of an amino groups provide mono- or di-silylamino groups. Silylation of aminoalcohol compounds can lead to a N,N,O-trisilyl derivative. Removal of the silyl function from a silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during a reaction with the alcohol group. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyl-dimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethyl silyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

[0108] Protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of a protecting group, such as removal of a benzyloxycarbonyl group by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. A t-butoxycarbonyl protecting group can be removed utilizing an inorganic or organic acid, such as HCl or trifluoroacetic acid, in a suitable solvent system, such as dioxane or methylene chloride. The resulting amino salt can readily be neutralized to yield the free amine. Carboxy protecting group, such as methyl, ethyl, benzyl, tert-butyl, 4-methoxyphenylmethyl and the like, can be removed under hydrolysis and hydrogenolysis conditions well known to those skilled in the art.

[0109] It should be noted that compounds of the invention may contain groups that may exist in tautomeric forms, such as cyclic and acyclic amidine and guanidine groups, heteroatom substituted heteroaryl groups (Y' = O, S, NR), and the like, which are illustrated in the following examples:



and though one form is named, described, displayed and/or claimed herein, all the tautomeric forms are intended to be inherently included in such name, description, display and/or claim.

[0110] Prodrugs of the compounds of this invention are also contemplated by this invention. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a patient. The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and Bundgaard Design of Prodrugs, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bungaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH

group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

[0111] The specification and claims contain listing of species using the language "selected from . . . and . . ." and "is . . . or . . ." (sometimes referred to as Markush groups). When this language is used in this application, unless otherwise stated it is meant to include the group as a whole, or any single members thereof, or any subgroups thereof. The use of this language is merely for shorthand purposes and is not meant in any way to limit the removal of individual elements or subgroups as needed.

PHARMACEUTICAL COMPOSITIONS, DOSING, AND ROUTES OF ADMINISTRATION

[0112] 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.

[0113] 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.

[0114] 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 e" 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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.

[0120] 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).

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] In some embodiments, all the necessary components for the treatment of KIF18A-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.

[0134] 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 KIF18A 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%.

[0135] 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. While individual needs vary, determination of optimal ranges of effective amounts of the compound is within the skill of the art. Such doses may be administered in a single dose or it may be divided into multiple doses.

[0136] The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, without limitation, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer, pancreatic cancer, cervical cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer, ovarian cancer, and endometrial cancer. While the term "cancer" as used herein is not limited to any one specific form of the disease, it is believed that the methods of the invention will be particularly effective for cancers which are found to be accompanied by unregulated levels of KIF18A or dependent on KIF18A for proper chromosome segregation and survival in the mammal.

[0137] The terms "treat", "treating" and "treatment" as used herein refer to therapy, including without limitation, curative therapy, prophylactic therapy, and preventative therapy. Prophylactic treatment generally constitutes either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals.

[0138] The term "patient", "subject", or "mammal" as used herein refers to any "patient", "subject", or "mammal" including humans, cows, horses, dogs and cats. In one embodiment of the invention, the mammal is a human.

[0139] The term "comprising" is meant to be open ended, including the indicated component(s) but not excluding other elements.

[0140] The terms "Formula I" include any sub formulas.

METHODS OF USING KIF18A INHIBITORS

[0141] The present disclosure provides compounds having MT-based KIF18A modulatory activity in general, and inhibitory activity in particular. In one embodiment of the invention, there is provided a method of modulating KIF18A protein in a subject, the method comprising administering to the subject an effective dosage amount of a compound of Formulas I. As such, the compounds of the invention may be used to treat cellular proliferation disorders, including uncontrolled cell growth, aberrant cell cycle regulation, centrosome abnormalities (structural and or numeric, fragmentation). Other diseases or disorders associated with the accumulation of extra centrosomes (>2) include human papillomavirus (HPV) infection, including HPV-associated neoplasias. The compounds are also useful for cilia-related dieases as well as ablating haploid germ cell population which could be used as a male contraceptive.

[0142] In addition, compounds of the invention are useful for, but not limited to, the prevention or treatment of cancer and other KIF18A-mediated diseases or disorders. For example, compounds of the invention would be useful for the treatment of various solid and hematologically derived tumors, such as carcinomas, including, without limitation, cancer of the bladder, breast, colon, kidney, liver, lung (including squamous cell and small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

[0143] The compounds of the invention are also useful in the treatment of cancer related indications such as solid tumors, sarcomas (especially Ewing's sarcoma and osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including leukemia and lymphoma, tumor- induced pleural or pericardial effusions, and malignant ascites.

[0144] Based on the ability to modulate kinesin impacting angiogenesis, the compounds of the invention are also useful in treatment and therapy of proliferative diseases. Particularly, these compounds can be used for the treatment of an inflammatory disease, especially of manifestations at the locomotor apparatus, such as various inflammatory rheumatoid diseases, especially chronic polyarthritis including rheumatoid arthritis, juvenile arthritis or psoriasis arthropathy; paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis, such as systemic Lupus erythematosus, poly-myositis, dermato-myositis, systemic sclerodermia or mixed collagenosis; postinfectious arthritis (where no living pathogenic organism can be found at or in the affected part of the body), seronegative spondylarthritis, such as spondylitis ankylosans; vasculitis, sarcoidosis, or arthrosis; or further any combinations thereof.

[0145] The compounds of the invention can also be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein- Leventhal syndrome)) since such diseases require a proliferation of blood vessel cells for growth and/or metastasis.

[0146] Besides being useful for human treatment, these compounds are useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. For example, animals including horses, dogs, and cats may be treated with compounds provided by the invention.

COMBINATIONS

[0147] While the compounds of the invention can be dosed or administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or in conjunction with other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered simultaneously or sequentially at different times, or the therapeutic agents can be given as a single composition.

[0148] The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

[0149] Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of cancer, such as with radiation therapy, small molecule targeted agents (e.g. PARP inhibitors, kinase inhibitors), therapeutic antibodies (e.g. naked and drug-conjugate) immunotherapy antibodies (checkpoint inhibitors, bi-specific T-cell engagers) with neoplastic or cytotoxic agents.

[0150] If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formula I may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anticancer or cytotoxic agent.

[0151] There are large numbers of anticancer agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such agents fall into several major categories such as antibiotic-type agents, alkylating and

alkylating-like agents, antimitotic agents, targeted small molecule agents, antimetabolite agents, hormonal agents, immunological agents, anti-angiogenic agents, interferon-type agents and a category of miscellaneous agents.

[0152] 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, targeted small molecule agents, and radiation treatment, to provide a synergistic or additive therapeutic effect.

[0153] 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 antimitotic agents, 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), and Adriamycin as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXANTM); 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, cholophosphamide, 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, CasodexTM, 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, Nab-paclitaxel; retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

[0154] 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, (NolvadexTM), 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, oxaliplatin, carboplatin; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vinblastine vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; topotecan; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO),

[0155] 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®, Abraxane, 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, Talazoparib, Niraparib, 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, CDK4/6 inhibitors (Palbociclib, Ibrance; Ribociclib, Kisqali; Abemaciclib, Verzenio).

[0156] 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.

[0157] 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.

[0158] 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.

[0159] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloprotienase 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.

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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".

[0164] 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).

[0165] 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).

[0166] 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.

[0167] 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 386; AMG 479; AMG 655; AMG 745; AMG 951; and AMG 706, or a pharmaceutically acceptable salt thereof.

[0168] 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, AMG 900, AZD-1152), 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, Talazoparib, Niraparib 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.

[0169] 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.

[0170] 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.

[0171] 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, and immune therapies, including anti-PD-1, anti-PDL-1, anti-CTLA4, anti-LAG1, and anti-OX40 agents, GITR agonists, CAR-T cells, and BiTEs.

[0172] 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.

[0173] 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.

[0174] 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.

[0175] MEK inhibitors include, but are not limited to, CI-1040, AZD6244, PD318088, PD98059, PD334581, RDEA119, ARRY-142886, ARRY-438162, and PD-325901.

[0176] 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.

[0177] 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).

[0178] TOR inhibitors include, but are not limited to, inhibitors include 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).

[0179] 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. 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: 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).

[0180] 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.

[0181] 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.

[0182] 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.

EXPERIMENTAL

[0183] Abbreviations: The following abbreviations may be used herein:

aq or aq.	aqueous
BOC or Boc	*tert*-butyloxycarbonyl
DAST	diethylaminosulfur trifluoride
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
ESI or ES	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOH	ethyl alcohol
EtOAc	EtOAc
G	grams
H	hour
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
iPr	isopropyl
iPr_2NEt or DIPEA	*N*-ethyl diisopropylamine (Hünig's base)
LDA	lithium diisopropylamide
LC MS, LCMS, LC-MS or LC/MS	liquid chromatography mass spectroscopy
LG	leaving group (e.g., halogen, mesylate, triflate)
m/z	mass divided by charge
Me	Methyl
MeCN or ACN	Acetonitrile
MeOH	Methanol

Met	metal species for cross-coupling (e.g., MgX, ZnX, SnR_3, SiR_3, $B(OR)_2$)
Mg	Milligrams
Min	Minutes
mL	Milliliters
MS	mass spectrum
MsCl	methanesulfonyl chloride
MTBE	*tert*-butyl methyl ether
NMP	1-methyl-2-pyrrolidine
n-BuLi	n-butyllithium
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2 \cdot DCM$	[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 or rbf	round-bottom flask
RP-HPLC	reverse phase high pressure liquid chromatography
RT or rt	room temperature
sat. or satd.	Saturated
SFC	supercritical fluid chromatography
TBAF	tetra-*n*-butylammonium fluoride
$TMSCF_3$	trimethyl(trifluoromethyl)silane
t-BuOH	*tert*-butanol
TEA or Et_3N	Trimethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
T_3P	2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide
TsCl	*p*-toluenesulfonyl chloride

[0184] Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All parts are by weight and temperatures are in degrees centigrade unless otherwise indicated. All microwave assisted reactions were conducted with a Smith Synthesizer™ from Biotage™. All compounds showed NMR spectra consistent with their assigned structures. Melting points were

determined on a Buchi apparatus and are uncorrected. Mass spectral data was determined by electrospray ionization technique. All examples were purified to >90% purity as determined by high-performance liquid chromatography. Unless otherwise stated, reactions were run at room temperature.

[0185] In synthesizing compounds of the present invention, it may be desirable to use certain leaving groups. The term "leaving groups" ("LG") generally refer to groups that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH_3), N-hydroxysuccinimide, N-hydroxybenzotriazole, and the like. Examples of nucleophiles include, but are not limited to, amines, thiols, alcohols, Grignard reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

[0186] The examples presented below illustrate specific embodiments of the present invention. These examples are meant to be representative and are not intended to limit the scope of the claims in any manner.

[0187] It is noted that when a percent (%) is used with regard to a liquid, it is a percent by volume with respect to the solution. When used with a solid, it is the percent with regard to the solid composition. Materials obtained from commercial suppliers were typically used without further purification. Reactions involving air or moisture sensitive reagents were typically performed under a nitrogen or argon atmosphere. Purity was measured using high performance liquid chromatography (HPLC) system with UV detection at 254 nm and 215 nm (System A: Agilent Zorbax Eclipse XDB-C8 4.6 x 150 mm, 5 μm, 5 to 100% CH_3CN in H_2O with 0.1% TFA for 15 min at 1.5 mL/min; System B: Zorbax SB-C8, 4.6 x 75 mm, 10 to 90% CH_3CN in H_2O with 0.1% formic acid for 12 min at 1.0 mL/min) (Agilent Technologies, Santa Clara, CA). Silica gel chromatography was generally performed with prepacked silica gel cartidges (Biotage, Uppsala, Sweden or Teledyne-Isco, Lincoln, NE). ^1H NMR spectra were recorded on a Bruker AV-400 (400 MHz) spectrometer (Bruker Corporation, Madison, WI) or a Varian (Agilent Technologies, Santa Clara, CA) 400 MHz spectrometer at ambient temperature. All observed protons are reported as parts per million (ppm) downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants, and number of protons. Low-resolution mass spectral (MS) data were determined on an Agilent 1100 Series (Agilent Technologies, Santa Clara, CA) LC/MS with UV detection at 254 nm and 215 nm and a low resonance electrospray mode (ESI).

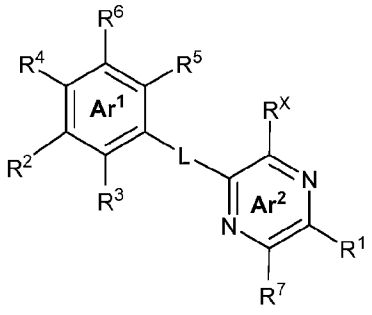
GENERAL SYNTHETIC SCHEME

[0188] Unless otherwise stated, starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Bachem (Torrance, Calif.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various

modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates, and the final products of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0189] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about −78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 °C.

[0190] For the purpose of clarity in this general synthesis section, Compounds of Formula (I) as defined in the summary of the inventions can be schematically drawn to contain Ring Ar^1 and Ring Ar^2 as follows:



(I);

[0191] wherein the group L is $-NR^8-(C=O)-$ or $-(C=O)-NR^8-$; Ring Ar^1 is located to the left of the linker, and ring Ar^2 is located to the right of linker

[0192] Generally, compounds of Formula (I), can be synthesized via three general steps as follows:

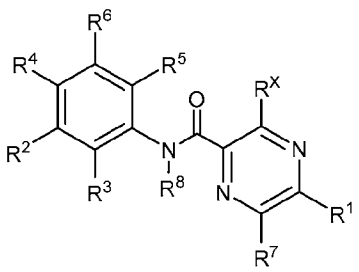
[0193] Step 1: Preparation of Ring Ar^1 compound.

[0194] Step 2: Preparation of Ring Ar^2 compound.

[0195] Step 3: Coupling of Ring Ar^1 compound to Ring Ar^2 compound

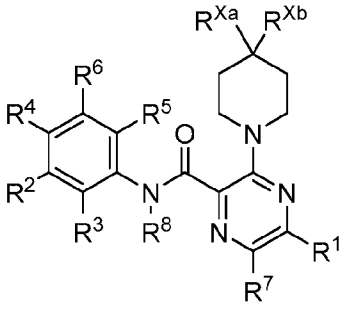
[0196] The generic Schemes A-D below are meant to provide guidance to the ordinarily skilled synthetic chemist, who will readily appreciate that the solvent, concentration, reagent, protecting group, order of synthetic steps, time, temperature, and the like can be modified as necessary, well within the skill and judgment of the ordinarily skilled artisan.

[0197] In one embodiment, Schemes A-C below provide generic preparation of a compound of Formula (I) wherein L is $-NR^8-(C=O)$; having the following formula **(I-A)**:



(I-A); wherein preferably R^5 is H.

[0198] An example of a compound of formula (Ia) includes, but is not limited **(I-A-1)**; wherein preferably R^5 is H.

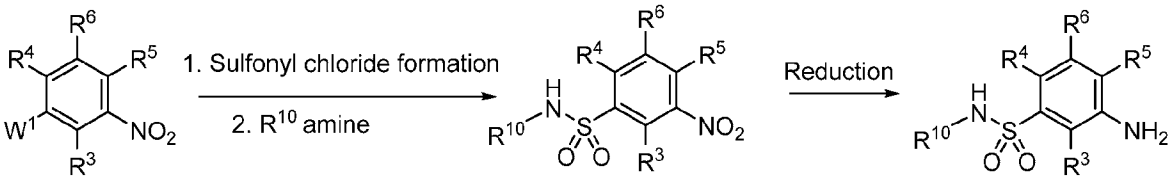


(I-A-1).

[0199] SCHEME A: PREPARATION OF COMPOUND **(I-A)**:

[0200] According to Scheme A, in one embodiment, a compound of Formula (I) as disclosed herein can be synthesized as follows:

[0201] Step A-1: Preparation of Ring Ar^1 compound:



A-1 **A-2** **A-3**

[0202] Compound A-1, wherein W^1 is H, can be converted into the corresponding sulfonyl chloride compound intermediate by treatment with chlorosulfonic acid.

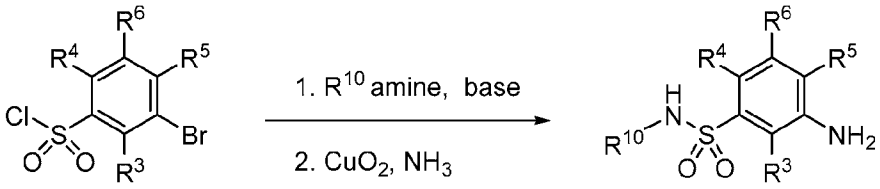
[0203] Alternatively, compound A-1, wherein W^1 is F, can be converted into the corresponding sulfonyl chloride compound intermediate by a two-step procedure, which is treatment with benzyl mercaptan followed up by oxidative chlorination with 1,3-dichloro-5,5-dimethylhydantoin.

[0204] Compound A-1 is commercially available or can be synthesized by known methods by those skilled in the art. Examples of compound A-1 include, but are not limited to, 1-methyl-3-nitrobenzene, 1-chloro-4-nitrobenzene, 1-methoxy-4-nitrobenzene, 1-methoxy-3-nitrobenzene, or 3,5-difluoronitrobenzene.

[0205] Further reaction of the sulfonyl chloride intermediate compound obtained above with an R^{10} group containing amine in the presence of a suitable base, in a suitable organic solvent such as NMP, dioxane, acetonitrile, tetrahydrofuran, DMF, methylene chloride, and the like give sulfonamides A-2, wherein $R^2 = SO_2R^{10}$. Examples of bases include, but are not limited to diisopropylethylamine amine, potassium carbonate, or sodium hydride. Examples of R^{10} amines include, but not limited to *tert*-butyl amine, cyclopropyl amine, cyclohexylamine, piperidine, or 4,4-difluoropiperidine.

[0206] Compound A-2 can then be reacted with a suitable reducing agent, such as palladium catalyst and a hydrogen source, such as Pd/C in the presence of hydrogen gas, to form compound A-3.

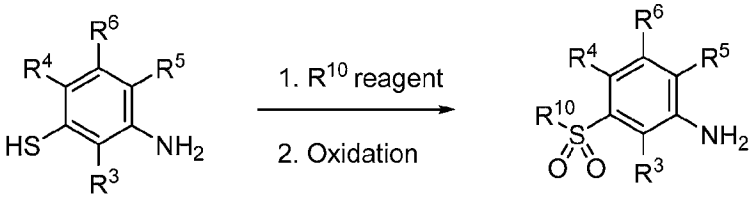
[0207] Step A-1-a: Preparation of Ring Ar^1 compound:



A-4 A-3

[0208] Alternatively, compound A-4, can be reacted with a R^{10} amine reagent, followed up by metal catalyzed amination reaction, wherein a suitable palladium or copper catalyst and a base can be used, to form compound A-3, wherein $R^2 = SO_2R^{10}$, as defined in step A-1.

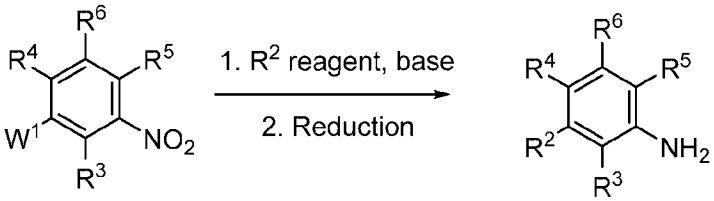
[0209] Step A-1-b: Preparation of Ring Ar^1 compound:



A-5 A-3

[0210] Yet alternatively, thiol compound A-5 can be reacted with an R^{10} reagent via thiol alkylation reaction followed up by oxidation reaction to form compound A-3, wherein $R^2 = SO_2R^{10}$. Examples of R^{10} reagents that can be used in this manner include, but not limited to methylenecyclobutane, trifluoroethanol, or cyclopent-2-enone.

[0211] Step A-1-c: Preparation of Ring Ar^1 compound:



A-1 A-3

[0212] Yet alternatively, compound A-1, wherein W^1 is halo, for example fluoro, chloro, or bromo can be reacted with a suitable R^2 reagent in the presence of a suitable base, in a suitable organic solvent such as NMP, dioxane, acetonitrile, tetrahydrofuran, DMF, methylene chloride, and the like, followed by reacting with a suitable reducing agent, such as palladium catalyst and a hydrogen source, such as Pd/C in the presence of hydrogen gas, to form compound A-3.

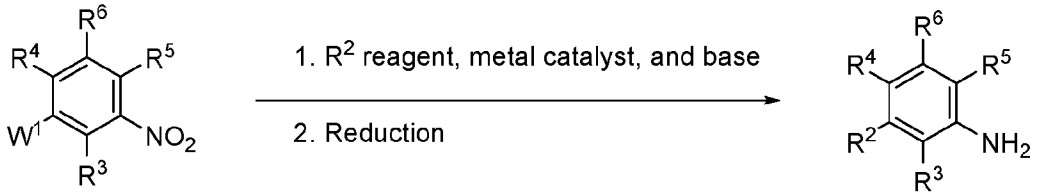
[0213] Compound A-1 is commercially available or can be synthesized by known methods by those skilled in the art.

[0214] Examples of compound A-1 include, but are not limited to, 1-fluoro-3-nitrobenzene, 1,3-difluoro-5-nitrobenzene, 1-fluoro-3-methylbenzene, or 2-bromo-1-fluoro-4-nitrobenzene.

[0215] Examples of R^2 reagents include, but not limited to (1) (*R*)-2-methylmorpholine, (2) 4,4-difluoropiperidine hydrochloride, (3) 3,3-difluoroazetidine hydrochloride, (4) 3,3,3-trifluoropropan-1-ol, (5) 2-aminoethan-1-ol, or (6) 2-amino-3-methylpropan-1-ol.

[0216] Examples of bases include, but are not limited to diisopropylethylamine amine, potassium carbonate, or sodium hydride.

