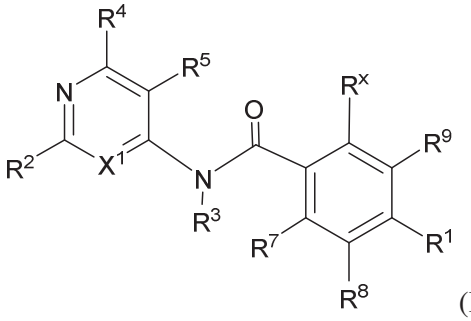
driven lethality or death after mitotic slippage in interphase. Accordingly, there has been a strong interest in finding inhibitors of KIF18A proteins.

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

SUMMARY

[0007] The present disclosure provides 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.

[0007a] In one aspect, the present disclosure refers to a compound of formula I:



(I);

or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is N or $-CR^6$;

R^1 is -CN, or a group $-Z-R^{12}$ wherein Z is $-C_{0-4}$alk-, $-NR^{11}$-, $-NR^{11}SO_2$-, $-SO_2NR^{11}$-, $-NR^{11}$-S(=O)(=NH), -S(=O)(=NH)-, -S-, -S(=O)-, $-SO_2$-, C_{0-4}alk-O-, -(C=O)-, -(C=O)NR^{11}-, -C=N(OH)-, or $-NR^{11}$(C=O); or

the group $-Z-R^{12}$ is $-N=S(=O)-(R^{12})_2$, wherein the two R^{12} pair can alternatively combine with the sulfur atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, or 6-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0, 1, or 2 atoms selected from O and S;

R^2 is halo or a group $-Y-R^{13}$, wherein Y is $-C_{0-4}$alk-, -NH-C_{0-4}alkylene-, -N(CH_3)-C_{0-4}alkylene- ~~N(C_{0-1}alk) C_{0-4}alk~~ -, -C(=O)NR^a~~R~~^{a}(C_{1-4}alk), -O-C_{0-4}alk-, S, S=O, $S(=O)_2$, $-SO_2NR^{13}$, or -S(=O)(=NH)-;

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

R^4 is H, halo, R^{4a} or R^{4b};

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

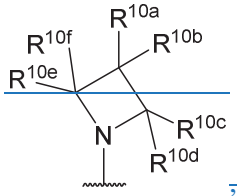
R^6 is H, halo, C_{1-8}alk, C_{1-4}haloalk, -O-C_{1-8}alk, or -O-$R^{6a;}$ wherein R^{6a} is a saturated or partially-saturated 3-, 4-, 5-, or 6-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0, 1, or 2 atoms selected from O and S;

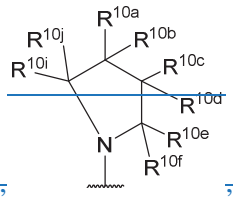
R^7 is H, halo, C_{1-8}alk, or C_{1-4}haloalk;

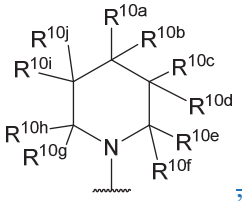
R^8 is H, halo, C_{1-8}alk, C_{1-4}haloalk, -OH, -O-R^{8a}, or -O-R^{8b};

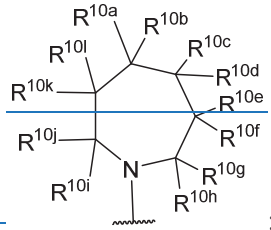
R^9 is H, halo, C_{1-8}alk, or C_{1-4}haloalk;

R^x is ~~selected from the group consisting of~~represented by the following formula:



, 

, 

~~, and~~ 

;

Each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, and R^{10j} is H, halo, R^{10k}, or R^{10l};

or alternatively, each of R^{10a} and R^{10b} pair, R^{10c} and R^{10d} pair, R^{10e} and R^{10f} pair, R^{10g} and R^{10h} pair, or R^{10i} and R^{10j} 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 R^x ring; wherein said 3-, 4-, 5-, 6-membered monocyclic ring contains 0, 1, 2 or 3 N atoms and 0, 1, or 2 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;

R^{11} is H, R^{11a}, or R^{11b};

R^{12} is H, R^{12a}, or R^{12b};

R^{13} is R^{13a} or R^{13b};