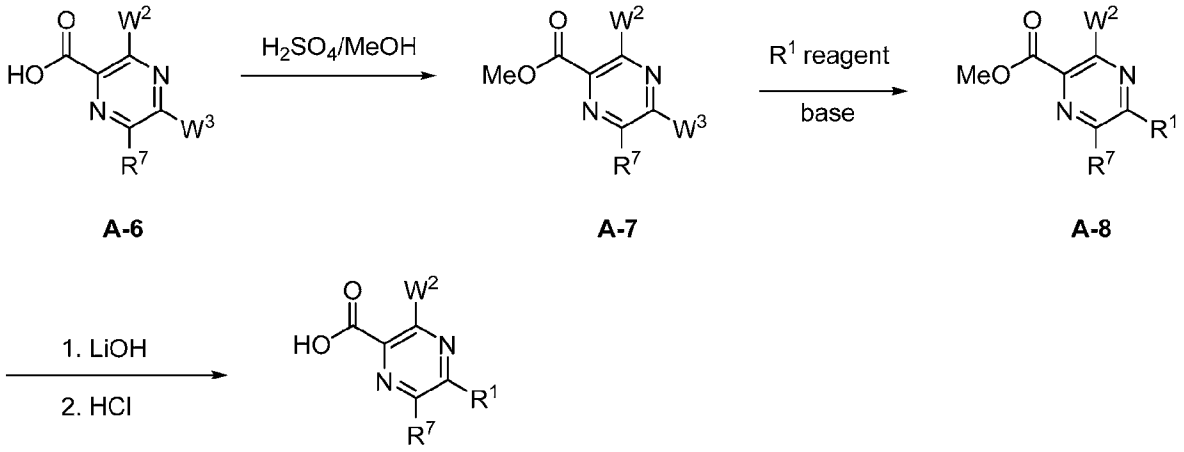
[0217] Step A-1-d: Preparation of Ring Ar^1 compound:



A-1 **A-3**

[0218] Yet alternatively, compound A-1, wherein W^1 is halo, as defined in step A-1-c, can be reacted with a suitable R^2 reagent in the presence of a metal catalyst, such as palladium or copper catalyst, and in the presence of a base, such as cesium carbonate, potassium carbonate or potassium phosphate in an amination reaction, followed by reacting with a suitable reducing agent, such as palladium catalyst and a hydrogen source, such as Pd/C in the presence of hydrogen gas, to form compound A-3.

[0219] Step A-2: Preparation of Ring Ar^2 compound:

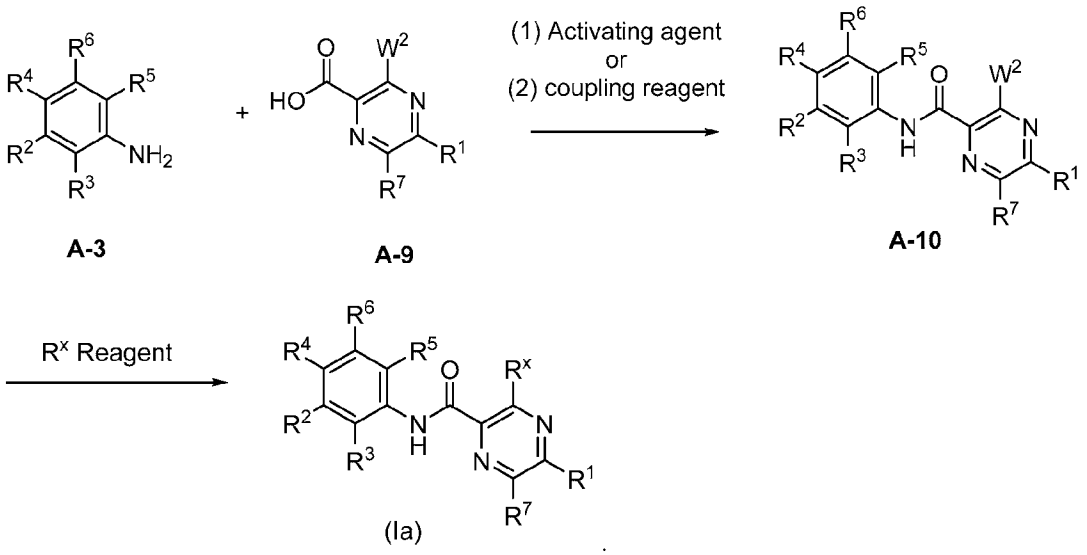


A-6 **A-7** **A-8**

A-9

[0220] In Step A-2, Compound A-6, wherein each of W^2 and W^3 is independently halo, for example fluoro, chloro, bromo, or iodo, can be reacted with MeOH in the presence of H_2SO_4 to form the methyl ester A-7 that is then reacted with an R^1, such as 2-amino-2-methyl-1-propanol, (1-aminocyclopropyl)methanol, or 2-aminoethan-1-ol, in a suitable organic solvent such as NMP, acetonitrile, tetrahydrofuran, DMF, DMSO, and the like, to form Compound A-8. Compound A-8 is then hydrolyzed using lithium chloride and neutralized with HCl to form A-9

[0221] Step A-3a: Coupling of Ring Ar^1 compound to Ring Ar^2 compound followed by introduction of R^1:



[0222] In Step A-3a, compound A-9, which was obtained from Step A-2, can be reacted with an activating agent such as acid chloride $(COCl)_2$ or $SOCl_2$, in a suitable organic solvent such as tetrahydrofuran, methylene chloride, and the like, to form an acid chloride derivative, which can then be reacted with compound A-3 to form compound A-10.

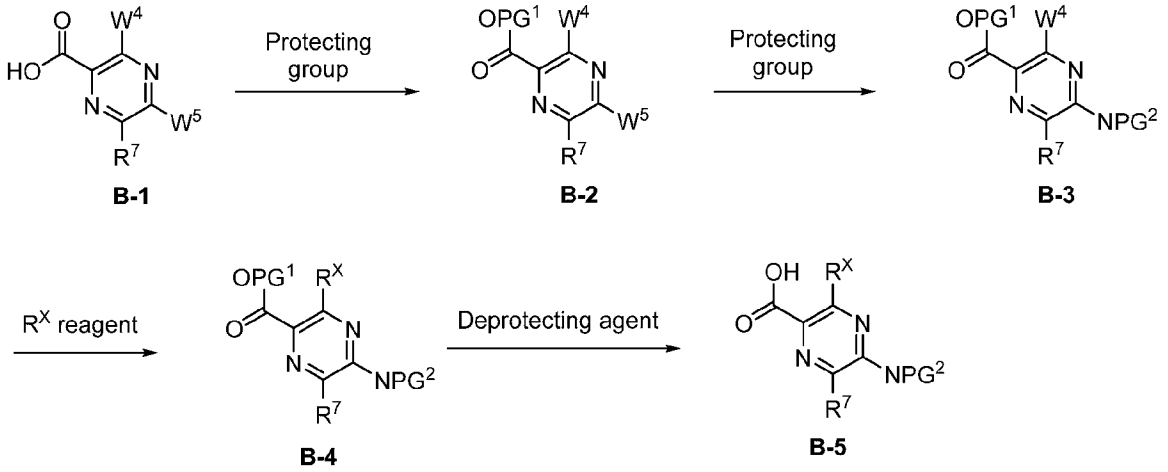
[0223] Alternatively, compound A-3 can be directly coupled with compound A-9, which was obtained from Step A-2, in a suitable organic solvent such as acetonitrile, tetrahydrofuran, DMF, methylene chloride, and the like, in the presence of a coupling reagent, such as N, N'-diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, *O*-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, thionyl chloride, carbonyl diimidazole, and polyphosphonic anhydride.

[0224] Those ordinary skilled synthetic chemists will readily understand that other coupling agents can be used. Further manipulation of halogen group W^2 by reacting with an R^X reagent, such as (1) 6-azaspiro[2.5]octane hydrochloride, (2) 4,4-dimethylpiperidine hydrochloride, (3) 3,4,4-trimethylpiperidine hydrochloride, (4) 4-methyl-6-azaspiro[2.5]octane hydrochloride, or (5) 7-azaspiro[3.5]nonane hydrochloride, in a suitable organic solvent such as NMP, acetonitrile, tetrahydrofuran, DMF, methylene chloride, DMSO, can be used to form Compound (Ia). Those ordinary skilled in the art will readily understand that coupling reaction such as shown in Step A-3 can be performed under various known conditions. Alternative, the halogen group W^2 can be reacted in a palladium catalyzed coupling reaction with a boronic acid and a palladium catalyst forming compound (Ia)

[0225] SCHEME B: ALTERNATIVE PREPARATION OF COMPOUND **(I-A)**:

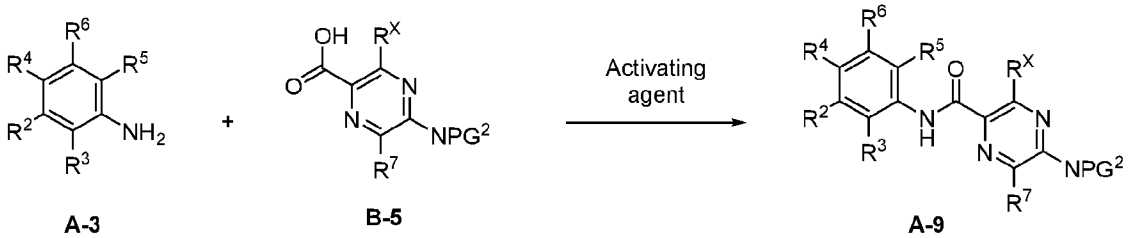
[0226] Step B-1: Preparation of Ring Ar^1 compound: see Steps A-1 to A-1d of SCHEME A above

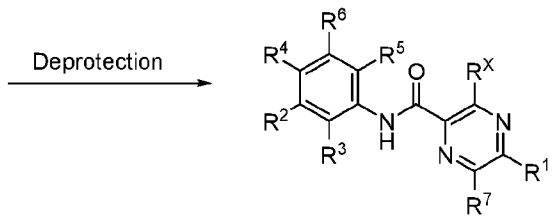
[0227] Step B-2: Preparation of Ring Ar^2 compound:



[0228] Scheme B provides an alternative method for formation of compounds of Formula (Ia) as disclosed herein. After any of the Steps A-1 to A-1d as described in Scheme A, the group R^1 can alternatively be introduced to Ring Ar^2 in Step B-2 rather that in Step B-3 as in Scheme A. According to Step 2b, compound B-1, wherein each of W^4 and W^5 is independently halo, for example fluoro, chloro, bromo, or iodo, can be reacted with an appropriate carboxylic acid protecting group (PG_1 reagent), such as methyl iodide in the presence of a base such as potassium carbonate, to form a methyl ester, or other appropriate protecting group to form other ester such as benzyl ester, in a suitable organic solvent such as NMP, acetonitrile, tetrahydrofuran, DMF, methylene chloride and the like, to form compound B-2, wherein each of W^4 and W^5 are as defined in compound B-1. Compound B-2, can be reacted with the appropriate protected amine (PG^2 reagent), for example 4,4-dimethyloxazolidin-2-one, in the presence of a base such as potassium *tert*-butoxide to form compound B-3. This can be reacted with an R^X reagent, such as (1) 6-azaspiro[2.5]octane hydrochloride, (2) 4,4-dimethylpiperidine hydrochloride, (3) 3,4,4-trimethylpiperidine hydrochloride, (4) 4-methyl-6-azaspiro[2.5]octane hydrochloride, or (5) 7-azaspiro[3.5]nonane hydrochloride, in a suitable organic solvent such as NMP, acetonitrile, tetrahydrofuran, DMF, methylene chloride, DMSO, and the like, to form Compound B-4, which can then be reacted further with an appropriate carboxylic acid deprotecting agent to form compound B-5. Appropriate carboxylic acid protecting groups and deprotection agents are known to those skilled in the art, e.g., as discussed in Greene's Protective Groups in Organic Synthesis.

[0229] Step B-3: Coupling of Ring Ar^1 compound to Ring Ar^2 compound and removal of protecting group:





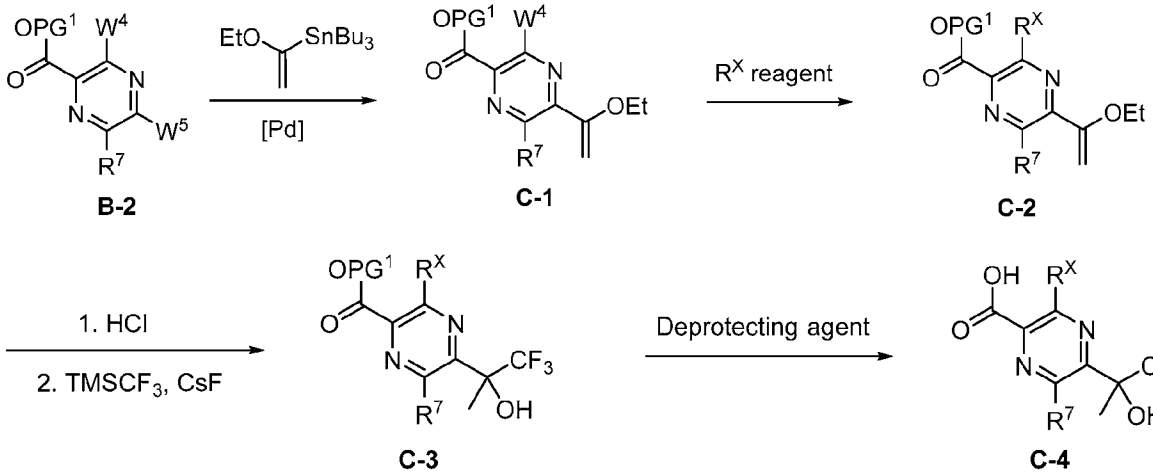
(I-A)

[0230] Step B-3 can be performed under similar condition to the coupling reaction as described above in Step A-3.

[0231] SCHEME C: ALTERNATIVE PREPARATION OF COMPOUND (I-A):

[0232] Step C-1: Preparation of Ring Ar^1 compound: see Steps A-1 to A-1d of SCHEME A above

[0233] Step C-2: Preparation of Ring Ar^2 compound:



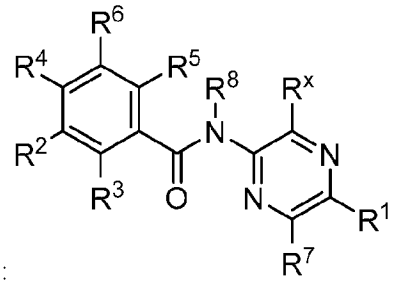
[0234] Scheme C provides an alternative method for formation of compounds of Formula (I-A) as disclosed herein. According to Step C-2, compound B-2, wherein each of W^4 and W^5 is independently halo, for example chloro, bromo, or iodo, can be reacted with tributyl(1-ethoxyvinyl)tin, in the presence of a palladium catalyst such as bis-(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium to give the enol ether C-1. Compound C-1 can be reacted with an R^X reagent, such as (1) 6-azaspiro[2.5]octane hydrochloride, (2) 4,4-dimethylpiperidine hydrochloride, (3) 3,4,4-trimethylpiperidine hydrochloride, (4) 4-methyl-6-azaspiro[2.5]octane hydrochloride, or (5) 7-azaspiro[3.5]nonane hydrochloride, in a suitable organic solvent such as NMP, acetonitrile, tetrahydrofuran, DMF, methylene chloride, DMSO, and the like, to form Compound C-2, which is then treated with HCl followed by trimethylsilyl trifluorometane to give

compound C-3. Compound C-3, can then be reacted further with an appropriate carboxylic acid deprotecting agent to form compound C-4. Appropriate carboxylic acid protecting groups and deprotection agents are known to those skilled in the art, e.g., as discussed in Greene's Protective Groups in Organic Synthesis.

[0235] Step C-3 can be performed under similar condition to the coupling reaction as described above in Step A-3 of Scheme A.

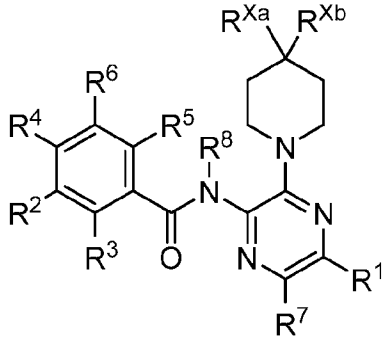
[0236] SCHEME D: PREPARATION OF COMPOUND (I-B):

[0237] In another embodiment, a compound of formula (I) wherein L is -(C=O)-NR^8- having the formula



(I-B): **(I-B)**, wherein preferably R^5 is H, can be prepared according to Scheme D below.

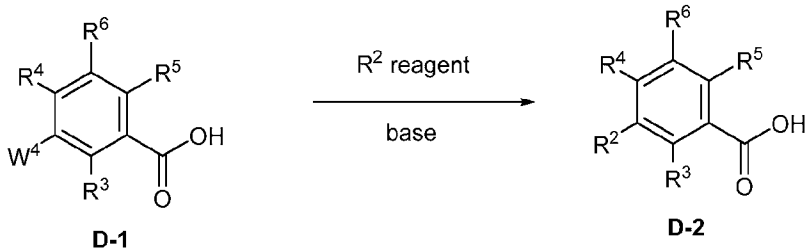
[0238] An example of a compound of formula **(I-B)** includes, but is not limited to:



(I-B-1); wherein preferably R^5 is H.

[0239] Step D-1: Preparation of Ring Ar^1 compound:

[0240] Preparation of Ring Ar^1 compound: one embodiment of Ring Ar^1 compounds include compound D-1, having the formula:

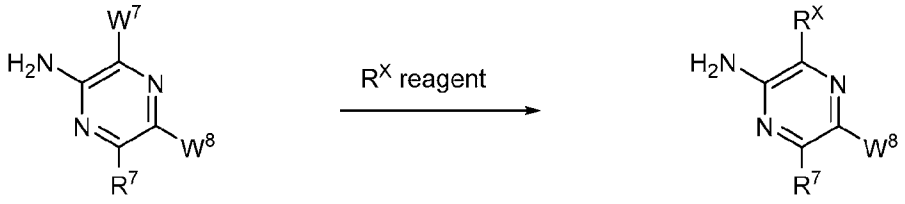


D-1 **D-2**

In step D-1, compound **D-1**, wherein W^4 is a halogen, for example fluoro or chloro, can be reacted with an R^2 reagent in the presence of a suitable base, in a suitable organic solvent such as NMP, dioxane, acetonitrile, tetrahydrofuran, DMF, methylene chloride, and the like, to form compound **D-2**. Examples of compound **D-1** include, but are not limited to, 3-fluorobenzoic acid or, 3-fluoro-3-methylbenzoic acid. Examples of R^2 reagents include, but not limited to (1) (*R*)-2-methylmorpholine, (2) 4,4-difluoropiperidine

hydrochloride, or (3) 3,3-difluoroazetidine hydrochloride. Examples of bases include, but are not limited to diisopropylethyl amine, potassium carbonate.

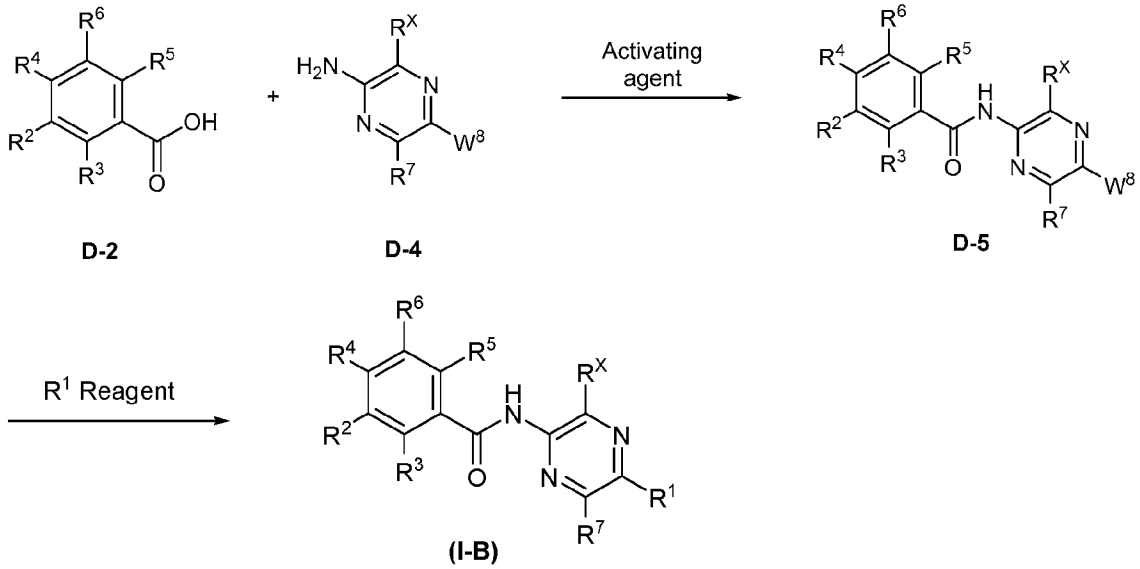
[0241] Step D-2: Preparation of Ring Ar^2 compound:



D-3 **D-4**

[0242] In step D-2, compound D-3, wherein each of W^7 and W^8 is independently halo, for example fluoro, chloro, bromo, or iodo, can be reacted with an R^X reagent, such as (1) 6-azaspiro[2.5]octane hydrochloride, (2) 4,4-dimethylpiperidine hydrochloride, (3) 3,4,4-trimethylpiperidine hydrochloride, (4) 4-methyl-6-azaspiro[2.5]octane hydrochloride, or (5) 7-azaspiro[3.5]nonane hydrochloride, in a suitable organic solvent such as NMP, acetonitrile, tetrahydrofuran, DMF, methylene chloride, DMSO, and the like, to form compound D-4. Examples of compound D-3 include, but are not limited to: (1) 5-bromo-3-chloropyrazin-2-amine, (2) 5-bromo-6-chloro-6-methylpyrazin-2-amine, or (3) 3,5-dichloropyrazin-2-amine.

[0243] Step D-3: Coupling of Ring Ar^1 compound to Ring Ar^2 compound:



[0244] In step D-3, compound D-2, which was obtained from Step D-1, can be reacted with compound D-4, which was obtained from Step D-2, in a suitable organic solvent such as acetonitrile, tetrahydrofuran, DMF, methylene chloride, and the like, in the presence of a coupling agent, such as N, N'-diisopropylcarbodiimide, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, *O*-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, carbonyl diimidazole, or polyphosphonic anhydride to form compound D-5. Those skilled in the art will readily understand that other coupling agents can be used. Further manipulation of halo group W^8 by transformation reactions such as, SNAr, metal-catalyzed sulfoamidation, sulfination, or

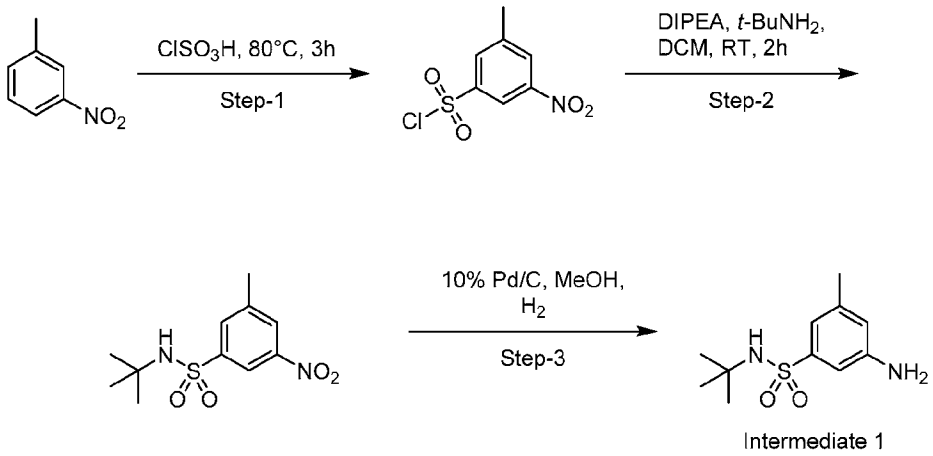
sulfonylation, in a suitable organic solvent such as DMSO, acetonitrile, tetrahydrofuran, DMF, and the like, in the presence of a metal catalyst and an R^1 reagent, such as (1) oxetane 3-amine, (2) 2-amino-2-methylpropan-1-ol, (3) (3-aminooxetan-3-yl)methanol, (4) ethyl 2-sulfamoylpropanoate, (5) 2-hydroxypropane-1-sulfonamide, (6) 2-hydroxyethane-1-sulfonamide, (7) 2-mercaptopropan-1-ol, (8) 2-mercapto-2-methylpropan-1-ol, (9) 2-aminoethan-1-ol, or (10) cyclopropanethiol can then be performed to form compound (I-B).

[0245] Those skilled in the art will readily understand that coupling reaction such as shown in Step D-3 can be performed under various known conditions. It will be recognized by a person skilled in the art that the above transformations could also be carried out at earlier stages in the synthetic process based on feasibility of the transformations.

[0246] PREPARATION OF SYNTHETIC INTERMEDIATES

[0247] PREPARATION OF RING AR[1] INTERMEDIATES

[0248] Intermediate 1: 3-Amino-*N*-(*tert*-butyl)-5-methylbenzenesulfonamide



Intermediate 1

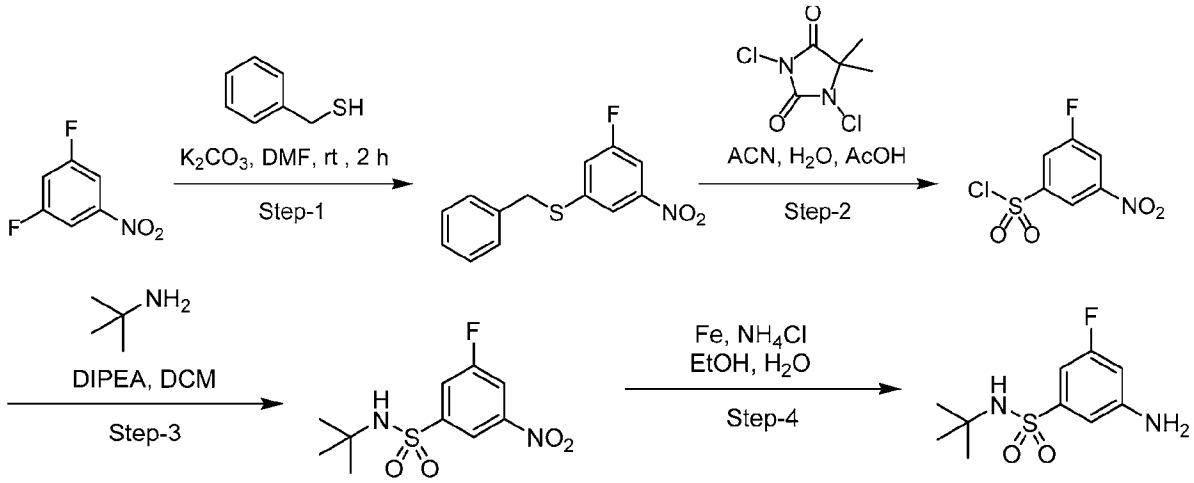
[0249] Step 1: To ice cold 1-methyl-3-nitrobenzene (2 g, 14.58 mmol), chlorosulfonic acid (14.57 mL, 219 mmol) was added slowly 15 minutes. The resulting mixture was heated to 80 °C for 3h. The reaction mixture was quenched with crushed ice and extracted with EtOAc (50 mL). The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-methyl-5-nitrobenzenesulfonyl chloride as a brown liquid. The crude product was taken to the next step immediately. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (t, *J* = 1.9 Hz, 1H), 8.52 – 8.39 (m, 1H), 8.18 (t, *J* = 1.7 Hz, 1H), and 2.66 (s, 3H).

[0250] Step 2: To an ice-cold solution of 2-methylpropan-2-amine (1.09 g, 14.94 mmol) in DCM (50 mL), was slowly added DIPEA (3.56 mL, 20.37 mmol) and a solution of 3-methyl-5-nitrobenzene-1-sulfonyl chloride (3.2 g, 13.58 mmol) in DCM (50 mL). After the addition, the reaction mixture was slowly warmed to ambient temperature and stirred for 2h. Then, water (100 mL) was added, stirred for 10 min, and the aqueous layer was extracted with DCM (100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was absorbed onto a plug of silica gel and purified by chromatography eluting with 10% EtOAc in petroleum ether, to provide *N*-(*tert*-butyl)-3-methyl-5-nitrobenzene sulfonamide (1.9 g, 6.98 mmol, 51% yield) as a light yellow solid. ^{1}H NMR (300

MHz, Chloroform-*d*) δ 8.56 (d, *J* = 5.8 Hz, 1H), 8.27 – 8.16 (m, 1H), 8.10 – 7.99 (m, 1H), 4.86 (s, 1H), 2.57 (s, 3H), and 1.27 (s, 9H). MS (ESI negative ion) m/z: 271.2 (M-1).

[0251] Step 3: A mixture of *N*-(*tert*-butyl)-3-methyl-5-nitrobenzene sulfonamide (1.9 g, 6.98 mmol) and 10% Pd/C (0.6 g, 0.56 mmol) in MeOH (50 mL) was stirred under a hydrogen atmosphere (balloon pressure) for 3 h and then filtered through a CELITE® pad. The pad was washed with MeOH (150 mL) and the filtrate was concentrated under reduced pressure to afford a white residue. The crude material was absorbed onto a plug of silica gel and purified by chromatography eluting with a gradient of 15-20% EtOAc in petroleum ether, to provide 3-amino-*N*-(*tert*-butyl)-5-methylbenzene sulfonamide (1.2 g, 4.95 mmol, 71% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 – 7.13 (m, 1H), 6.83 (dq, *J* = 4.7, 2.2 Hz, 1H), 6.76 (dd, *J* = 3.8, 2.2 Hz, 1H), 6.52 (q, *J* = 3.5, 2.6 Hz, 1H), 5.55 – 5.29 (m, 2H), 2.16 (s, 3H), and 1.09 (s, 9 H). *m/z* (ESI): 243.1 (M+1).

[0252] Intermediate 2: 3-Amino-*N*-(*tert*-butyl)-5-fluorobenzenesulfonamide



Intermediate 2

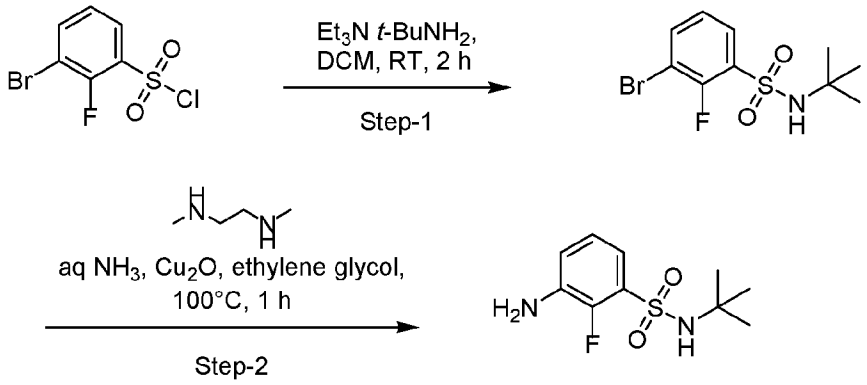
[0253] Step 1: To a 25-mL round-bottomed flask was added 3,5-difluoronitrobenzene (1 mL, 8.80 mmol), potassium carbonate (0.59 mL, 9.68 mmol), benzyl mercaptan (1.1 mL, 9.24 mmol), and DMF (10 mL) at 0 °C, then it was stirred at RT for 2 h, and water was added (10 mL). The resulting mixture was extracted with EtOAc (3x 100 mL), the combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the crude product, that was used without further purification.

[0254] Step 2: To a 100-mL round-bottomed flask was added benzyl(3-fluoro-5-nitrophenyl)sulfane (1.63g, 6.19 mmol), acetonitrile (12 mL), water (0.3 mL), and acetic acid (0.45 mL). The reaction mixture was cooled to 0 °C and 1,3-dichloro-5,5-dimethylhydantoin (1.14 mL, 8.67 mmol) was added portionwise. When the addition was finished, the reaction mixture was stirred at 0 °C for 20 min. The reaction mixture was then diluted with satd $NaHCO_3$ and extracted with EtOAc. The organic extract was washed with water and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give 3-fluoro-5-nitrobenzene-1-sulfonyl chloride (1.48 g, 6.19 mmol, 100 % yield) as a white solid that was used without further purification. *m/z* (ESI): 240.2 (M+1).

[0255] Step 3: To a 100-mL round-bottomed flask was added 3-fluoro-5-nitrobenzene-1-sulfonyl chloride (1.66 g, 6.92 mmol), DCM (10 mL), *tert*-butylamine (0.51 mL, 6.92 mmol), and DIPEA (1.81 mL, 10.38 mmol). The reaction mixture was stirred at RT for 3 h, diluted with satd $NaHCO_3$, and extracted with DCM (6 mL). The organic extract was washed with water and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give the crude material as a white oil. The crude material was absorbed onto a plug of silica gel and purified by chromatography through silica gel column, eluting with a gradient of 0-25% EtOAc in heptane to provide *N*-(*tert*-butyl)-3-fluoro-5-nitrobenzenesulfonamide (1.02 g, 3.70 mmol, 54 % yield) as a white solid. *m/z* (ESI): 290.2 (M+Na).

[0256] Step 4: To a 25-mL glass vial (red cap) was added iron (0.30 g, 5.43 mmol), ammonium chloride (48 mg, 0.91 mmol), followed by *N*-(*tert*-butyl)-3-fluoro-5-nitrobenzenesulfonamide (0.50 g, 1.81 mmol) in EtOH (6 mL), and water (0.5 mL). The reaction mixture was stirred at 80 °C for 1 h, cooled to rt, filtered through CELITE®, and the solvent removed under vacuum. The reaction mixture was diluted with satd NH_4Cl (10 mL) and extracted with EtOAc (10 mL). The organic extract was washed with water (10 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo to give the crude material as a white oil. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column, eluting with a gradient of 0-40% EtOAc in heptane to provide 3-amino-*N*-(*tert*-butyl)-5-fluorobenzenesulfonamide (0.33 g, 1.36 mmol, 75 % yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 6.99 (t, *J*=1.76 Hz, 1H), 6.93 (td, *J*=1.91, 8.12 Hz, 1H), 6.51 (td, *J*=2.35, 10.17 Hz, 1H), 4.52 (s, 1H), 1.26 (s, 9H). *m/z* (ESI): 247.1 (M+1).

[0257] Intermediate 3: 3-Amino-*N*-(*tert*-butyl)-2-fluorobenzenesulfonamide



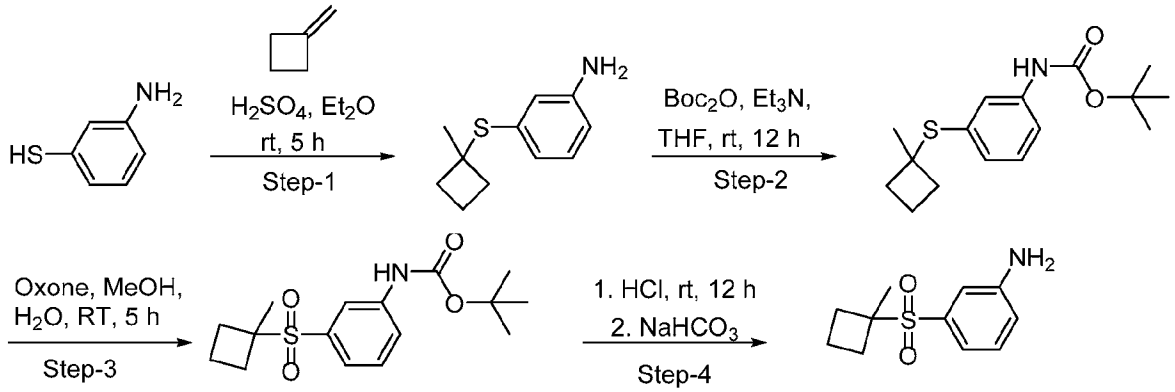
Intermediate 3

[0258] Step 1: To a solution of 3-bromo-2-fluorobenzenesulfonyl chloride (4.0 g, 14.62 mmol) in DCM (40 mL) was added triethyl amine (6.12 mL, 43.9 mmol) and *tert*-butyl amine (2.33 mL, 21.94 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water (30 mL) and the bi-phasic mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was absorbed onto a plug of silica gel (60-120 mesh) and purified by silica gel chromatography, eluting with 5-8% EtOAc in hexanes, to give 3-bromo-*N*-(*tert*-butyl)-2-

fluorobenzenesulfonamide (3.5 g, 77% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01-7.95 (m, 2H), 7.85-7.80 (m, 1H), 7.36-7.31 (m, 1H), 1.13 (s, 9H). *m/z* (ESI): 308.1 [M-1].

[0259] Step 2: To a solution of 3-bromo-*N*-(*tert*-butyl)-2-fluorobenzenesulfonamide (3.2 g, 10.32 mmol) in ethylene glycol (5 mL) were added N^1,N^2-dimethylethane-1,2-diamine (0.091 g, 1.032 mmol), potassium carbonate (0.285 g, 2.06 mmol), copper(I) oxide (0.074 g, 0.516 mmol), and aqueous ammonia (7.5 mL) under nitrogen atmosphere. The reaction vessel was sealed and stirred at 100 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with water (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine solution (50 mL), dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The crude residue was absorbed onto a plug of silica gel and purified by silica gel chromatography, eluting with 25-35% EtOAc in hexanes, to give 3-amino-*N*-(*tert*-butyl)-2-fluorobenzenesulfonamide (0.9 g, 3.65 mmol, 35 % yield) as an off-white solid.^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (s, 1H), 6.98-6.88 (m, 3H), 5.50 (s, 2H), 1.12 (s, 9H). *m/z* (ESI): 247.2 [M+1]

[0260] Intermediate 4: 3-((1-Methylcyclobutyl)sulfonyl)aniline



Intermediate 4

[0261] Step 1: To a mixture of 3-aminobenzenethiol (3.0 g, 23.96 mmol) and methylenecyclobutane (2.94 g, 43.1 mmol) in diethyl ether (30.0 mL) was added concentrated H_2SO_4 (3.83 mL, 71.9 mmol) cautiously and stirred at room temperature for 45 min. The reaction mixture was quenched by pouring into a cold satd aqueous $NaHCO_3$ solution (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with cold water (5 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was absorbed onto a plug of silica gel (60-120 mesh) and purified by flash chromatography through a silica gel column, eluting with a gradient of 1-15% EtOAc in hexanes, to give 3-((1-methylcyclobutyl)thio)aniline (3.2 g, 69% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.02 – 6.95 (m, 1H), 6.63 (s, 1H), 6.55 – 6.45 (m, 2H), 2.27 – 2.14 (m, 2H), 2.08 – 1.84 (m, 4H), 1.45 (m, 3H), NH_2 protons were not visible. *m/z* (ESI): 194.2 [M+1].

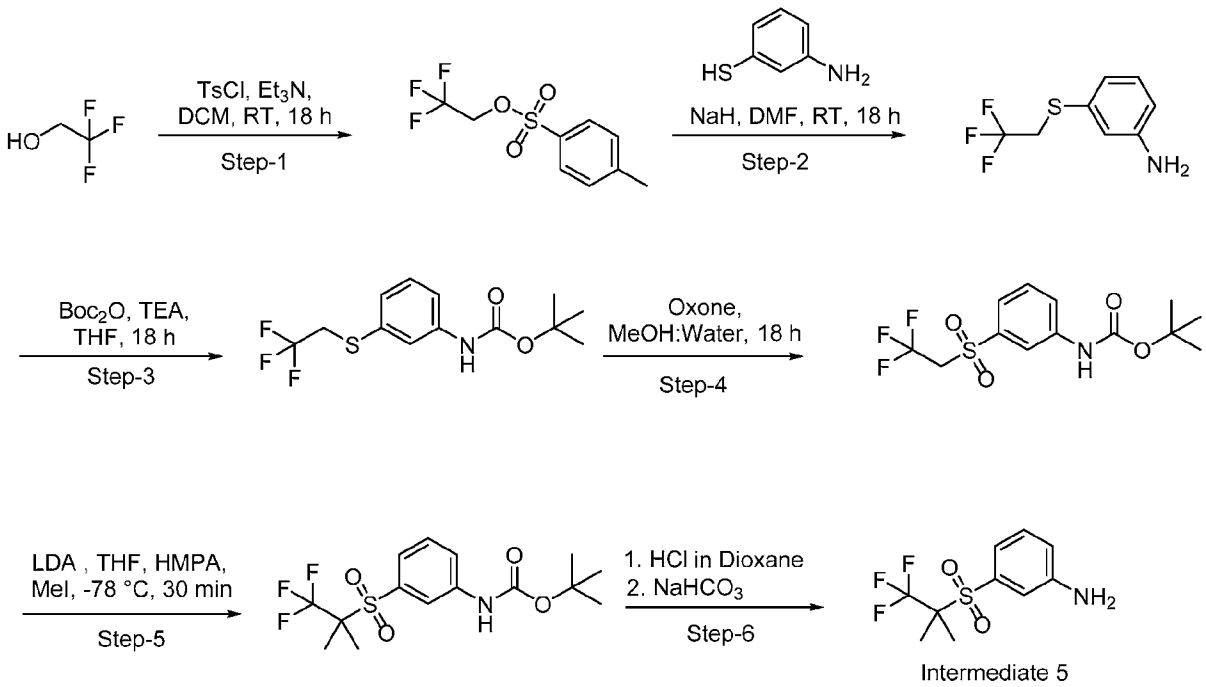
[0262] Step 2: To a solution of 3-((1-methylcyclobutyl)thio)aniline (3.0 g, 15.5 mmol) in THF (30 mL) was added Boc anhydride (7.21 mL, 31.0 mmol) and Et_3N (3.24 mL, 23.28 mmol) at room temperature and stirred for 18 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (200 mL). The organic layer was washed with water (50 mL), dried over Na_2SO_4, filtered, and

concentrated under reduced pressure. The crude residue was absorbed onto a plug of silica gel and purified by flash chromatography through a silica gel column, eluting with a gradient of 5-8 % EtOAc in hexanes, to give *tert*-butyl (3-((1-methylcyclobutyl)thio)phenyl)carbamate (3.2 g, 70% yield) as a white solid. ^{1}H NMR (300 MHz, Chloroform-*d*): δ 7.44 – 7.33 (m, 2H), 7.30 – 7.20 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.50 (s, 1H), 2.42 – 2.26 (m, 2H), 2.16 – 1.93 (m, 4H), 1.57 (s, 9H), 1.54 (s, 3H). *m/z* (ESI): 294.2 [M+1].

[0263] Step 3: To a solution of *tert*-butyl (3-((1-methylcyclobutyl)thio)phenyl)carbamate (2.0 g, 6.82 mmol) in MeOH (40 mL) and water (20 mL) was added oxone (9.22 g, 15.00 mmol) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure, adjusted to pH 7 using 10% aqueous $NaHCO_3$ solution (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was absorbed onto a plug of silica gel (60-120 mesh) and purified by flash chromatography through a silica gel column, eluting with a gradient of 1-40% EtOAc in hexanes, to give *tert*-butyl (3-((1-methylcyclobutyl)sulfonyl)phenyl)carbamate (1.8 g, 81% yield) as a white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.05 (s, 1H), 7.78 – 7.68 (m, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 2.72 – 2.64 (m, 2H), 2.00 (dt, *J* = 10.8, 7.8 Hz, 1H), 1.91 – 1.68 (m, 3H), 1.49 (s, 9H), 1.35 (s, 3H). *m/z* (ESI): 326.1 [M+1].

[0264] Step 4: To solution of *tert*-butyl (3-((1-methylcyclobutyl)sulfonyl)phenyl)carbamate (1.8 g, 5.53 mmol) in 1,4-dioxane (20 mL) was added HCl (6.91 mL, 27.7 mmol, 4M in dioxane) at 0 °C and stirred at ambient temperature for 18 h. The reaction mixture was concentrated under reduced pressure, adjusted to pH 7-8 using 10% aqueous $NaHCO_3$ solution. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was triturated with diethyl ether (100 mL) to give 3-((1-methylcyclobutyl)sulfonyl)aniline (1.05 g, 84% yield) as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 – 7.21 (m, 1H), 7.00 (s, 1H), 6.93 – 6.79 (m, 2H), 5.66 (s, 2H), 2.73 – 2.59 (m, 2H), 2.07 – 1.93 (m, 1H), 1.85 – 1.76 (m, 3H), 1.35 (s, 3H). *m/z* (ESI): 226.1 [M+1].

[0265] Intermediate 5: 3-((1,1,1-Trifluoro-2-methylpropan-2-yl)sulfonyl)aniline



[0266] Step 1: To a solution of 2,2,2-trifluoroethan-1-ol (5.0 g, 50.0 mmol) in DCM (300 mL) was added Et_3N (4.64 mL, 33.3 mmol) and *p*-toluenesulfonyl chloride (6.35 g, 33.3 mmol) and the reaction mixture stirred at room temperature for 18 h. The reaction mixture was quenched with water (200 mL) and extracted with DCM (2 x 500 mL). The combined organic extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (5 g, 5 9% yield) as an off-white solid. ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.85 (d, J = 8.5Hz, 2H), 8.43 (d, J = 8.5 Hz, 2H), 5.38 (q, J = 10.2 Hz, 2H), 3.50 (s, 3H). *m/z* (ESI): 255.1 [M+1].

[0267] Step 2: To a solution of 3-aminobenzenethiol (4.43 g, 35.4 mmol) in DMF (225 mL) was added sodium hydride (1.77 g, 44.3 mmol) at 0 °C and stirred for 30 min followed by the addition of 2,2,2-trifluoroethyl 4-methylbenzenesulfonate (9.0 g, 35.4 mmol) and stirred for 18 h. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography through a silica gel column, eluting with a gradient of 5-10% EtOAc in hexanes, to give 3-((2,2,2-trifluoroethyl)thio)aniline (5.0 g, 68% yield) as a pale brown oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.99 (d, J = 7.7 Hz, 1H), 6.66 - 6.58 (m, 2H), 6.47 (d, J = 8.0 Hz, 1H), 5.22 (s, 2H), 3.87 (q, J = 10.2 Hz, 2H). *m/z* (ESI): 208.2 [M+1].