R^{4a}, R^{8a}, R^{10k}, R^{11a}, R^{12a}, and R^{13a} 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 4 ~~,~~ 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic ring containing 0, 1, 2 or 3 N atoms and 0, 1, or 2 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, -$N(R^a)C(=O)R^b$, -$N(R^a)C(=O)OR^b$,-$N(R^a)C(=O)N$
R^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}alkO
R^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^{14}, and oxo;

R^{4b}, R^{8b}, R^{10l}, R^{11b}, R^{12b}, and R^{13b} 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, -OR^a, -OC_{1-4}haloalk, or CN;

R^{14} 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 4-, 5-, 6-, 7-, 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$C(=O)OR^a$, and oxo;

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.

[0007b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound according to the disclosure, or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

[0007c] In another aspect, the present disclosure refers to a ~~use of KIF18a inhibitors~~compound in accordance with the disclosure, or the pharmaceutical composition according to the disclosure in the preparation of a medicament for treating a condition, 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~~ and (f) a melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer or Kaposi's sarcoma.

[0007d] In another aspect, the present disclosure refers to a use of the compound in accordance with the disclosure, or the pharmaceutically acceptable salt thereof, or the composition according to the disclosure in the manufacture of a medicament for reducing the size of a solid tumor in a subject.

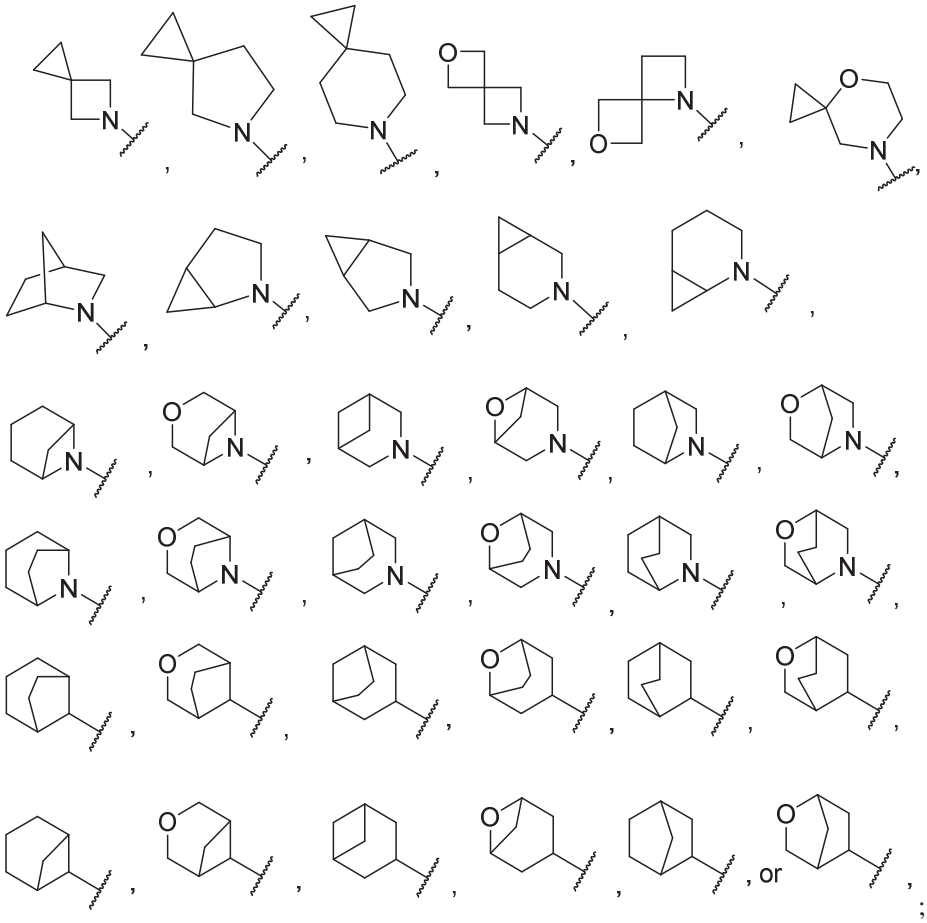
[0007e] In another aspect, the present disclosure refers to a use of the compound in accordance with the disclosure, or the pharmaceutically acceptable salt thereof, or the composition according to the disclosure in the manufacture of a medicament for treating a cell proliferation disorder in a subject.