[0268] Step 3: To a solution of 3-((2,2,2-trifluoroethyl)thio)aniline (5.0 g, 24.13 mmol) in THF (50 mL) were added Et_3N (6.73 mL, 48.3 mmol) and Boc_2O (8.40 mL, 36.2 mmol) and stirred at room temperature for 18 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (200 mL). The organic layer was washed with water (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was absorbed onto a plug of silica gel (60-120 mesh) and purified by flash chromatography through a silica gel column (50 g), eluting with a gradient of 5% to 8% EtOAc in hexanes,

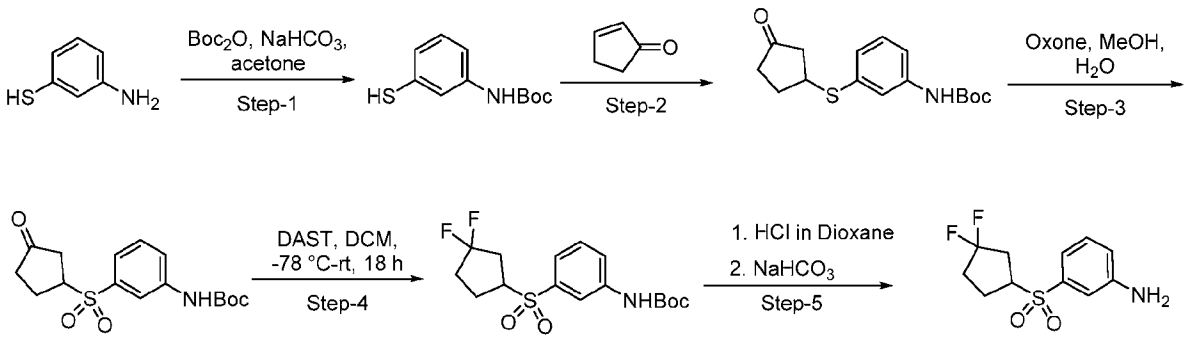
to give *tert*-butyl (3-((2,2,2-trifluoroethyl)thio)phenyl)carbamate (4.2 g, 57% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.43 (s, 1H), 7.62 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.27 – 7.21 (m, 2H), 3.93 (q, J = 10.0 Hz, 2H), 1.48 (s, 9H). *m/z* (ESI): 308.1 [M+1].

[0269] Step 4: To a solution of *tert*-butyl (3-((2,2,2-trifluoroethyl)thio)phenyl)carbamate (4.2 g, 13.67 mmol) in MeOH (40 mL) and water (20 mL) was added oxone (9.24 g, 30.1 mmol) and stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure. The reaction mixture was neutralized with 10% aqueous $NaHCO_3$ solution and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with water (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl (3-((2,2,2-trifluoroethyl)sulfonyl)phenyl)carbamate (3.2 g, 69 % yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.86 (s, 1H), 8.22 (s, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.64 – 7.56 (m, 2H), 4.92 (q, J = 10.0 Hz, 2H), 1.49 (s, 9H). *m/z* (ESI): 338.0 [M-1].

[0270] Step 5: To a solution of *tert*-butyl (3-((2,2,2-trifluoroethyl)sulfonyl)phenyl)carbamate (8.5 g, 25.05 mmol) in dry THF (50 mL) was added methyl iodide (15.66 mL, 250 mmol) and HMPA (43.6 mL, 250 mmol) at 0 °C. The reaction mixture was cooled to -78 °C and was added LDA (31.3 mL, 62.6 mmol, 2 M solution in THF) under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 30 min and allowed to warm to room temperature. The reaction mixture was diluted with aqueous saturated NH_4Cl solution (100 mL) and extracted with diethyl ether (3 x 250 mL). The organic layer was washed with brine solution (250 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was absorbed onto a plug of silica gel (60-120 mesh) and purified by silica gel chromatography, eluting with 5-7% EtOAc in hexanes, to give *tert*-butyl(3-((1,1,1-trifluoro-2-methylpropan-2-yl)sulfonyl)phenyl) carbamate (1.9 g, 21 % yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.15 (s, 1H), 7.80 (d, J = 8.7 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.50 (d, J = 7.9 Hz, 1H), 1.58 – 1.43 (m, 15H). *m/z* (ESI): 366.2 [M-1].

[0271] Step 6: To solution of *tert*-butyl(3-((1,1,1-trifluoro-2-methylpropan-2-yl)sulfonyl)phenyl) carbamate (1.8 g, 4.90 mmol) in 1,4-dioxane (20.0 mL) was added hydrochloric acid (12.3 mL, 49.0 mmol, 4 M in dioxane) at 0 °C and stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure and adjusted to pH 7-8 using 10% aqueous $NaHCO_3$ solution. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was absorbed onto a plug of silica gel (60-120 mesh) and purified by silica gel chromatography, eluting with 17-19% EtOAc in hexanes, to give 3-((1,1,1-trifluoro-2-methylpropan-2-yl)sulfonyl)aniline (0.9 g, 69 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (d, J = 7.9 Hz, 1H), 7.08 (s, 1H), 7.00 – 6.89 (m, 2H), 5.75 (s, 2H), 1.49 (s, 6H). *m/z* (ESI): 268.1 [M+1].

[0272] Intermediate 6: 3-((3,3-Difluorocyclopentyl)sulfonyl)aniline



[0273] Step 1: To a solution of 3-aminobenzenethiol (10.0 g, 80 mmol) in acetone (160 mL) was added Boc anhydride (37.1 mL, 160 mmol) and 10 % aqueous sodium carbonate solution (20 mL, 160 mmol). The reaction mixture was stirred at room temperature for 18 h, quenched with water (250 mL) and extracted with EtOAc (3 x 250 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was absorbed onto a plug of silica gel and purified by flash chromatography through a silica gel column, eluting with a gradient of 1-15% EtOAc in hexanes, to give *tert*-butyl (3-mercaptophenyl)carbamate (11 g, 61% yield) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.1 (s, 1H), 7.56 (s, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.31 (dd, J = 7.6, 7.2 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 6.54 (s, 1H), 1.52 (s, 9H).

[0274] Step 2: A mixture of *tert*-butyl (3-mercaptophenyl)carbamate (10.0 g, 44.4 mmol) and cyclopent-2-enone (14.58 g, 178 mmol) was stirred at 120 °C for 24 h. The reaction mixture was directly absorbed onto a plug of silica gel (60-120 mesh) and purified by silica gel chromatography eluting with 9-12% EtOAc in hexanes, to give *tert*-butyl (3-((3-oxocyclopentyl)thio)phenyl)carbamate (10.0 g, 73% yield) as a colorless viscous oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.54 (s, 1H), 7.28 – 7.17 (m, 2H), 7.07 (d, J = 8.8 Hz, 1H), 6.55 (s, 1H), 3.94 (t, J = 8.0 Hz, 1H), 2.71 – 2.58 (m, 1H), 2.45 – 2.20 (m, 4H), 2.12 – 1.97 (m, 1H), 1.53 (s, 9H). *m/z* (ESI): 308.6 [M+1].

[0275] Step 3: To a solution of *tert*-butyl (3-((3-oxocyclopentyl)thio)phenyl)carbamate (5.0 g, 16.27 mmol) in MeOH (100 mL) was added a solution of oxone (22 g, 35.8 mmol) in water (50 mL) and stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure to remove MeOH and the resultant aqueous solution was extracted with DCM (3 x 100 mL). The organic combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl (3-((3-oxocyclopentyl)sulfonyl)phenyl)carbamate (4.5 g, crude) as a pale-yellow oil which was taken to the next step as such. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 8.14 (s, 1H), 7.71 (d, J = 7.92 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.48 (d, J = 7.7 Hz, 1H), 4.08 (t, J = 7.4 Hz, 1H), 2.45 - 2.16 (m, 6H), 1.50 (s, 9H).

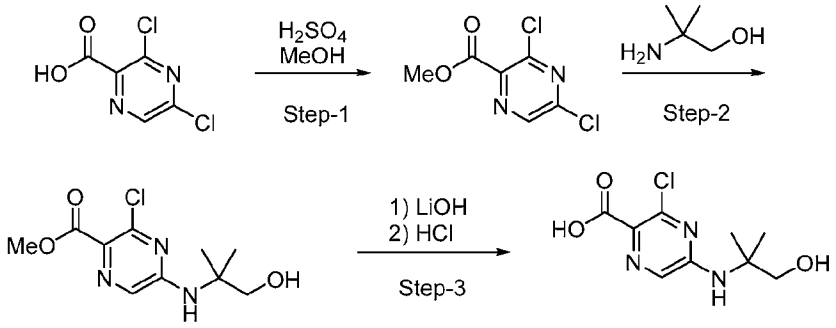
[0276] Step 4: To a solution of *tert*-butyl (3-((3-oxocyclopentyl)sulfonyl)phenyl)carbamate (1.65 g, 4.86 mmol) in DCM (20 mL) was added DAST (1.61 mL, 12.15 mmol) at -78 °C under nitrogen atmosphere and stirred at -78 °C for 30 min. The reaction mixture was slowly warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with 1N aqueous NaOH solution

(10 mL), diluted with water (25 mL), and extracted with DCM (3 x 50 mL). The combined organic phases were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was absorbed onto a plug of silica gel and purified silica gel chromatography eluting with 6-8% EtOAc in hexanes, to give *tert*-butyl (3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)carbamate (0.95 g, 54 % yield) as a colorless viscous oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.84 (s, 1H), 8.14 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.61 – 7.43 (m, 2H), 4.13 – 3.98 (m, 1H), 2.41 – 1.95 (m, 6H), 1.49 (s, 9H). *m/z* (ESI): 360.2 [M-1].

[0277] Step 5: To solution of *tert*-butyl (3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)carbamate (1.0 g, 2.77 mmol) in 1,4-dioxane (10 mL) was added HCl (10 mL, 40 mmol, 4 M in dioxane) at 0 °C and stirred at RT for 24 h. The reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in water (15 mL) and the pH was adjusted to ~ 7 using 10% aqueous $NaHCO_3$ solution, diluted with water (20 mL), and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was adsorbed onto a plug of silica gel (60-120 mesh) and purified by silica gel chromatography, eluting with 20-25% EtOAc in hexanes, to give 3-((3,3-difluorocyclopentyl)sulfonyl)aniline (250 mg, 35% yield) as a viscous oil. ^{1}H NMR (400 MHz, MeOD): δ 7.27 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 8.0, 2.0 Hz, 1H), 6.95 (dd, J = 8.0, 2.0 Hz, 1H), 3.90 – 3.84 (m, 1H), 2.51 – 2.05 (m, 6H), NH_2 protons were not visible. *m/z* (ESI): 262.1 [M+1].

[0278] PREPARATION OF RING AR^2 INTERMEDIATES

[0279] Intermediate 7: 3-Chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxylic acid



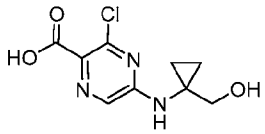
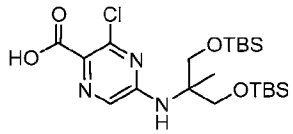
Intermediate 7

[0280] Step 1: To a solution of 3,5-dichloropyrazine-2-carboxylic acid (3.25 g, 16.84 mmol, Frontier Scientific, Inc.) in MeOH (20 mL) was added 10 drops of conc. sulfuric acid. The reaction was stirred at reflux for 16 h, cooled to RT, and concentrated in vacuo. The material was taken up in EtOAc (25 mL) and washed with satd $NaHCO_3$ (20 mL). The aqueous layer was back extracted with EtOAc (2 x 20 mL). The combined EtOAc layers were dried over $MgSO_4$ and concentrated in vacuo to give crude methyl 3,5-dichloropyrazine-2-carboxylate (3.15 g, 15.22 mmol, 90% yield) as a brown solid. The material was carried forward without any further purification. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.58 (s, 1 H), 4.04 (s, 3 H).

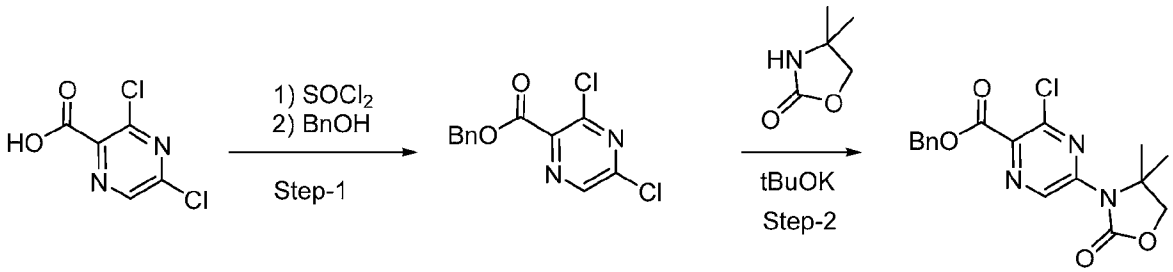
[0281] Step 2: To a solution of methyl 3,5-dichloropyrazine-2-carboxylate (2.02 g, 9.78 mmol) in DMSO (40 mL) was added DIPEA (3.41 mL, 19.56 mmol) and 2-amino-2-methyl-1-propanol (0.93 mL, 9.78 mmol, Aldrich). The solution was stirred at RT for 4 d, then treated with water (150 mL) and extracted with EtOAc (5 x 20 mL). The combined organic extracts were concentrated in vacuo and adsorbed onto a plug of silica gel and chromatographed through silica gel column eluting with 0-75% EtOAc in heptane, to provide methyl 3-chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxylate (1.46 g, 5.63 mmol, 58 % yield) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.94 (s, 1 H), 7.80 (s, 1 H), 4.84 (t, J=5.9 Hz, 1 H), 3.78 (s, 3 H), 3.55 (d, J=5.9 Hz, 2 H), 1.31 (s, 6 H). m/z (ESI): 260.0 $(M+H)^+$.

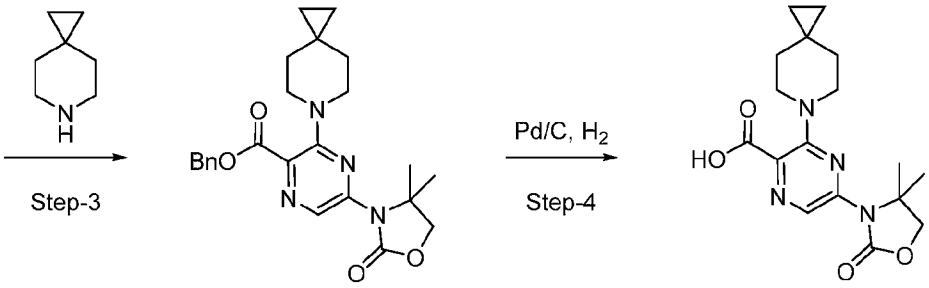
[0282] Step 3: To a solution of methyl 3-chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxylate (1.46 g, 5.62 mmol) in THF (40 mL) and MeOH (13 mL) was added LiOH (20 mL of 1 M aqueous solution, 20.00 mmol). The resulting dark brown solution was stirred at RT for 16 h, then concentrated in vacuo to removed organic solvents. The aqueous solution was neutralized with HCl (2 N) to ~pH 7 and extracted with EtOAc (2 x 10 mL). The combined organic extracts were concentrated in vacuo to give 3-chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxylic acid (1.15 g, 4.68 mmol, 83% yield) as a yellow solid. m/z (ESI): 246.1 $(M+H)^+$.

[0283] Table 1: Intermediates 7-1 and 7-2 were prepared analogous to preparation of Intermediate 7:

Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) m/z
7-1		3-chloro-5-((1-(hydroxymethyl)cyclopropyl)amino)pyrazine-2-carboxylic acid	244.1
7-2		3-chloro-5-((2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)amino)pyrazine-2-carboxylic acid	490.2

[0284] Intermediate 8: 5-(4,4-Dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylic acid.





Intermediate 8

[0285] Step 1: A mixture of 3,5-dichloropyrazine-2-carboxylic acid (17.0 g, 88 mmol) in thionyl chloride (50 mL, 820 mmol) was heated in an oil bath at 90 °C for 16 h. The dark solution was evaporated to dryness under reduced pressure. Benzyl alcohol (10 ml, 96 mmol) and Et_3N (25 mL, 178 mmol) were dissolved in dry THF (100 mL) and cooled in an ice bath. The crude acid chloride was added slowly keeping the internal temperature < 35 °C. Once the addition was complete the mixture was removed from the cold bath and stirred for another 10 min. Satd ammonium chloride (75 mL), water (100 mL), and EtOAc (200 mL) were added and the phases mixed and separated. The organic layer was evaporated to dryness under reduced pressure and purified on a silica gel column (10-40% EtOAc in heptane) to give benzyl 3,5-dichloropyrazine-2-carboxylate (22.4 g, 79 mmol, 90% yield). *m/z* (ESI): 304.8 $(M+Na)^+$.

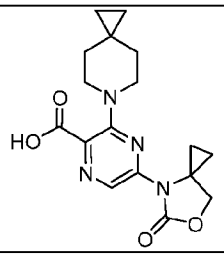
[0286] Step 2: 4,4-Dimethyloxazolidin-2-one (4.1 g, 35.6 mmol) was dissolved in DMF (80 mL) in a jacketed reactor. The temperature was set to 15 °C. Potassium *tert*-butoxide solution (35.5 mL, 35.5 mmol, 1 M in THF) was added and the mixture became a thick gel. A solution of benzyl 3,5-dichloropyrazine-2-carboxylate (10.0 g, 35.3 mmol) in DMF (50 mL) was added in one portion and the mixture was stirred for 2 h. Water (100 mL), satd ammonium chloride (50 mL) and EtOAc (100 mL) were added and the mixture stirred for 5 min. The aqueous was allowed to settle and then drained. The organic was washed with water (100 mL) then dried over Na_2SO_4 and evaporated to dryness under reduced pressure. Purification on a silica gel column (0-100% EtOAc in heptane) gave benzyl 3-chloro-5-(4,4-dimethyl-2-oxooxazolidin-3-yl)pyrazine-2-carboxylate (10.7 g, 29.6 mmol, 84% yield) as an off-white solid. *m/z* (ESI): 362.3 $(M+H)^+$.

[0287] Step 3: Benzyl 3-chloro-5-(4,4-dimethyl-2-oxooxazolidin-3-yl)pyrazine-2-carboxylate (10.7 g, 29.6 mmol), 6-azaspiro[2.5]octane (3.5 g, 31.5 mmol), and cesium carbonate (12 g, 36.8 mmol) were combined in DMF (75 mL) under nitrogen. The mixture was stirred at RT for 16 h. Water (200 mL) and EtOAc (200 mL) were added and the phases mixed and separated. The organic was washed with water (200 mL) then evaporated to dryness under reduce pressure. The crude material was suspended in methyl tert-butyl ether (50 mL) and stirred for 10 min. Heptane (50 mL) was added slowly and the mixture stirred for another 10 min. It was filtered through a sintered glass frit and the solid washed with 2:1 heptane : methyl tert-butyl ether (10 mL). The solid was dried under vacuum to give benzyl 5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylate (12.2 g, 27.9 mmol, 95% yield) as a light yellow solid. The filtrate was evaporated to dryness under reduced pressure to give a

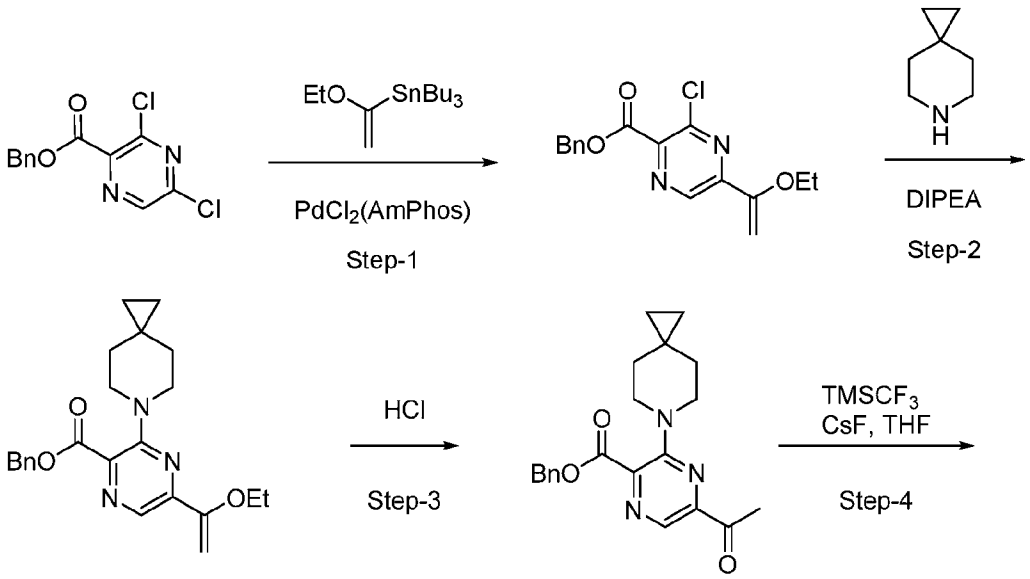
yellow oil (0.7 g). Purification using the ISCO (heptane to EtOAc gradient) gave another 0.5 g. *m/z* (ESI): 437.2 $(M+H)^+$.

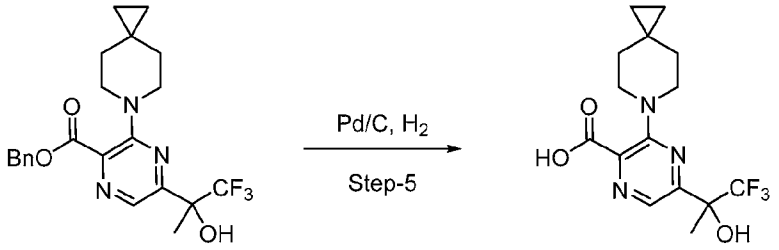
[0288] Step 4: Benzyl 5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylate (12.2 g, 27.9 mmol) was dissolved in DCM:EtOH (1:1, 120 mL). Palladium on carbon (5 wt% Pd) (0.350 g, 0.082 mmol) was added and the suspension hydrogenated under 40 psi for 1 h. The suspension was filtered through a pad of CELITE® and the solids were washed with DCM (10 mL). The filtrate was evaporated to dryness under reduced pressure to give 5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylic acid (9.17 g, 26.5 mmol, 95% yield) as a light yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.1 (br s, 1 H) 8.60 - 8.78 (m, 1 H) 4.06 - 4.26 (m, 2 H) 3.49 - 3.63 (m, 4 H) 1.65 - 1.81 (m, 6 H) 1.49 - 1.61 (m, 4 H) 0.34 - 0.50 (m, 4 H). *m/z* (ESI): 347.1 $(M+H)^+$.

[0289] Table 2: Intermediate 8-1 was prepared analogous to preparation of Intermediate 8:

Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
8-1		5-(5-oxo-6-oxa-4-azaspiro[2.4]heptan-4-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylic acid	345.1

[0290] Intermediate 9: 3-(6-Azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxylic acid





Intermediate 9

[0291] Step 1: A mixture of benzyl 3,5-dichloropyrazine-2-carboxylate (3.03 g, 10.70 mmol), tributyl(1-ethoxyvinyl)tin (4.25 g, 11.77 mmol, Aldrich), and bis-(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium (0.30 g, 0.42 mmol) in toluene (1 mL) was heated at 80 °C in 2 h. The reaction mixture was cooled to RT and treated with 15 mL of 1M aqueous KF and stirred for 30 min. The mixture was diluted with *t*-butyl methyl ether, and the precipitated solid was collected by filtration. The filtrate was separated, and the organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified on a silica gel column (10% EtOAc in heptane) to give a mixture of benzyl 3-chloro-5-(1-ethoxyvinyl)pyrazine-2-carboxylate and benzyl 5-chloro-3-(1-ethoxyvinyl)pyrazine-2-carboxylate (3.03 g). *m/z* (ESI): 319.5 $(M+H)^+$.

[0292] Step 2: A mixture of benzyl 3-chloro-5-(1-ethoxyvinyl)pyrazine-2-carboxylate and benzyl 5-chloro-3-(1-ethoxyvinyl)pyrazine-2-carboxylate (2.81 g, 8.82 mmol), DIPEA (4.62 mL, 26.4 mmol), and 6-azaspiro[2.5]octane (1.18 g, 10.58 mmol, Wuxi Apptec) in DMSO (10 mL) was heated at 70 °C for 3 h. The reaction mixture was cooled to RT, diluted with water (10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were concentrated, and the residue was purified on ISCO column (0-20% EtOAc in heptane) to give benzyl 5-(1-ethoxyvinyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylate (1.33 g, 3.40 mmol, 38% yield): ^{1}H NMR (CHLOROFORM-d) δ: 8.30 (s, 1H), 7.45-7.51 (m, 2H), 7.31-7.40 (m, 3H), 5.42 (s, 2H), 5.40 (d, J=1.8 Hz, 1H), 4.41 (d, J=2.0 Hz, 1H), 3.96 (q, J=7.0 Hz, 2H), 3.41-3.47 (m, 4H), 1.43 (t, J=6.9 Hz, 3H), 1.38 (dd, J=6.5, 4.7 Hz, 4H), 0.33 (s, 4H). *m/z* (ESI): 394.1 $(M+H)^+$.

[0293] Step 3: To a stirred solution of benzyl 5-(1-ethoxyvinyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylate (1.33 g, 3.38 mmol) in THF (15 mL) was added 5 N HCl (3.38 mL, 16.90 mmol). After the addition, the mixture was stirred at RT for 3 h. The mixture was diluted with EtOAc, and slowly neutralized with satd aqueous $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, and concentrated to provide benzyl 5-acetyl-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylate. ^{1}H NMR (CHLOROFORM-d) δ: 8.51 (s, 1H), 7.46-7.50 (m, 2H), 7.31-7.41 (m, 3H), 5.44 (s, 2H), 3.42-3.52 (m, 4H), 2.62 (s, 3H), 1.33-1.41 (m, 4H), 0.36 (s, 4H). *m/z* (ESI): 366.1 $(M+H)^+$.

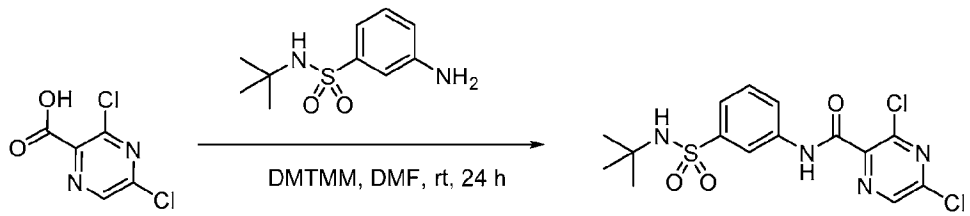
[0294] Step 4: To a stirred mixture of benzyl 5-acetyl-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylate (1.21g, 3.31 mmol) and cesium fluoride (2.01 g, 13.23 mmol) in THF (2 mL) was added trimethyl(trifluoromethyl)silane (0.59 mL, 3.97 mmol, Aldrich). After the addition, the reaction mixture was stirred for 16 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was concentrated and the residue was purified on a silica gel column (0-30% EtOAc in heptane) to give

benzyl 3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxylate (1.21 g, 2.78 mmol, 84% yield) ^{1}H NMR (CHLOROFORM-d) δ: 8.10 (s, 1H), 7.49 (dd, J=7.8, 1.4 Hz, 2H), 7.37 (dd, J=7.5, 1.9 Hz, 3H), 5.44 (s, 2H), 5.21 (s, 1H), 3.40-3.47 (m, 4H), 1.74 (s, 3H), 1.39 (dd, J=6.5, 4.7 Hz, 4H), 0.36 (s, 4H). *m/z* (ESI): 436.3 $(M+H)^+$.

[0295] Step 5: A solution of benzyl 3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxylate (1.2 g, 2.76 mmol) in ethanol (15 mL) was hydrogenated at 50 psi in the presence of Pd/C (0.293 g of 10% wt., 0.276 mmol) for 2 h. The catalyst was filtered off through a pad of CELITE® and the solids were rinsed with EtOH. The filtrate was concentrated to afford 3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxylic acid (0.90 g, 95% yield) as a yellow solid. *m/z* (ESI): 346.3 $(M+H)^+$.

[0296] Coupling Ar^1 and Ar^2 Intermediates

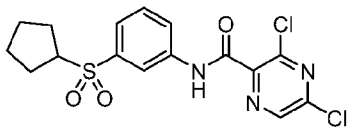
[0297] Intermediate 10: *N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-3,5-dichloropyrazine-2-carboxamide



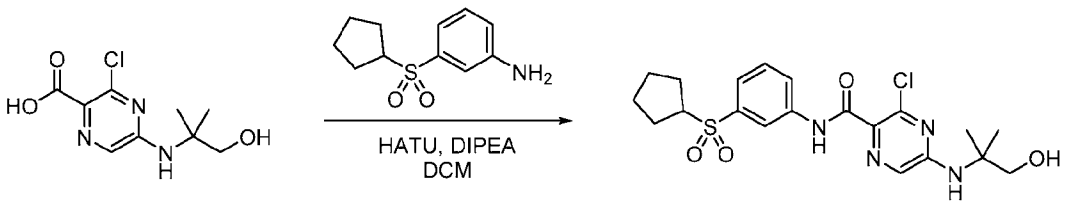
Intermediate 10

To a stirred mixture of 3,5-dichloropyrazine-2-carboxylic acid (2.19 g, 11.35 mmol), 3-amino-*N*-(*tert*-butyl)benzenesulfonamide (2.85 g, 12.48 mmol) in DMF (20 mL) at rt was added 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (4.71 g, 17.02 mmol). The reaction mixture was stirred at RT for 24 h and water was added to the mixture. The precipitate obtained was filtered off, washed with water, and dried. *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-2,6-dichloronicotinamide (4.10 g, 90 % yield) was obtained as a white solid. *m/z* (ESI): 425.0 $(M+Na)^+$.

[0298] Table 3: Intermediate 10-1 was prepared analogous to preparation of Intermediate 10:

Int. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
10-1		3,5-dichloro-*N*-(3-(cyclopentylsulfonyl)phenyl)pyrazine-2-carboxamide	401.2

[0299] Intermediate 11: 3-Chloro-*N*-(3-(cyclopentylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide

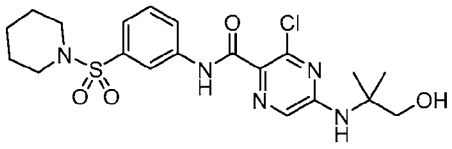
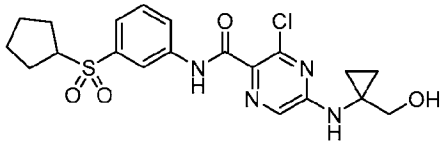
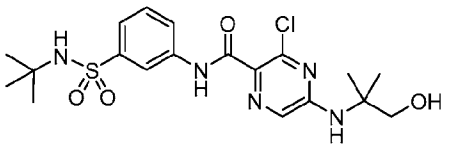
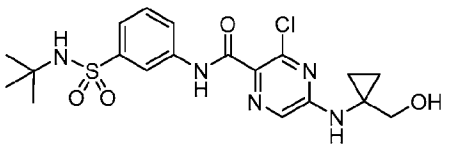


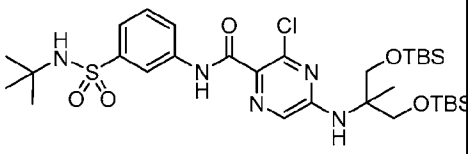
Intermediate 11

[0300] To a solution of 3-chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxylic acid (0.15 g, 0.60 mmol, Intermediate 7), 3-(cyclopentylsulfonyl)aniline (0.16 g, 0.72 mmol, Combi-Blocks Inc.), DIPEA (0.367 mL, 2.11 mmol, Sigma-Aldrich), and DCM (5 mL) in a vial equipped with a red-pressure relief cap was added HATU (344 mg, 0.904 mmol, Sigma-Aldrich). The solution was stirred at room temperature for 3 h and diluted with DCM (10 mL) and water (20 mL). The organic layer was taken, and the aqueous layer was back extracted with DCM (10 mL). The combined organic extracts

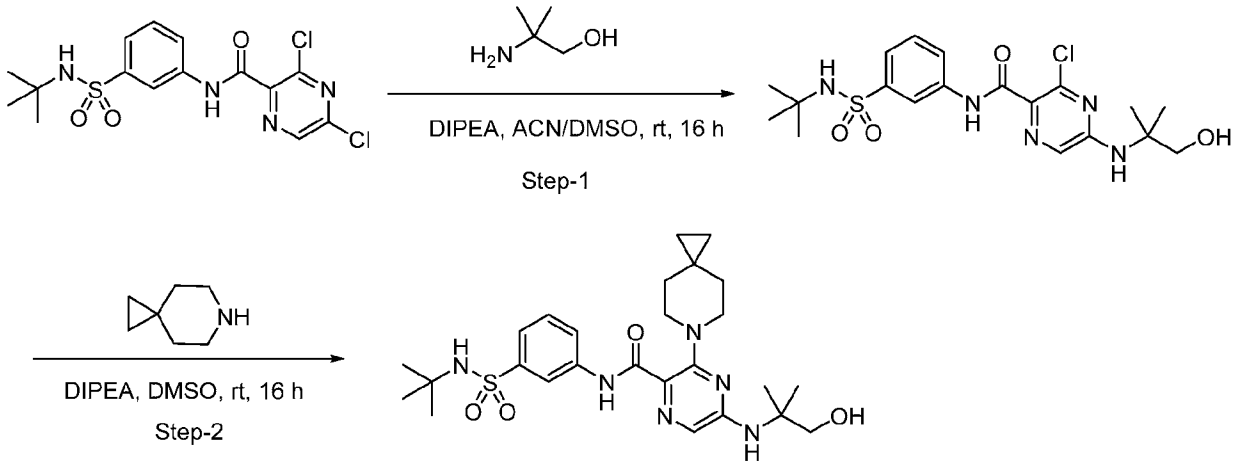
[0301] were concentrated in vacuo and adsorbed onto a plug of silica gel and chromatographed through a silica gel column, eluting with 0-50% EtOAc in heptane, to provide the title compound (112 mg, 0.247 mmol, 41% yield), as a light yellow solid. *m/z* (ESI): 453.0 $(M+H)^+$.

[0302] Table 4: Intermediates 11-1 to 11-5 were prepared analogous to preparation of Intermediate 11:

Int. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
11-1		3-chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)pyrazine-2-carboxamide	468.0
11-2		3-chloro-*N*-(3-(cyclopentylsulfonyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)pyrazine-2-carboxamide	451.0
11-3		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	456.1
11-4		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-chloro-5-((1-(hydroxymethyl)cyclopropyl)amino)pyrazine-2-carboxamide	454.1

Int. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
11-5		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-chloro-5-((2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)amino)pyrazine-2-carboxamide	701.2

[0303] Example 100: *N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide.

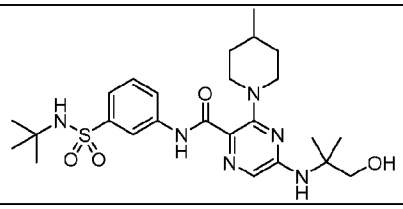
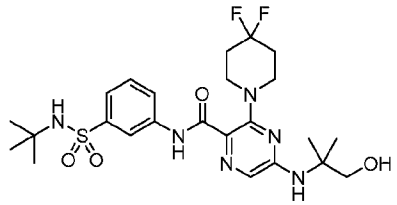
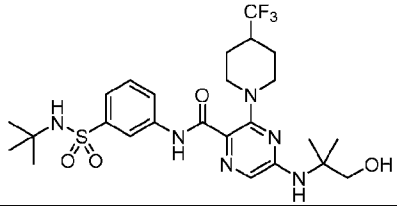
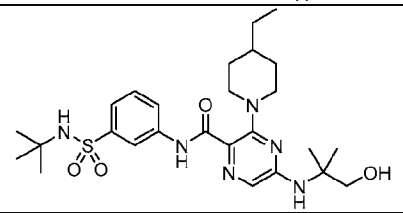
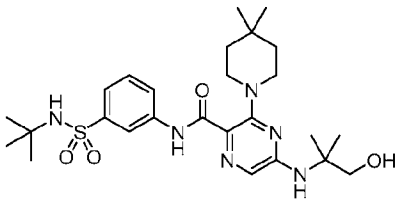
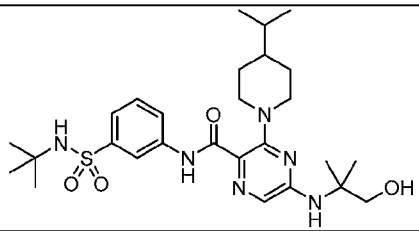
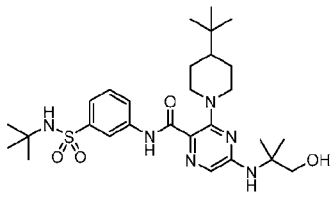


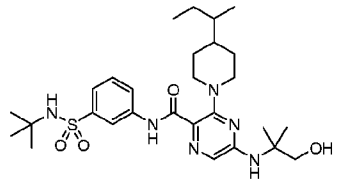
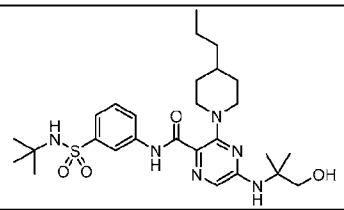
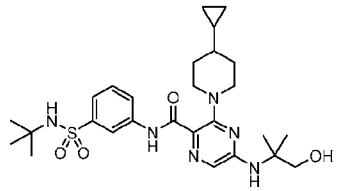
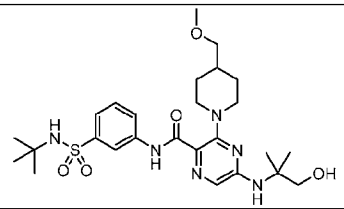
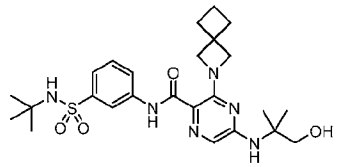
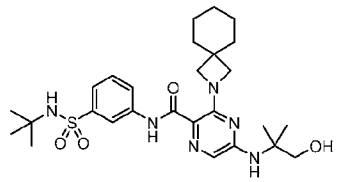
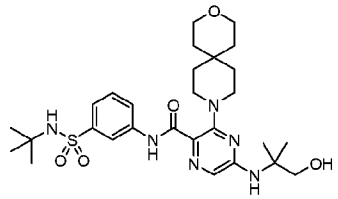
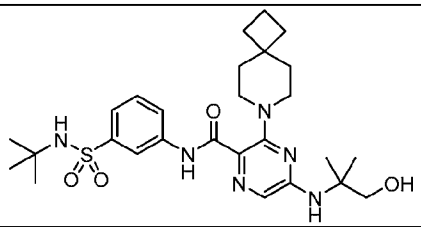
[0304] Step 1: A mixture of *N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-3,5-dichloropyrazine-2-carboxamide (3.71 g, 9.20 mmol, Intermediate 10), DIPEA (2.12 mL, 11.96 mmol), and 2-amino-2-methyl-1-propanol (0.97 mL, 10.12 mmol) in ACN:DMSO (4:1, 50 mL) was stirred at RT for 16 h. Then, water was added and extracted with DCM (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum. The crude was purified by silica gel chromatography using 0-30 % EtOAc/EtOH (3:1) in heptane to give *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-chloro-3-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide (1.50 g, 3.29 mmol, 36 % yield). ^{1}H NMR (DMSO-d_6) δ: 10.85 (s, 1H), 9.03 (s, 1H), 8.44 (s, 1H), 7.87-7.94 (m, 2H), 7.50-7.61 (m, 3H), 5.05 (t, J=5.5 Hz, 1H), 3.53 (d, J=5.5 Hz, 2H), 1.39 (s, 6H), 1.11 (s, 9H). *m/z* (ESI): 456.0 $(M+H)^+$.

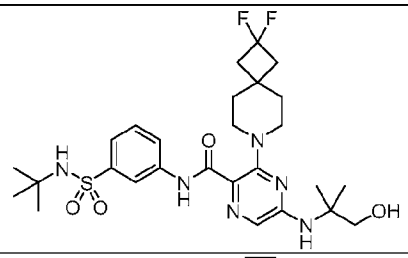
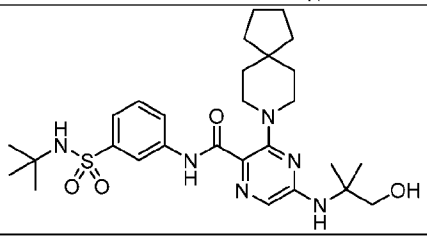
[0305] Step 2: To a solution of *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide (60 mg, 0.13 mmol) and DMSO (1.5 mL) was added DIPEA (0.046 mL, 0.26 mmol) and 6-azaspiro[2.5]octane (26 mg, 0.23 mmol). The solution was stirred at room temperature for 16 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were concentrated in vacuo and adsorbed onto a plug of silica gel and chromatographed through a silica gel column eluting with 0-60% EtOAc in heptane, to provide *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (39 mg, 0.073 mmol, 55 % yield) as a light-yellow solid. ^{1}H NMR (DMSO-d_6) δ: 10.29 (s, 1H), 8.42 (s, 1H), 7.87 (d, *J* = 5.9 Hz, 1H), 7.40-7.51 (m, 4H), 6.99 (s,

1H), 4.74 (t, J = 4.8 Hz, 1H), 3.58 (d, J = 4.5 Hz, 2H), 3.36 – 3.45 (m, 4H), 1.42 (br s , 4H), 1.34 (s, 6H), 1.11 (s, 9H), 0.32 (s, 4H). m/z (ESI): 531.2 $(M+H)^+$.

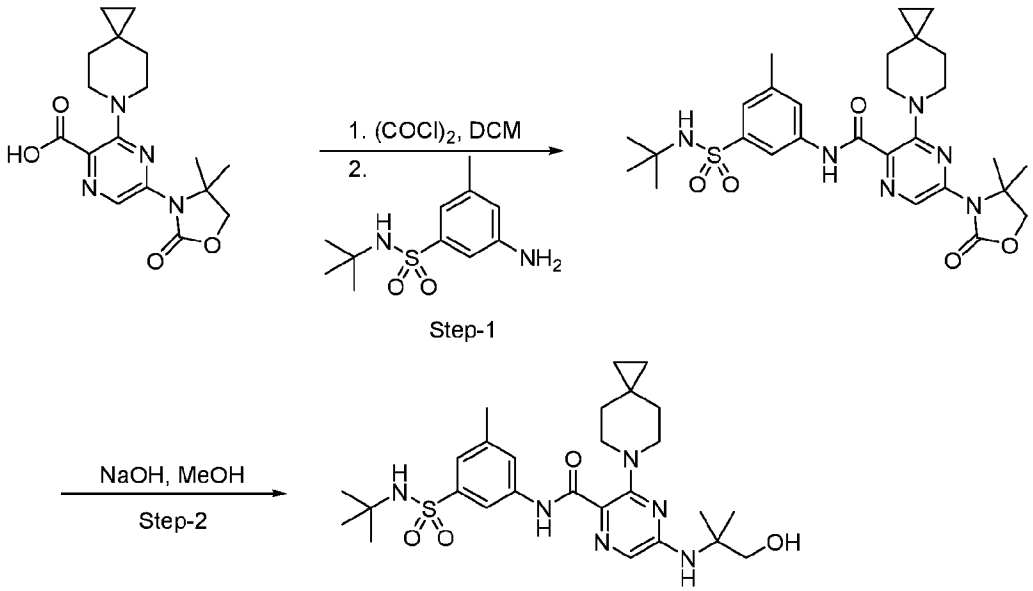
[0306] Table 5: Examples 100-1 to 100-17 were prepared analogous to preparation of Example 100:

Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) m/z
100-1		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-methylpiperidin-1-yl)pyrazine-2-carboxamide	519.1
100-2		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4,4-difluoropiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	541.2
100-3		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(trifluoromethyl)piperidin-1-yl)pyrazine-2-carboxamide	573.1
100-4		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-ethylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	533.2
100-5		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4,4-dimethylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	533.1
100-6		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-isopropylpiperidin-1-yl)pyrazine-2-carboxamide	547.1
100-7		3-(4-(*tert*-butyl)piperidin-1-yl)-*N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	561.1

Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
100-8		3-(4-(*sec*-butyl)piperidin-1-yl)-*N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	561.1
100-9		N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-propylpiperidin-1-yl)pyrazine-2-carboxamide	547.1
100-10		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-cyclopropylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	545.1
100-11		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(methoxymethyl)piperidin-1-yl)pyrazine-2-carboxamide	549.1
100-12		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(2-azaspiro[3.3]heptan-2-yl)pyrazine-2-carboxamide	517.1
100-13		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(2-azaspiro[3.5]nonan-2-yl)pyrazine-2-carboxamide	545.1
100-14		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(3-oxa-9-azaspiro[5.5]undecan-9-yl)pyrazine-2-carboxamide	575.1
100-15		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(7-azaspiro[3.5]nonan-7-yl)pyrazine-2-carboxamide	545.1

Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
100-16		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(2,2-difluoro-7-azaspiro[3.5]nonan-7-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	581.1
100-17		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(8-azaspiro[4.5]decan-8-yl)pyrazine-2-carboxamide	559.2

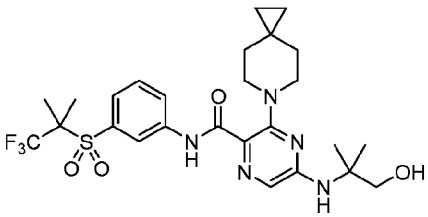
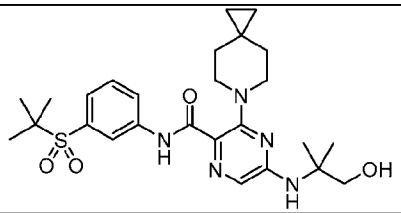
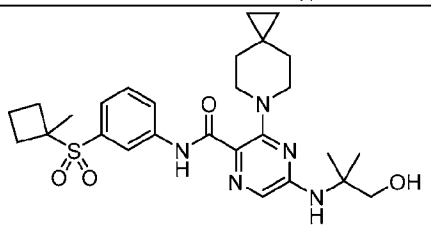
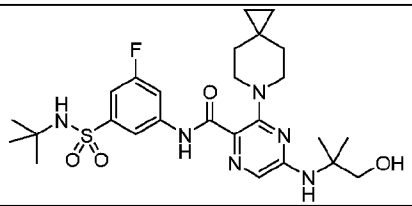
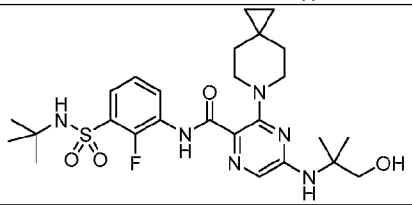
[0307] Example 101: *N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-methylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide.