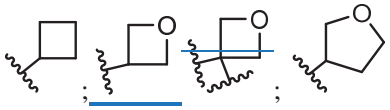
[0007f] In another aspect, the present disclosure refers to a ~~use of a~~ compound, or pharmaceutically acceptable salts thereof, in accordance with the disclosure, or the pharmaceutically acceptable salt thereof, or the composition according to the disclosure ~~in the manufacture of a medicament for inhibiting KIF18A in a cell~~for use in therapy.

~~**[0007g]** In another aspect, the present disclosure refers to a use of the compound or the pharmaceutically acceptable salt of said compound according to the disclosure, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to the disclosure, in the preparation of a medicament for treating a condition that may be treated with KIF18a inhibitors; wherein the 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.~~

[0008] The compounds provided by the disclosure have MT-based KIF18A modulatory activity and, in particular, KIF18A inhibitory activity. To this end, the disclosure 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 disclosure are

and R^{13} is morpholinyl, piperidinyl, azetidinyl, pyrrolidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperazinyl, tetrahydrofuranyl,



; wherein each said ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, CF_3, -OH, -$OCHF_2$, CN, and oxo; or (c) a group –Y-R^{13}, wherein Y is NH, -O-, -O-(CH_2)-, -O-(CH_2)-(CH_2)-, or -O-(CH_2)-(CH_2)-(CH_2)-, and wherein R^{13} is  ; or R^{13} is $C_{1\text{-}6}$alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, methyl, CF_3, -OH, or CN.

[0025] In example 17, the present disclosure provides compounds in accordance with examples 1-16, or pharmaceutically acceptable salts thereof, wherein R^2 is morpholinyl or piperidinyl substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, CF_3, -OH, -$OCHF_2$, CN, or oxo

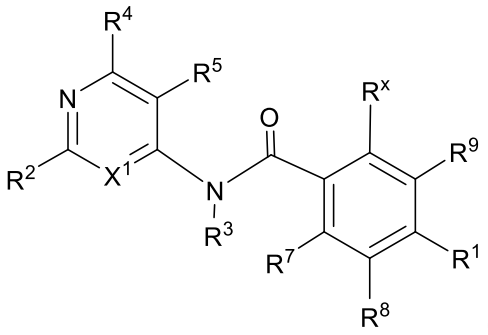
[0026] In example 18, the present disclosure provides compounds in accordance with examples 1-17, or pharmaceutically acceptable salts thereof, wherein R^2 is morpholinyl substituted by 1, 2 or 3 methyl group(s).

[0027] In example 19, the present disclosure provides compounds in accordance with examples 1-18, or pharmaceutically acceptable salts thereof, wherein R^2 is piperidinyl substituted by 1, 2 or 3 fluoro group(s).

[0028] In example 20, the present disclosure provides compounds in accordance with examples 1-19, or pharmaceutically acceptable salts thereof, wherein R^2 is

CLAIMS

1. A compound of formula I:



(I);

or any pharmaceutically-acceptable salt thereof, wherein:

X^1 is N or -CR^6;

R^1 is -CN, or a group -Z-R^{12} wherein Z is -C_{0-4}alk-, -NR^{11}-, -$NR^{11}SO_2$-, -SO_2NR^{11}-, -NR^{11}-S(=O)(=NH), -S(=O)(=NH)-, -S-, -S(=O)-, -SO_2-, C_{0-4}alk-O-, -(C=O)-, -(C=O)NR^{11}-,
-C=N(OH)-, or -NR^{11}(C=O); or

the group -Z-R^{12} is -N=S(=O)-$(R^{12})_2$, wherein the two R^{12} pair can alternatively combine with the sulfur atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, or 6-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0, 1, or 2 atoms selected from O and S;

R^2 is halo or a group –Y-R^{13}, wherein Y is -C_{0-4}alk-, -NH-C_{0-4}alkylene-, -$N(CH_3)$-C_{0-4}alkylene- ~~-N(C$_{0-1}$alk)-C$_{0-4}$alk-~~,
-C(=O)NR^a~~R~~^{a}(C_{1-4}alk), -O-C_{0-4}alk-, S, S=O, $S(=O)_2$, -SO_2NR^{13}, or -S(=O)(=NH)-;

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

R^4 is H, halo, R^{4a} or R^{4b};