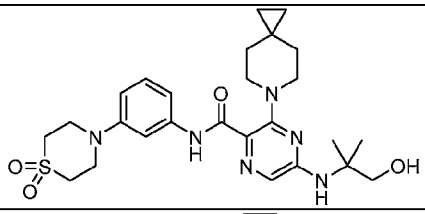
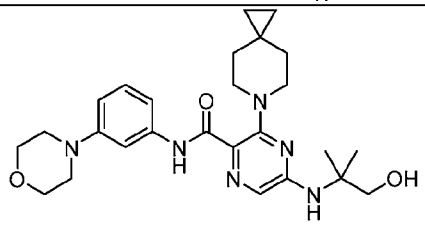
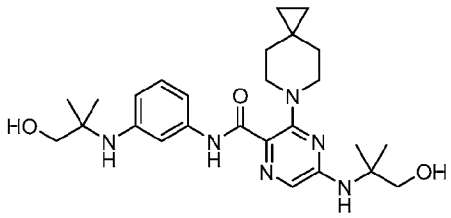


[0308] Step 1: To a 50-mL round-bottomed flask was added 5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylic acid (111 mg, 0.320 mmol, Intermediate 8) and DCM (4 mL). Then oxalyl chloride, (0.24 mL, 0.48 mmol, 2M in DCM) was added followed by a couple of drops of DMF. The reaction mixture was stirred at RT for 30 min and the solvent was removed under vacuum. The residue was redissolved in DCM (4 mL), treated with 3-amino-*N*-(*tert*-butyl)-5-methylbenzenesulfonamide (78 mg, 0.32 mmol, Intermediate 1) and DIPEA (0.17 mL, 0.96 mmol). The reaction mixture was stirred for 18 h at RT and the solvent was removed under vacuum. The crude material was absorbed onto a plug of silica gel and purified by chromatography through a silica gel column, eluting with a gradient of 0-50% EtOAc in heptane to provide *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)-5-methylphenyl)-5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (117 mg, 0.205 mmol, 64 % yield) as a light yellow solid. *m/z* (ESI): 571.3 $(M+H)^+$.

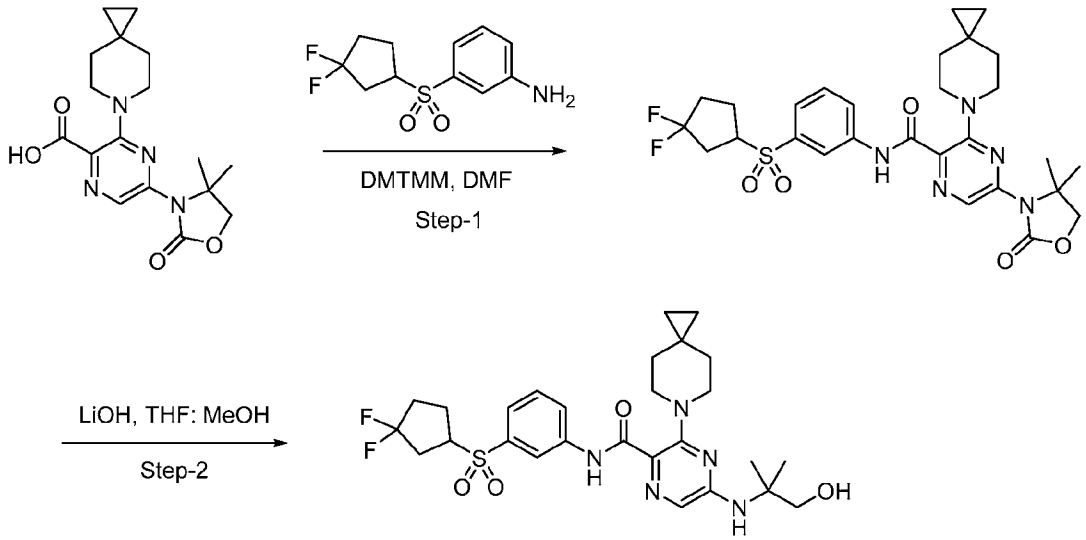
[0309] Step 2: To a 15-mL reaction vial was added *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)-5-methylphenyl)-5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (117 mg, 0.205 mmol), sodium hydroxide (0.410 mL, 2.050 mmol, 1N), and MeOH (3 mL). the reaction mixture was heated at 70 °C for 1.5 h, cooled to rt and the solvent was removed under vacuum. Added HCl (2N) and extracted with EtOAc. The organic extract was washed with satd $NaHCO_3$, water, and dried over Na_2SO_4. *N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-methylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (86 mg, 0.16 mmol, 77 % yield) was obtained as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.20 (s, 1H), 7.73 (s, 1H), 7.41 (s, 1H), 7.29 (s, 1H), 6.98 (s, 1H), 4.79 (t, *J*=5.77 Hz, 1H), 3.59 (d, *J*=5.67 Hz, 2H), 3.35-3.48 (m, 4H), 2.35 (s, 3H), 1.38-1.47 (m, 4H), 1.34 (s, 6H), 1.13 (s, 9H), 0.33 (s, 4H). *m/z* (ESI): 545.3 $(M+H)^+$.

[0310] Table 6: Examples 101-1 to 101-8 were prepared analogous to preparation of Example 101:

Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
101-1		5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)-N-(3-((1,1,1-trifluoro-2-methylpropan-2-yl)sulfonyl)phenyl)pyrazine-2-carboxamide	570.2
101-2		*N*-(3-(*tert*-butylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	516.2
101-3		5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-methylcyclobutyl)sulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	528.2
101-4		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)-5-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	549.2
101-5		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)-2-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	549.2

Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
101-6		*N*-(3-(1,1-dioxidothiomorpholino)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	529.3
101-7		5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-morpholinophenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	481.2
101-8		5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-hydroxy-2-methylpropan-2-yl)amino)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	483.3

[0311] Examples 102-1 and 102-2: (*S*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide and (*R*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide.



[0312] Step 1: To a solution of 5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxylic acid (71 mg, 0.21 mmol, Intermediate 8) and DMF (2 mL) was added 3-((3,3-

difluorocyclopentyl)sulfonyl)aniline (54 mg, 0.21 mmol, Intermediate 6) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride (86 mg, 0.31 mmol). The solution was stirred at room temperature for 16 h. The reaction was treated with additional 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholin-4-ium chloride (50 mg). After a further 24 h, the reaction was diluted with water (40 mL) and stirred for 20 min. The aqueous solution was filtered, and the yellow solids dried under vacuum while in the filter. The material was adsorbed onto a plug of silica gel and chromatographed through a silica gel column, eluting with 0-50% EtOAc in heptane, to provide *N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (88 mg, 0.15 mmol, 72 % yield) as a light-yellow solid.

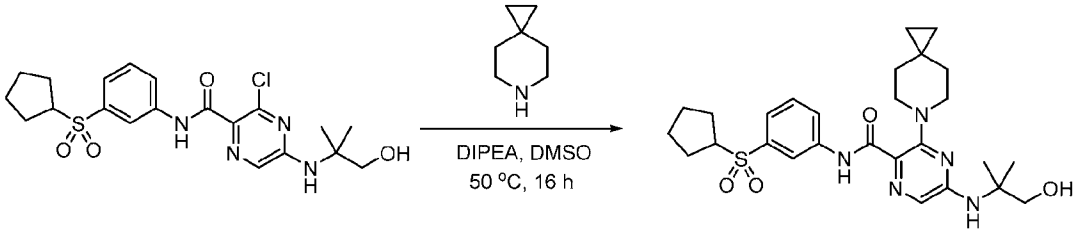
[0313] Step 2: To a solution of *N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (88 mg, 0.15 mmol) and THF (2 mL):MeOH (0.5 mL) was added 1M aqueous LiOH (0.45 mL, 0.45 mmol). The solution was stirred at room temperature. After 2 h, the reaction was diluted with water and extracted with EtOAc (2 x 15 mL). The combined organic extracts were concentrated in vacuo, adsorbed onto a plug of silica gel, and chromatographed through a silica gel column, eluting with 0-100% EtOAc in heptane, to provide *N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (61 mg, 0.11 mmol, 73 % yield) as an off-white solid. *m/z* (ESI): 590.2 $(M+H)^+$. This material was separated by chiral preparative SFC using an OX column (250 x 21 mm, 5 mic) with a mobile phase of 60% Liquid CO_2 and 40% MeOH, and a flowrate of 75 mL/min to give:

[0314] Example 102-1: (*S*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide. First eluting peak; ee > 99%, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.43 (s, 1 H), 8.43 (t, *J*=1.8 Hz, 1 H), 8.13 (d, *J*=7.7 Hz, 1 H), 7.59 (t, *J*=7.9 Hz, 1 H), 7.51 (d, *J*=8.0 Hz, 1 H), 7.45 (s, 1 H), 7.03 (s, 1 H), 4.72 - 4.89 (m, 1 H), 4.01 - 4.11 (m, 1 H), 3.56 - 3.60 (m, 2 H), 3.38 - 3.44 (m, 4 H), 2.37 - 2.46 (m, 1 H), 1.99 - 2.24 (m, 4 H), 1.76 (dt, *J*=6.8, 3.2 Hz, 1 H), 1.37 - 1.47 (m, 4 H), 1.34 (s, 6 H), 0.33 (s, 4 H). ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -92.52 - -90.43 (m, 2 F). *m/z* (ESI): 564.2 $(M+H)^+$.

[0315] Example 102-2: (*R*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide. Second eluting peak; ee 98%, . ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.42 (s, 1 H), 8.43 (t, *J*=1.8 Hz, 1 H), 8.13 (d, *J*=8.4 Hz, 1 H), 7.58 (t, *J*=7.9 Hz, 1 H), 7.50 (d, *J*=7.8 Hz, 1 H), 7.44 (s, 1 H), 7.03 (s, 1 H), 4.79 (br s, 1 H), 4.05 (br t, *J*=8.2 Hz, 1 H), 3.58 (br s, 2 H), 3.38 - 3.45 (m, 4 H), 2.35 - 2.47 (m, 2 H), 1.98 - 2.24 (m, 4 H), 1.37 - 1.45 (m, 4 H), 1.33 (s, 6 H), 0.32 (s, 4 H). *m/z* (ESI): 564.2 $(M+H)^+$.

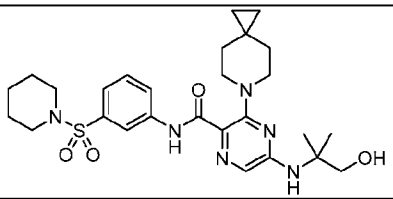
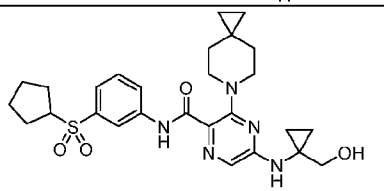
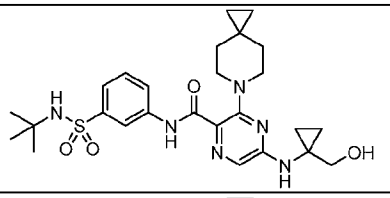
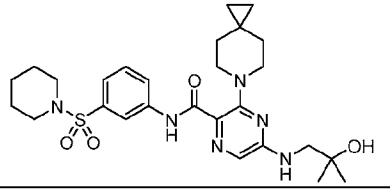
[0316] The stereochemistry was arbitrarily assigned.

[0317] Example 103: *N*-(3-(Cyclopentylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide

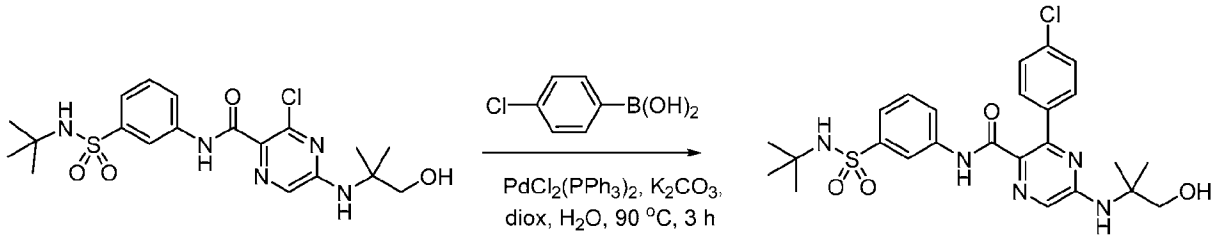


To a solution of 3-chloro-*N*-(3-(cyclopentylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide (110 mg, 0.243 mmol, Intermediate 11), DIPEA (0.085 mL, 0.486 mmol, Sigma-Aldrich), and DMSO (2 mL) was added 6-azaspiro[2.5]octane (45 mg, 0.405 mmol, AstaTech, Inc.). The solution was stirred at 50 °C for 16 h. After cooling to rt, water was added, and the solids were filtered, and adsorbed onto a plug of silica gel and chromatographed through a silica gel column, eluting with 0-50% EtOAc in heptane, to provide the title compound (104 mg, 0.20 mmol, 81 % yield), as a light-yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 9.80 (s, 1 H), 8.15 (br d, *J*=8.2 Hz, 1 H), 8.08 (s, 1 H), 7.56 - 7.60 (m, 1 H), 7.52 (d, *J*=8.0 Hz, 1 H), 7.25 (s, 1 H), 4.90 (s, 1 H), 3.76 (d, *J*=5.7 Hz, 2 H), 3.69 (br d, *J*=5.9 Hz, 1 H), 3.55 (br t, *J*=5.5 Hz, 5 H), 2.06 - 2.15 (m, 2 H), 1.74 - 1.96 (m, 4 H), 1.59 - 1.64 (m, 2 H), 1.53 - 1.55 (m, 4 H, obscured by water peak), 1.45 (s, 6 H), 0.38 (s, 4 H). *m/z* (ESI): 528.2 $(M+H)^+$.

[0318] Table 7: Examples 103-1 to 103-4 were prepared analogous to preparation of Example 103:

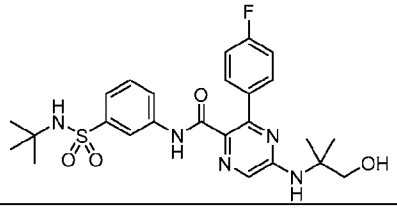
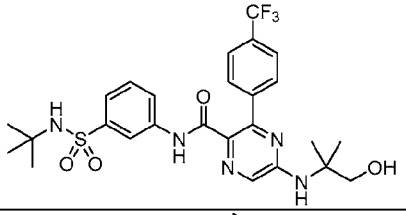
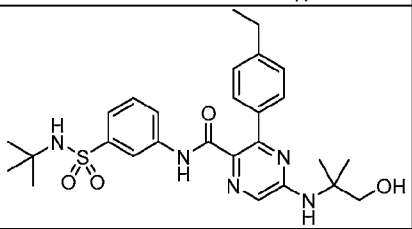
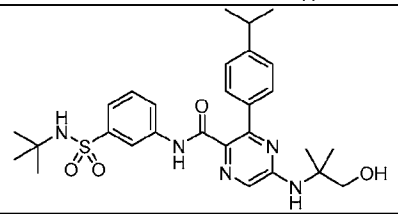
Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
103-1		5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	543.2
103-2		*N*-(3-(cyclopentylsulfonyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	526.1
103-3		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	529.1
103-4		5-((2-hydroxy-2-methylpropyl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	543.2

[0319] Example 104: *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-chlorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide.

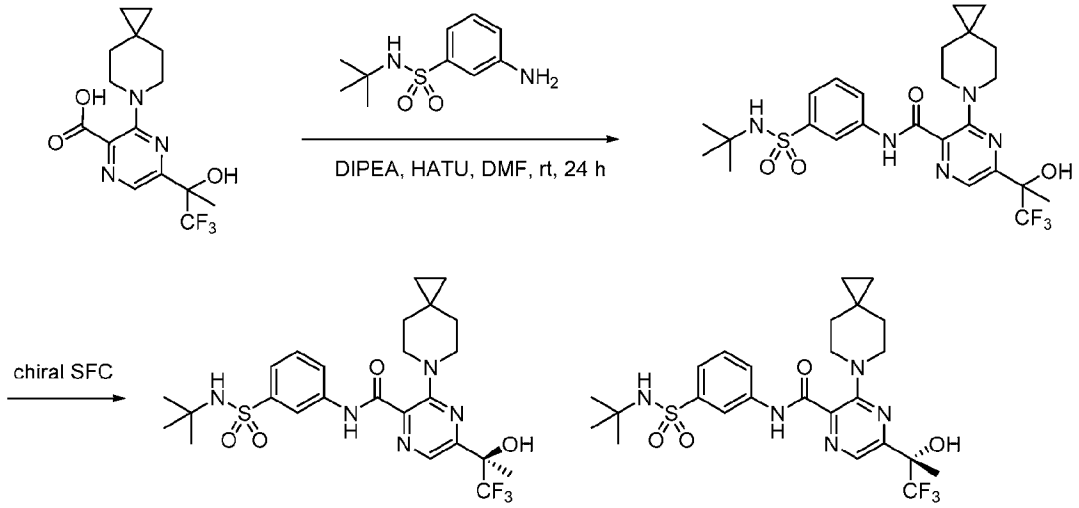


[0320] A mixture of *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-chloro-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide (137 mg, 0.302 mmol, Intermediate 11-3), (4-chlorophenyl)boronic acid (71 mg, 0.45 mmol), potassium carbonate (125 mg, 0.91 mmol), and $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol) in dioxane (2 mL)/water (0.4 mL) was stirred at 90 °C for 3 h. The reaction mixture was cooled, diluted with EtOAc, washed with H_2O, brine, dried over MgSO4, concentrated, and purified by silica gel chromatography (0-50% EtOAc:EtOH (3:1) in heptane) to give *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-chlorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide (84 mg, 0.16 mmol, 53 % yield). ^{1}H NMR (DMSO-d_6) δ: 10.60 (s, 1H), 8.33 (s, 1H), 8.02 (s, 1H), 7.83 (br d, J=7.3 Hz, 1H), 7.54-7.62 (m, 2H), 7.44-7.53 (m, 5H), 7.37 (s, 1H), 4.86 (t, J=5.7 Hz, 1H), 3.61 (d, J=5.8 Hz, 2H), 1.36 (s, 6H), 1.10 (s, 9H). *m/z* (ESI): 532.1 $(M+H)^+$.

[0321] Table 8: Examples 104-1 to 104-4 were prepared analogous to preparation of Example 104:

Ex. #	Chemical Structure	Name	LRMS: (ESI + ve ion) *m/z*
104-1		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	516.2
104-2		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(trifluoromethyl)phenyl)pyrazine-2-carboxamide	566.2
104-3		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-ethylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	526.1
104-4		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-isopropylphenyl)pyrazine-2-carboxamide	540.2

[0322] Examples 105-1 and 105-2: (*R*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide and (*S*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide.



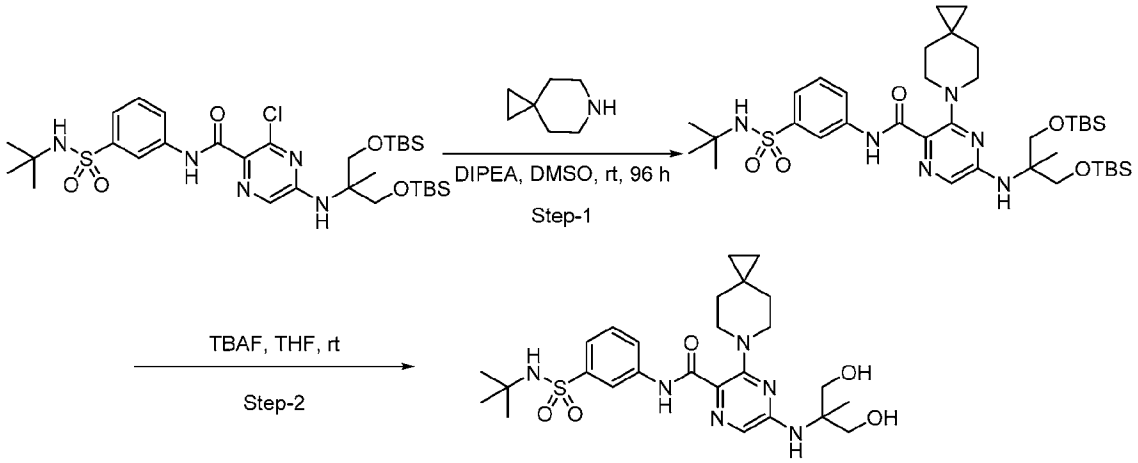
[0323] To a stirred mixture of 3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxylic acid (150mg, 0.434 mmol, Intermediate 9), 3-amino-*N*-(*tert*-butyl)benzenesulfonamide (119 mg, 0.52 mmol), and DIPEA (0.19 mL, 1.09 mmol) in DMF (2 mL) was added HATU (0.21 g, 0.56 mmol). The reaction mixture was stirred at rt for 18 h and diluted with water. The precipitated solid was collected by filtration, washed with water and dried. The crude material was purified by silica gel chromatography (0-30% EtOAc:EtOH (3:1) in heptane) to give *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide (192 mg, 0.346 mmol, 80 % yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ: 10.98 (s, 1H), 8.37 (s, 1H), 8.26 (s, 1H), 7.87 (dt, J=6.9, 2.1 Hz, 1H), 7.51-7.61 (m, 3H), 6.94 (s, 1H), 3.50-3.59 (m, 4H), 1.69 (s, 3H), 1.34-1.41 (m, 4H), 1.11 (s, 9H), 0.32 (s, 4H).). *m/z* (ESI): 556.1 $(M+H)^+$. This racemic material was separated by chiral preparative SFC using a Chiralpack AD column (250 x 20 mm, 5 mic) with a mobile phase of 75% Liquid CO_2 and 25% MeOH and a flowrate of 60 mL/min to give:

[0324] Example 105-1: (*R*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide. First eluting peak; ee > 99%, ^{1}H NMR (DMSO-d_6) δ: 10.98 (s, 1H), 8.37 (s, 1H), 8.26 (s, 1H), 7.87 (dt, J=6.9, 2.1 Hz, 1H), 7.51-7.61 (m, 3H), 6.94 (s, 1H), 3.50-3.59 (m, 4H), 1.69 (s, 3H), 1.34-1.41 (m, 4H), 1.11 (s, 9H), 0.32 (s, 4H).). *m/z* (ESI): 556.1 $(M+H)^+$.

[0325] Example 105-2: (*S*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide. Second eluting peak; ee > 99%, ^{1}H NMR (DMSO-d_6) δ: 10.98 (s, 1H), 8.37 (s, 1H), 8.26 (s, 1H), 7.87 (dt, J=6.9, 2.1 Hz, 1H), 7.51-7.61 (m, 3H), 6.94 (s, 1H), 3.50-3.59 (m, 4H), 1.69 (s, 3H), 1.34-1.41 (m, 4H), 1.11 (s, 9H), 0.32 (s, 4H). *m/z* (ESI): 556.1 $(M+H)^+$.

[0326] The stereochemistry was arbitrarily assigned.

[0327] Example 106: *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1,3-dihydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide.

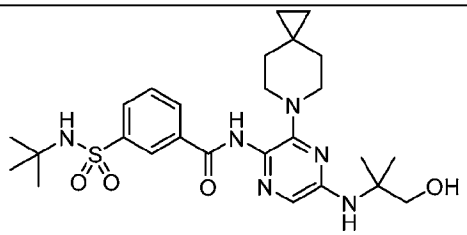
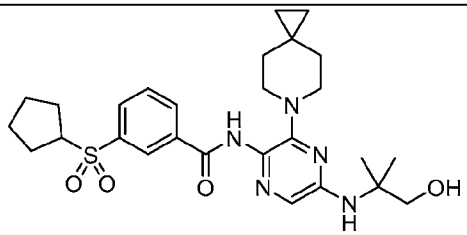
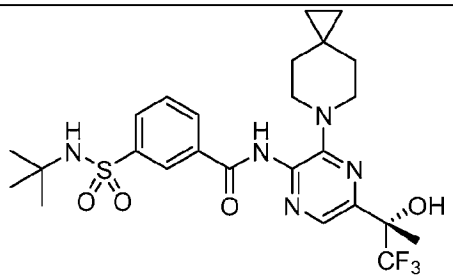
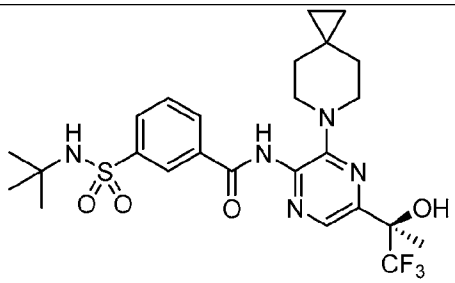
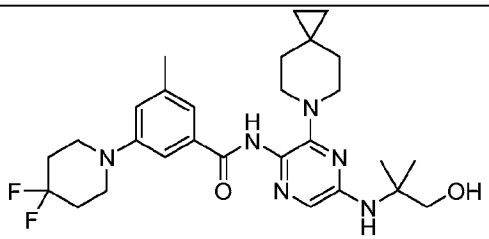
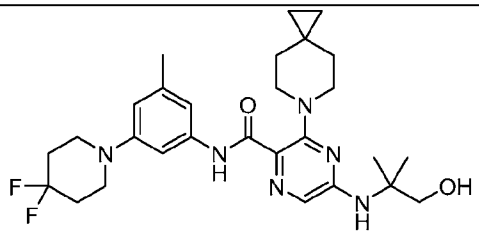


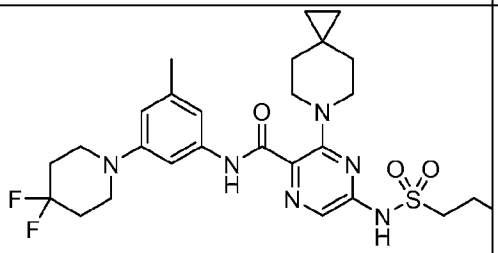
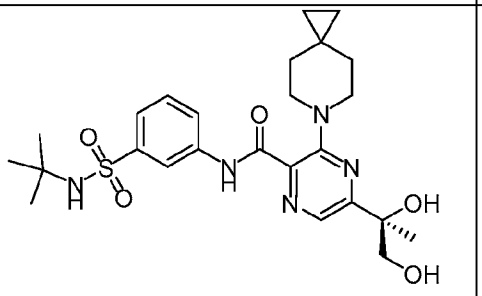
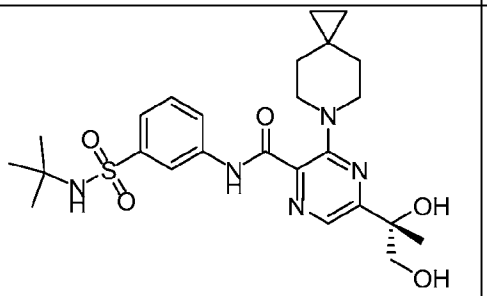
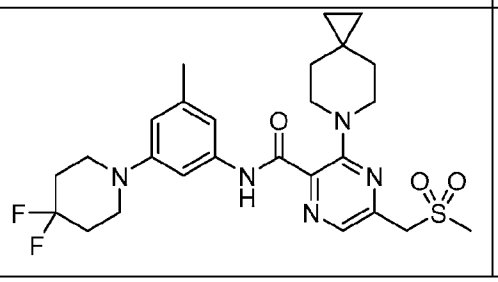
[0328] Step 1: To a solution of *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-chloro-5-((2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)amino)pyrazine-2-carboxamide (240 mg, 0.343 mmol, Intermediate 11-5) and DMSO (2 mL) was added 6-azaspiro[2.5]octane (46 mg, 0.41 mmol, AstaTech, Inc.) and DIPEA (0.119 mL, 0.685 mmol, Sigma-Aldrich). The reaction mixture was stirred at room temperature for 96 h, diluted with water, and stirred for 20 min, then filtered to give a yellow solid. The yellow solid was taken up in EtOAc, dried over $MgSO_4$, and concentrated in vacuo to give *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (285 mg, 0.368 mmol), as a yellow solid. *m/z* (ESI): 775.4 $(M+H)^+$, that was carried forward without further purification.

[0329] Step 2: To a solution of *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (266 mg, 0.257 mmol) in THF (5 mL) was added TBAF (1.6 mL, 1.6 mmol, 1 M in THF). The reaction mixture was stirred at RT for 16 h. Then the crude mixture was adsorbed onto a plug of silica gel and chromatographed through a Redi-Sep® pre-packed silica gel column eluting with 0-100% EtOAc in heptane to give *N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1,3-dihydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide (23.5 mg, 0.043 mmol, 17% yield), as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.30 (s, 1 H), 8.43 (s, 1 H), 7.84 - 7.90 (m, 1 H), 7.43 - 7.50 (m, 4 H), 6.79 (s, 1 H), 4.67 (t, *J*=5.7 Hz, 2 H), 3.59 - 3.71 (m, 4 H), 3.35 - 3.43 (m, 4 H), 1.38 - 1.46 (m, 4 H), 1.30 (s, 3 H), 1.11 (s, 9 H), 0.33 (s, 4 H). *m/z* (ESI): 547.1 $(M+H)^+$.

[0330] ADDITIONAL EXAMPLES

[0331] The following compounds can be made according to the procedure similar to the above examples by using starting commercially available materials or can be made according to procedure familiar to those skilled in the art.

Ex. #	Chemical Structure	Name
107		3-(*N*-(*tert*-Butyl)sulfamoyl)-*N*-(5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazin-2-yl)benzamide
108		3-(Cyclopentylsulfonyl)-*N*-(5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazin-2-yl)benzamide
109		(*S*)-*N*-(3-(6-Azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazin-2-yl)-3-(*N*-(*tert*-butyl)sulfamoyl)benzamide
110		(*R*)-*N*-(3-(6-Azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazin-2-yl)-3-(*N*-(*tert*-butyl)sulfamoyl)benzamide
111		3-(4,4-Difluoropiperidin-1-yl)-*N*-(5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazin-2-yl)-5-methylbenzamide
112		*N*-(3-(4,4-Difluoropiperidin-1-yl)-5-methylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide

Ex. #	Chemical Structure	Name
113		*N*-(3-(4,4-Difluoropiperidin-1-yl)-5-methylphenyl)-5-((2-hydroxyethyl)sulfonamido)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
114		(*R*)-*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-(1,2-dihydroxypropan-2-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
115		(*S*)-*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-(1,2-dihydroxypropan-2-yl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
116		*N*-(3-(4,4-Difluoropiperidin-1-yl)-5-methylphenyl)-5-((methylsulfonyl)methyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide

[0332] BIOLOGICAL EXAMPLES

[0333] For compounds in Table A, the following assay conditions were employed:

[0334] KIF18A Enzyme Assay: Microtubule-stimulated ATPase activity assay is used to measure KIF18A enzyme activity after treatment with compound. Compounds were 2-fold serially diluted in DMSO (Sigma Inc) over 22-point concentration range. Recombinant human KIF18A (1-467 His-tagged) protein was expressed using a baculovirus system and purified by affinity chromatography by Amgen Inc. Concentrations of KIF18A protein, microtubules (MT), and ATP in the reaction were optimized for standardized homogenous enzyme assay using ADP-Glo™ Kinase/ATPase Assay Kit (Promega Inc). The assay measures ADP formed from the ATPase reaction. Prepare reaction buffer [(15 mM Tris, pH 7.5 (Teknova Inc), 10 mM MgCl2 (JT Baker Inc), 0.01% Pluronic F-68 (Life Technologies Inc), 1 μM Taxol (Cytoskeleton Inc), and 30 μg/mL pig microtubules (Cytoskeleton Inc)]. Add compound and KIF18A protein (30 nM) to prepared reaction buffer and incubated for 15 minutes at room temperature, next add

ATP (at K_m, 75 μM) to the reaction mixture and incubated for an additional 15 minutes at room temperature. Mix 5 μl of ADP-Glo™ Reagent and 2.5 μl of the reaction mixture and incubate for 40 minutes at room temperature. Add 10 μl ADP-Glo™ Detection Reagent and incubate for 40 minutes at room temperature. Read luminescence using EnVision microplate reader with ultra-luminescence module (Perkin Elmer Inc). Concentration-response curve-fitting and IC_{50} determination was performed using Genedata Screener Software (Standard 15.0.1, Genedata Inc) with a four-parameter logistic regression fit model.

TABLE A: BIOLOGICAL DATA

Ex. #	Compound Name	KIF18A ATPase IC_{50} (μM)
100	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.082
100-1	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-methylpiperidin-1-yl)pyrazine-2-carboxamide	0.177
100-2	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4,4-difluoropiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.342
100-3	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(trifluoromethyl)piperidin-1-yl)pyrazine-2-carboxamide	0.455
100-4	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-ethylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.133
100-5	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4,4-dimethylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.190
100-6	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-isopropylpiperidin-1-yl)pyrazine-2-carboxamide	0.319
100-7	3-(4-(*tert*-butyl)piperidin-1-yl)-*N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.788
100-8	3-(4-(*sec*-butyl)piperidin-1-yl)-*N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.163
100-9	N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-propylpiperidin-1-yl)pyrazine-2-carboxamide	0.118
100-10	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-cyclopropylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.221
100-11	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(methoxymethyl)piperidin-1-yl)pyrazine-2-carboxamide	1.39
100-12	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(2-azaspiro[3.3]heptan-2-yl)pyrazine-2-carboxamide	0.931

Ex. #	Compound Name	KIF18A ATPase IC_{50} (μM)
100-13	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(2-azaspiro[3.5]nonan-2-yl)pyrazine-2-carboxamide	0.410
100-14	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(3-oxa-9-azaspiro[5.5]undecan-9-yl)pyrazine-2-carboxamide	1.38
100-15	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(7-azaspiro[3.5]nonan-7-yl)pyrazine-2-carboxamide	0.077
100-16	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(2,2-difluoro-7-azaspiro[3.5]nonan-7-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.215
100-17	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(8-azaspiro[4.5]decan-8-yl)pyrazine-2-carboxamide	0.129
101	*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-methylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.231
101-1	5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)-N-(3-((1,1,1-trifluoro-2-methylpropan-2-yl)sulfonyl)phenyl)pyrazine-2-carboxamide	0.108
101-2	*N*-(3-(*tert*-butylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.218
101-3	5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-methylcyclobutyl)sulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.204
101-4	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)-5-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.172
101-5	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)-2-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.527
101-6	*N*-(3-(1,1-dioxidothiomorpholino)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.545
101-7	5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-morpholinophenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.768
101-8	5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-hydroxy-2-methylpropan-2-yl)amino)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.240
102-1	(*S*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.067
102-2	(*R*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.111
103	*N*-(3-(Cyclopentylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.077

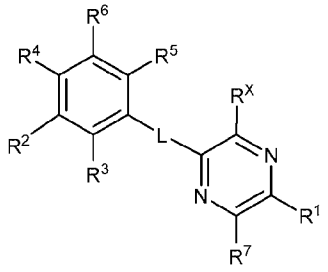
Ex. #	Compound Name	KIF18A ATPase IC_{50} (μM)
103-1	5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.135
103-2	*N*-(3-(cyclopentylsulfonyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.143
103-3	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.139
103-4	5-((2-hydroxy-2-methylpropyl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.406
104	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-chlorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.135
104-1	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.418
104-2	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(trifluoromethyl)phenyl)pyrazine-2-carboxamide	0.168
104-3	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-ethylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide	0.146
104-4	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-isopropylphenyl)pyrazine-2-carboxamide	0.141
105-1	(*R*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide	0.174
105-2	(*S*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide	0.356
106	*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1,3-dihydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide	0.103

[0335] The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. Those skilled in the art understand that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

[0336] All patents, patent applications and publications cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

We claim:

1. A compound of formula I:



(I);

or any pharmaceutically-acceptable salt thereof, wherein:

L is –(C=O)-NR^8- or -NR^8-(C=O)-;

R^1 is a group -Z-R^9; wherein Z is absent, -NR^{11}-, -$NR^{11}SO_2$-C_{1-4}alk-, -$NR^{11}SO_2NR^{11}$, -$NR^{11}SO_2NR^{11}$-C(=O)-O-, -N=S(=O)<, -SO_2NR^{11}-C_{0-4}alk-, C_{0-4}alk-S(=O)(=NH)-, C_{0-4}alk-S(=O)(=$N^+(CH_3)_2$)-, C_{1-4}alk-, C_{0-4}alk-S-, C_{0-4}alk-S(=O)-, C_{0-4}alk-SO_2-, -O-, -P-, -P(=O), -$P(=O)_2$, -(C=O)-, -(C=O)NR^{11}-, -C=N(OH)-, or -NR^{11}(C=O);

R^2 is a group –Y-R^{10}, wherein Y is absent, C_{0-4}alk-S-, C_{0-4}alk-S=O, C_{0-4}alk-$S(=O)_2$, -SO_2NR^{10c}-C_{0-4}alk-, -NR^{10c}-, -NR^{10c}-SO_2-C_{0-4}alk-, -C_{0-4}alk-S(=O)(=NH)-, -O-C_{0-4}alk-, -(C=O)-, -C_{0-4}alk-(C=O)-O-, or -N=S(=O)<;

R^3 is H, halo, C_{1-4}alk, or C_{1-4}haloalk;

R^4 is H, halo, C_{1-4}alk, or C_{1-4}haloalk;

R^5 is H, halo, C_{1-8}alk, or C_{1-4}haloalk;

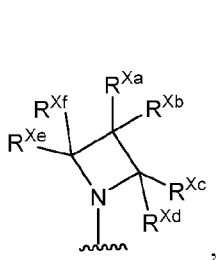
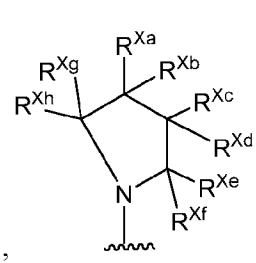
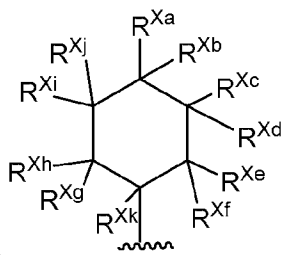
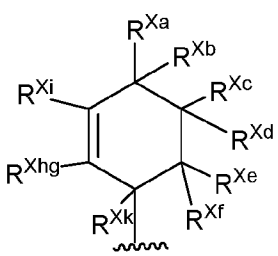
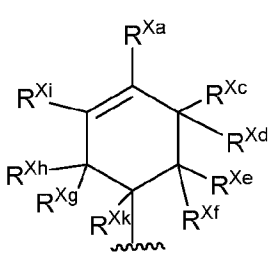
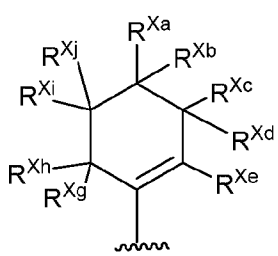
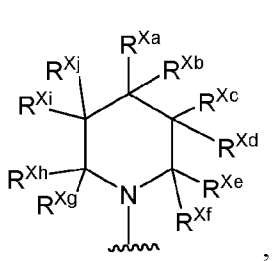
R^6 is H, halo, C_{1-8}alk, or C_{1-4}haloalk;

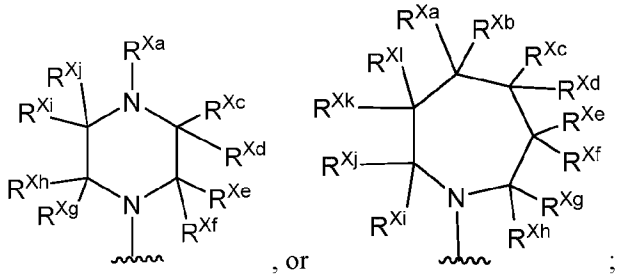
R^7 is H, halo, C_{1-4}alk, or C_{1-4}haloalk;

R^8 is H or C_{1-4}alk;

R^9 is H, R^{9a}, or R^{9b};

R^{10} is halo, R^{10a} or R^{10b};

R^X is selected from , , , , , , ,



, or ;

or R^X is an C_{2-8}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, $-CH_2F$, $-CHF_2$, $-CF_3$, $-C(=O)OR^a$, $-OR^a$, $-OC_{1-4}$haloalk, CN, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or R^{Xm};

or R^X is phenyl or unsaturated 5-membered monocyclic ring substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, $-C_{1-6}$alk, $-C_{1-6}$haloalk, $-C(=O)OR^a$, $-OR^a$, $-OC_{1-4}$haloalk, CN, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or R^{Xm}; wherein said 5-membered monocyclic ring contains 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S;

Each of R^{Xa}, R^{Xb}, R^{Xc}, R^{Xd}, R^{Xe}, R^{Xf}, R^{Xg}, R^{Xh}, R^{Xi}, R^{Xj}, R^{Xk}, and R^{Xl} is H, halo, R^{Xn}, or R^{Xo};

or alternatively, each of R^{Xa} and R^{Xb} pair, R^{Xc} and R^{Xd} pair, R^{Xe} and R^{Xf} pair, R^{Xg} and R^{Xh} pair, R^{Xi} and R^{Xj} pair, and R^{Xk} and R^{Xl} pair, independently, can combine with the carbon atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, 6-membered monocyclic ring spiro to the azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, or azepanyl ring; wherein said 3-, 4-, 5-, 6-membered monocyclic ring contains 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, and further wherein said 3-, 4-, 5-, 6-membered monocyclic ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, $-OR^a$, $-OC_{1-4}$haloalk, CN, $-NR^aR^a$, or oxo;

Each R^{Xm} and R^{Xn} is independently, at each instance, selected from the group consisting of a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic or 8-, 9-, 10-, 11-, or 12-membered bicyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, which is substituted by 0, 1, 2, 3, or 4 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, $-OR^a$, $-OC_{1-4}$haloalk, CN, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC_{2-6}$alkNR^aR^a, $-OC_{2-6}$alkOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}$alkNR^aR^a, $-NR^aC_{2-6}$alkOR^a, $-C_{1-6}$alkNR^aR^a, $-C_{1-6}$alkOR^a, $-C_{1-6}$alk$N(R^a)C(=O)R^b$, $-C_{1-6}$alk$OC(=O)R^b$, $-C_{1-6}$alk$C(=O)NR^aR^a$, $-C_{1-6}$alk$C(=O)OR^a$, and oxo;

R^{Xo} is independently, at each instance, selected from the group consisting of C_{1-8}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, $-CH_2F$, $-CHF_2$, $-CF_3$, $-C(=O)OR^a$, $-OR^a$, $-OC_{1-4}$haloalk, CN, NH_2, $NH(CH_3)$, or $N(CH_3)_2$;

R^{9a} and R^{10a} is independently, at each instance, selected from the group consisting of a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic or 8-, 9-, 10-, 11-, or 12-membered bicyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, which is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, $-OR^a$, $-OC_{1-4}$haloalk, CN, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$, $-OC_{2-6}$alkNR^aR^a, $-OC_{2-6}$alkOR^a, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$, $-N(R^a)C(=O)OR^b$, $-N(R^a)$

$C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$, $-NR^aC_{2-6}alkNR^aR^a$, $-NR^aC_{2-6}alkOR^a$, $-C_{1-6}alkNR^aR^a$, $-C_{1-6}alkOR^a$, $-C_{1-6}alkN(R^a)C(=O)R^b$, $-C_{1-6}alkOC(=O)R^b$, $-C_{1-6}alkC(=O)NR^aR^a$, $-C_{1-6}alkC(=O)OR^a$, R^{11}, and oxo;

R^{9b} and R^{10b} is independently, at each instance, selected from the group consisting of $C_{1-6}alk$ substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, $-CH_2F$, $-CHF_2$, $-CF_3$, $-C(=O)OR^a$, $-OR^a$, $-OC_{1-4}haloalk$, CN, NH_2, $NH(CH_3)$, or $N(CH_3)_2$;

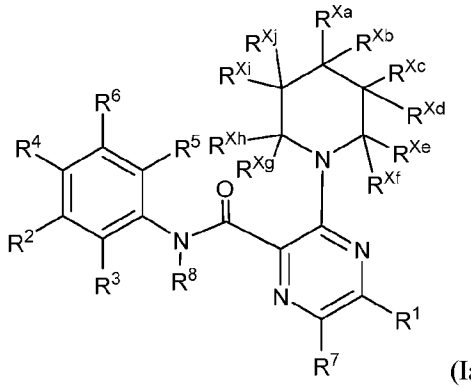
R^{10c} is H or $C_{1-4}alk$;

R^{11} is H or $C_{1-8}alk$;

R^a is independently, at each instance, H or R^b; and

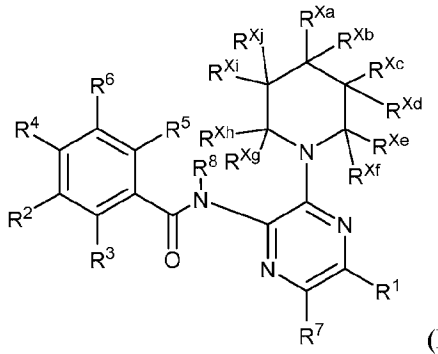
R^b is independently, at each instance, $C_{1-6}alk$, phenyl, or benzyl, wherein the $C_{1-6}alk$ is being substituted by 0, 1, 2 or 3 substituents selected from halo, -OH, $-OC_{1-4}alk$, $-NH_2$, $-NHC_{1-4}alk$, $-OC(=O)C_{1-4}alk$, or $-N(C_{1-4}alk)C_{1-4}alk$; and the phenyl or benzyl is being substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}alk$, $C_{1-3}haloalk$, -OH, $-OC_{1-4}alk$, $-NH_2$, $-NHC_{1-4}alk$, $-OC(=O)C_{1-4}alk$, or $-N(C_{1-4}alk)C_{1-4}alk$.