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

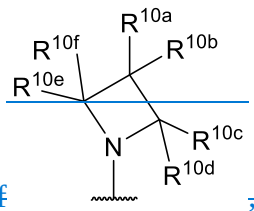
R^6 is H, halo, C_{1-8}alk, C_{1-4}haloalk, -O-C_{1-8}alk, or -O-$R^{6a;}$ wherein R^{6a} is a saturated or partially-saturated 3-, 4-, 5-, or 6-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0, 1, or 2 atoms selected from O and S;

R^7 is H, halo, C_{1-8}alk, or C_{1-4}haloalk;

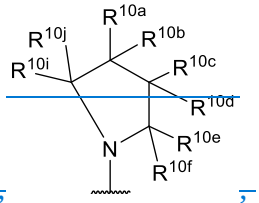
R^8 is H, halo, C_{1-8}alk, C_{1-4}haloalk, -OH, -O-R^{8a}, or -O-R^{8b};

R^9 is H, halo, C_{1-8}alk, or C_{1-4}haloalk;

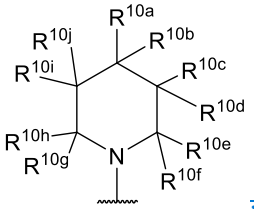
R^x is ~~selected from~~ the group represented by the following formula:~~consisting~~



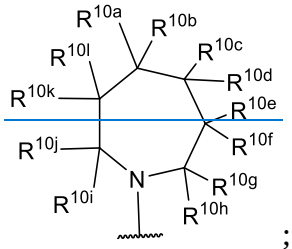
~~of~~ ~~;~~



~~;~~



~~, and~~



;

Each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, and R^{10j} is H, halo, R^{10k}, or R^{10l};

or alternatively, each of R^{10a} and R^{10b} pair, R^{10c} and R^{10d} pair, R^{10e} and R^{10f} pair, R^{10g} and R^{10h} pair, or R^{10i} and R^{10j} 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 R^x ring; wherein said 3-, 4-, 5-, 6-membered monocyclic ring contains 0, 1, 2 or 3 N atoms and 0, 1, or 2 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;

R^{11} is H, R^{11a}, or R^{11b};

R^{12} is H, R^{12a}, or R^{12b};

R^{13} is R^{13a} or R^{13b};

R^{4a}, R^{8a}, R^{10k}, R^{11a}, R^{12a}, and R^{13a} 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 ~~4-,~~ 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic ring containing 0, 1, 2 or 3 N atoms and 0, 1, or 2 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, -N

$R^aC_{2-6}alkOR^a$,

$-C_{1-6}alkNR^aR^a$, $-C_{1-6}alkOR^a$, $-C_{1-6}alkN(R^a)C(=O)R^b$, $-C_{1-6}alkOC(=O)R^b$, $-C_{1-6}alkC(=O)NR^aR^a$,

$-C_{1-6}alkC(=O)OR^a$, R^{14}, and oxo;

R^{4b}, R^{8b}, R^{10l}, R^{11b}, R^{12b}, and R^{13b} 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, $-OR^a$, $-OC_{1-4}haloalk$, or CN;

R^{14} 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 4-, 5-, 6-, 7-, 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, $-C(=O)R^b$, $-C(=O)OR^a$, $-C(=O)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-OC(=O)R^b$, $-OC(=O)NR^aR^a$,

$-OC_{2-6}alkNR^aR^a$, $-OC_{2-6}alkOR^a$, $-SR^a$, $-S(=O)R^b$, $-S(=O)_2R^b$, $-S(=O)_2NR^aR^a$, $-NR^aR^a$, $-N(R^a)C(=O)R^b$,

$-N(R^a)C(=O)OR^b$,$-N(R^a)C(=O)NR^aR^a$, $-N(R^a)C(=NR^a)NR^aR^a$, $-N(R^a)S(=O)_2R^b$, $-N(R^a)S(=O)_2NR^aR^a$,

$-NR^aC_{2-6}alkNR^aR^a$, $-NR^aC_{2-6}alkOR^a$, $-C_{1-6}alkNR^aR^a$, $-C_{1-6}alkOR^a$, $-C_{1-6}alkN(R^a)C(=O)R^b$,