2. The compound of any one of the previous Claims wherein L is $-NR^8-(C=O)$; having the formula (Ia):



(Ia); wherein said R^{Xa} and R^{Xb} pair can combine with the carbon atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, 6-membered monocyclic ring spiro to the piperidinyl ring; wherein said 3-, 4-, 5-, 6-membered monocyclic ring contains 0 N, O, and S atoms, and further wherein said 3-, 4-, 5-, 6-membered monocyclic ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, $C_{1-6}alk$, $C_{1-4}haloalk$, $-OR^a$, $-OC_{1-4}haloalk$, CN, $-NR^aR^a$, or oxo.

3. The compound of any one of the previous Claims wherein L is $-(C=O)-NR^8-$; having the formula (Ib):



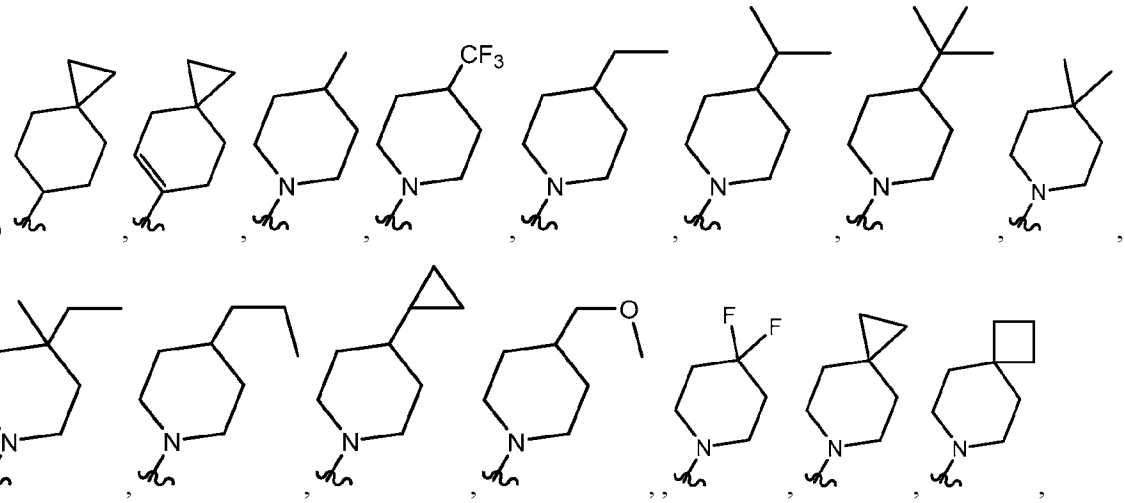
(Ib); wherein said R^{Xa} and R^{Xb} pair can combine with the carbon atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, 6-membered monocyclic ring spiro to the piperidinyl ring; wherein said 3-, 4-, 5-, 6-membered monocyclic ring contains 0 N, O, and S atoms, and further wherein said 3-, 4-, 5-, 6-membered monocyclic ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, -OR^a, -OC_{1-4}haloalk, CN, -NR^aR^a, or oxo.

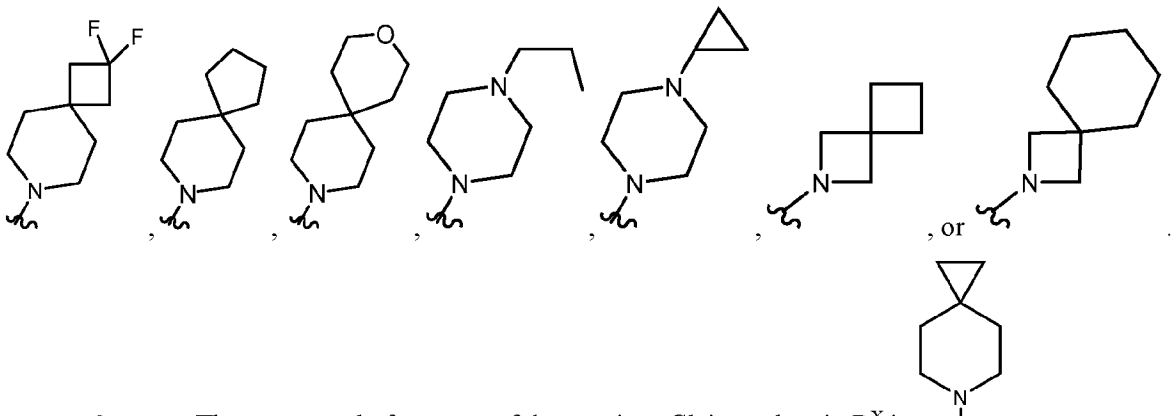
4. The compound of any one of the previous Claims wherein R^8 is H or methyl.

5. The compound of any one of the previous Claims wherein each of R^{Xc}, R^{Xd}, R^{Xe}, R^{Xf}, R^{Xg}, R^{Xh}, R^{Xi}, R^{Xj}, R^{Xk}, and R^{Xl} is H, halo, C_{1-6}alk, or C_{1-4}haloalk; and each of R^{Xa} and R^{Xb} pair combine with the carbon atom attached to each of them form a saturated 3-, 4-, or 5-membered monocyclic ring spiro to the piperidinyl ring; wherein said ring contains 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S.

6. The compound of any one of the previous Claims wherein each of R^{Xc}, R^{Xd}, R^{Xe}, R^{Xf}, R^{Xg}, R^{Xh}, R^{Xi}, R^{Xj}, R^{Xk}, and R^{Xl} is H, methyl, or ethyl; and each of R^{Xa} and R^{Xb} pair combine with the carbon atom attached to each of them form a cyclopropyl, cyclobutyl, or cyclopentyl ring spiro to the piperidinyl ring.

7. The compound of any one of the previous Claims wherein R^X is selected from (a) ethynyl substituted by isobutyl or cyclopentyl; (b) phenyl substituted by 0, 1, 2, or 3 F, Cl, CF_3, CH_2OCH_3, methyl, ethyl, propyl, isopropyl, *tert*-butyl, or cyclopropyl group(s); (c) or pyrazolyl substituted by 0, 1, 2, or 3 F, Cl, CF_3, CH_2OCH_3, methyl, ethyl, propyl, isopropyl, *tert*-butyl, or cyclopropyl group(s);

(d) 



8. The compound of any one of the previous Claims wherein R^X is .

9. The compound of any one of the previous Claims wherein Z is absent, -NH-, $-NHSO_2-$, $-SO_2NH-$, or $-CH_2SO_2-$.

10. The compound of any one of the previous Claims wherein R^9 is selected from:

a) H; (b) C_{1-6}alk substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, $-CF_3$, or -OH; or (c) a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, which is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, ethyl, $-CF_3$, $-CH_2OH$, -OH, $-OCH_3$, $-NH_2$, or oxo.

11. The compound of any one of the previous Claims wherein R^9 is selected from cyclopropyl, cyclobutyl, cyclopentyl, oxetanyl, azetidinyl, diazirinyl, oxazolidinyl, isothiazolidinyl, pyrazolyl, or pyrrolidinyl.

12. The compound of any one of the previous Claims wherein R^1 is a group $-Z-R^9$, wherein Z is absent, -NH-, $-NHSO_2-$, $-SO_2NH-$, or $-CH_2SO_2-$; and R^9 is cyclopropyl or oxazolinyl substituted by 0, 1, 2 or 3 OH, $-CH_2OH$, methyl, or oxo group(s), or R^9 is C_{1-6}alk substituted by 0, 1, 2 or 3 OH or CF_3 group(s).

13. The compound of any one of the previous Claims wherein R^1 is a group $-Z-R^9$, wherein Z is $-NHSO_2-$ and R^9 is $-CH_2-CH_2-OH$.

14. The compound of any one of the previous Claims wherein R^2 is a group $-Y-R^{10}$, wherein Y is absent, -NH-, $-NHSO_2-$, SO_2NH-, or SO_2-; and

R^{10} is a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, which is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, ethyl, CF_3, CH_2OH, -OH, $-OCH_3$, $-NH_2$, $-NH(CH_3)$, and oxo; or;

R^{10} is C_{1-6}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, -OH, or $-CF_3$.

15. The compound of any one of the previous Claims wherein R^2 is morpholinyl, thiomorpholinyl, cyclobutyl, cyclopentyl, or piperidinyl ring, wherein each of said ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, CF_3, -OH, $-OCHF_2$, or oxo.

16. The compound of any one of the previous Claims wherein R^2 is morpholinyl or piperidinyl substituted by 0, 1, 2 or 3 selected from F or methyl.

17. The compound of any one of the previous Claims wherein R^3 is H or F.

18. The compound of any one of the previous Claims wherein R^4 is H.

19. The compound of any one of the previous Claims wherein R^5 is H.

20. The compound of any one of the previous Claims wherein R^6 is H, F, or methyl.

21. The compound of any one of the previous Claims wherein R^7 is H.

22. The compound of claim 1, or any pharmaceutically-acceptable salt thereof, selected from the group consisting of:

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-methylpiperidin-1-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4,4-difluoropiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(trifluoromethyl)piperidin-1-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-ethylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4,4-dimethylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-isopropylpiperidin-1-yl)pyrazine-2-carboxamide;

3-(4-(*tert*-butyl)piperidin-1-yl)-*N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

3-(4-(*sec*-butyl)piperidin-1-yl)-*N*-(3-(*N*-(tert-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-propylpiperidin-1-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-cyclopropylpiperidin-1-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(methoxymethyl)piperidin-1-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(2-azaspiro[3.3]heptan-2-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(2-azaspiro[3.5]nonan-2-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(3-oxa-9-azaspiro[5.5]undecan-9-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(7-azaspiro[3.5]nonan-7-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(2,2-difluoro-7-azaspiro[3.5]nonan-7-yl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(8-azaspiro[4.5]decan-8-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-methylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)-N-(3-((1,1,1-trifluoro-2-methylpropan-2-yl)sulfonyl)phenyl)pyrazine-2-carboxamide;

N-(3-(*tert*-butylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-methylcyclobutyl)sulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)-5-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)-2-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(1,1-dioxidothiomorpholino)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-morpholinophenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-hydroxy-2-methylpropan-2-yl)amino)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

(*S*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

(*R*)-*N*-(3-((3,3-difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(Cyclopentylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((1-hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(cyclopentylsulfonyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

5-((2-hydroxy-2-methylpropyl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-chlorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-(trifluoromethyl)phenyl)pyrazine-2-carboxamide;

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(4-ethylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide;

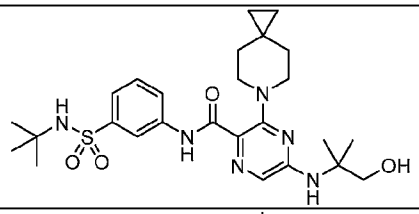
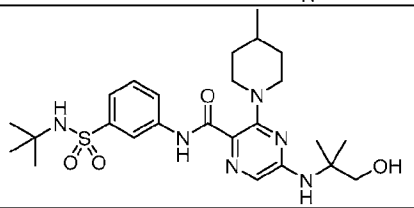
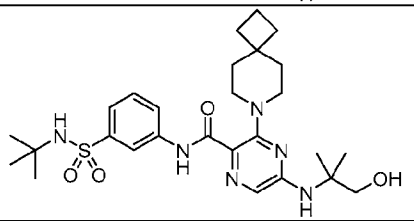
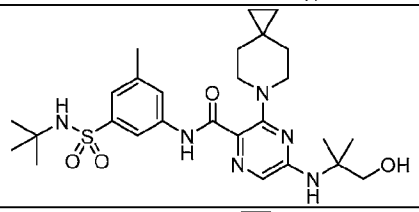
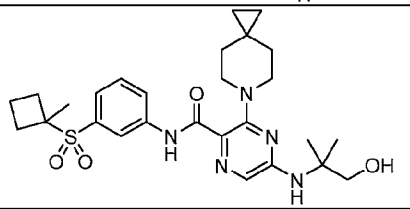
N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-isopropylphenyl)pyrazine-2-carboxamide;

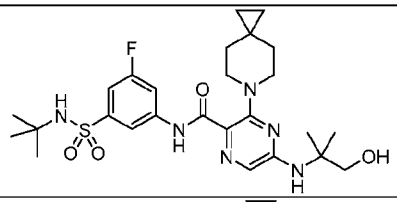
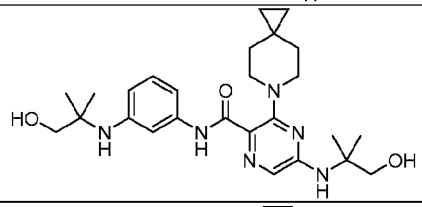
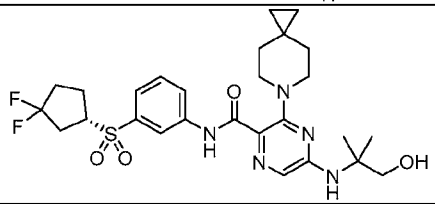
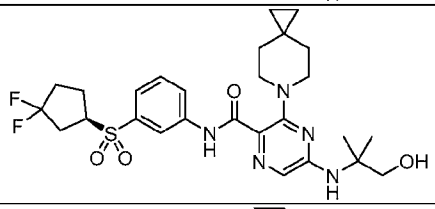
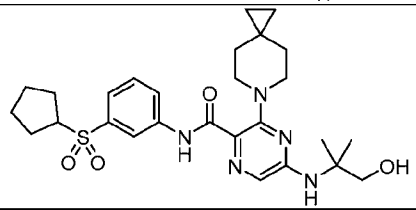
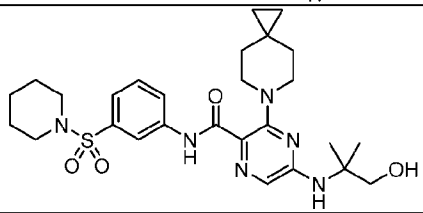
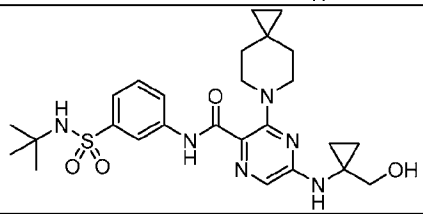
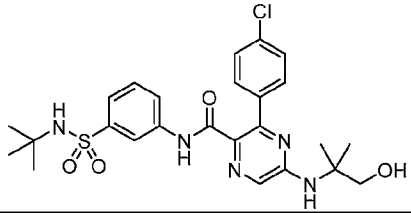
(*R*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide;

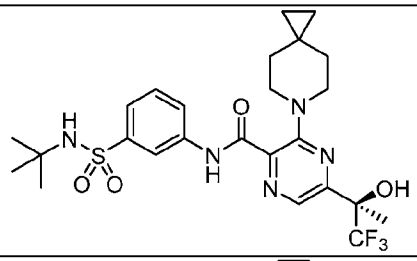
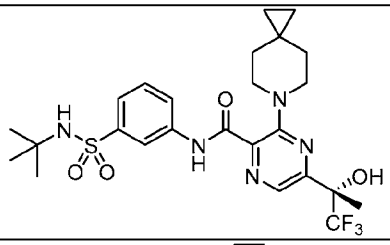
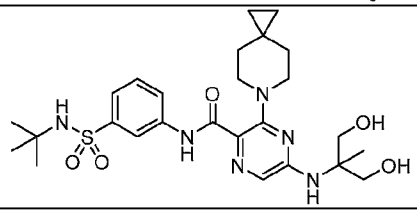
(*S*)-*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide; or

N-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1,3-dihydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide.

23. The compound of claim 1, selected from the group consisting of:

Example #	Chemical Structure	Name
100		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
100-1		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(4-methylpiperidin-1-yl)pyrazine-2-carboxamide
100-15		*N*-(3-(*N*-(*tert*-butyl)sulfamoyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(7-azaspiro[3.5]nonan-7-yl)pyrazine-2-carboxamide
101		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-methylphenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
101-3		5-((1-Hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-methylcyclobutyl)sulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide

Example #	Chemical Structure	Name
101-4		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)-5-fluorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
101-8		5-((1-Hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-((1-hydroxy-2-methylpropan-2-yl)amino)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
102-1		(*S*)-*N*-(3-((3,3-Difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
102-2		(*R*)-*N*-(3-((3,3-Difluorocyclopentyl)sulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
103		*N*-(3-(Cyclopentylsulfonyl)phenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
103-1		5-((1-Hydroxy-2-methylpropan-2-yl)amino)-*N*-(3-(piperidin-1-ylsulfonyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
103-3		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1-(hydroxymethyl)cyclopropyl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide
104		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-3-(4-chlorophenyl)-5-((1-hydroxy-2-methylpropan-2-yl)amino)pyrazine-2-carboxamide

Example #	Chemical Structure	Name
105-1		(*R*)-*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide
105-2		(*S*)-*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-3-(6-azaspiro[2.5]octan-6-yl)-5-(1,1,1-trifluoro-2-hydroxypropan-2-yl)pyrazine-2-carboxamide
106		*N*-(3-(*N*-(*tert*-Butyl)sulfamoyl)phenyl)-5-((1,3-dihydroxy-2-methylpropan-2-yl)amino)-3-(6-azaspiro[2.5]octan-6-yl)pyrazine-2-carboxamide

; or any pharmaceutically-acceptable salt thereof.

24. A pharmaceutical composition comprising the compound according to any one of the previous Claims or the pharmaceutically acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

25. A method of treating a condition that may be treated with KIF18a inhibitors, the method comprising administering to a patient in need thereof a therapeutically effective amount of the compound in accordance with any one of claims 1 to 23, or the composition according to claim 24.

26. The method of Claim 25 wherein said condition is a proliferative disorder selected from cancer, psoriasis, atopic dermatitis, an autoimmune disorder, or inflammatory bowel disease; wherein said cancer can be melanoma, prostate cancer, cervical cancer, breast cancer, colon cancer, sarcoma, or leukemia; wherein said autoimmune disorder can be rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, Scleroderma, mixed connective tissue disease, dermatomyositis, polymyositis, Reiter's syndrome, autoimmune lymphoproliferative syndrome (ALPS), also known as Canale-Smith syndrome, or autoimmune disease of the central nervous system, such as multiple Sclerosis, myasthenia gravis, and encephalomyelitis; and wherein the. inflammatory bowel disease can be ulcerative colitis or Crohn's Disease.

27. A method of reducing the size of a solid tumor in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of the compound in accordance with any one of claims 1 to 23, or the composition according to claim 24.

28. A method of treating a cell proliferation disorder in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of the compound in accordance with any one of claims 1 to 23, or the composition according to claim 24.

29. A method of inhibiting KIF18A in a cell, comprising contacting the cell with a compound, or pharmaceutically acceptable salts thereof, in accordance with any one of claims 1 to 23, or the composition according to claim 24.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/044798

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D241/28 C07D401/04 C07D401/14 A61P35/00 A61K31/497
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAGARAJA REDDY GANGARAPU ET AL: "NMI/MsCl-Mediated Amide Bond Formation of Aminopyrazines and Aryl/Heteroaryl Carboxylic Acids: Synthesis of Biologically Relevant Pyrazine Carboxamides.", CHEMISTRYSELECT, vol. 2, no. 25, 31 August 2017 (2017-08-31), pages 7706-7710, XP055729936, DE ISSN: 2365-6549, DOI: 10.1002/slct.201700801 compounds 5a-d,6b,7b,8b ----- -/--	1,4-7,9, 10,14, 17-21

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 2020	24/09/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Seelmann, Ingo

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/044798

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAGARAJA REDDY GANGARAPU ET AL: "Design, Synthesis, and Biological Evaluation of 3,5-Disubstituted 2-Pyrazineamide Derivatives as Antitubercular Agents", JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 56, no. 3, 30 March 2019 (2019-03-30) , pages 1117-1126, XP055729957, US ISSN: 0022-152X, DOI: 10.1002/jhet.3461 compounds 1-3,12-14	1,4-7,9, 10,14, 17-21
A	JOACHIM BRAUN ET AL: "Synthesis and Biological Evaluation of Optimized Inhibitors of the Mitotic Kinesin Kif18A", ACS CHEMICAL BIOLOGY, vol. 10, no. 2, 26 November 2014 (2014-11-26), pages 554-560, XP055671701, ISSN: 1554-8929, DOI: 10.1021/cb500789h the whole document	1-29
X,P	WO 2020/132649 A1 (AMGEN INC [US]) 25 June 2020 (2020-06-25) paragraph [0001]; claim 1	1-29
X,P	WO 2020/132653 A1 (AMGEN INC [US]) 25 June 2020 (2020-06-25) paragraph [0001]; claim 1	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/044798

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2020132649 A1	25-06-2020	NONE	
WO 2020132653 A1	25-06-2020	NONE	