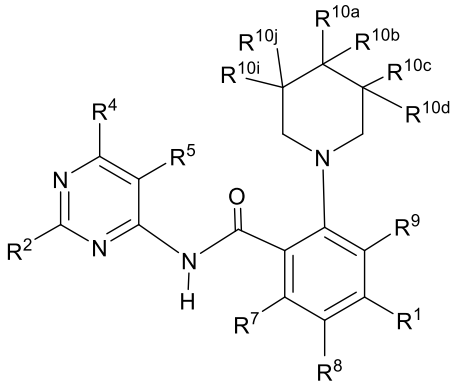
$-C_{1-6}alkOC(=O)R^b$, $-C_{1-6}alkC(=O)NR^aR^a$, $-C_{1-6}alkC(=O)OR^a$, and oxo;

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, $-OC_{1-4}alk$, $-NH_2$, $-NHC_{1-4}alk$,

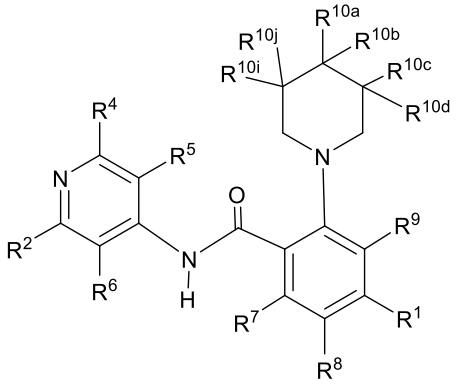
$-OC(=O)C_{1-4}alk$, or $-N(C_{1-4}alk)C_{1-4}alk$; and the phenyl or benzyl is being substituted by 0, 1, 2 or 3 substituents selected from halo, $C_{1-4}alk$, $C_{1-3}haloalk$, -OH, $-OC_{1-4}alk$, $-NH_2$, $-NHC_{1-4}alk$, $-OC(=O)C_{1-4}alk$, or $-N(C_{1-4}alk)C_{1-4}alk$.

2. The compound of claim 1, or the pharmaceutically-acceptable salt thereof, wherein X^1 is N; having the formula (Ia):



(Ia).

3. The compound of claim 1, or the pharmaceutically-acceptable salt thereof, wherein X^1 is -CR^6; having the formula (Ib):

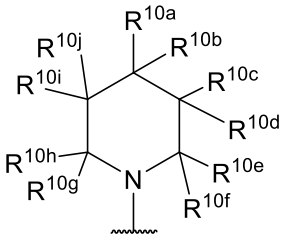


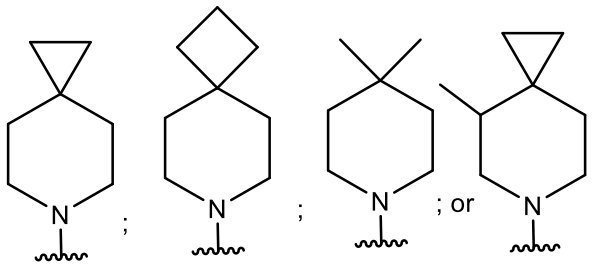
(Ib).

4. The compound of claim 1, or the pharmaceutically-acceptable salt thereof, wherein R^3 is H or methyl.

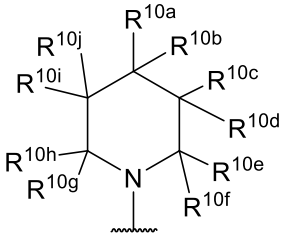
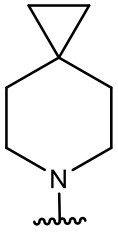
5. The compound of any one of claims 1 to 4, or the pharmaceutically-acceptable salt thereof, wherein each of R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, and R^{10j} is H, halo, $C_{1\text{-}6}$alk, or $C_{1\text{-}4}$haloalk; and each of R^{10a} and R^{10b} pair combine with the carbon atom attached to each of them form a saturated 3-, 4-, or 5-membered monocyclic ring spiro to the R^x ring; wherein said ring contains 0, 1, 2 or 3 N atoms and 0, 1, or 2 atoms selected from O and S.

6. The compound of any one of claims 1 to 5, or the pharmaceutically-acceptable salt thereof, wherein each of R^{10c}, R^{10d}, R^{10e}, R^{10f}, R^{10g}, R^{10h}, R^{10i}, and R^{10j} is H, methyl, or ethyl; and each of R^{10a} and R^{10b} pair combine with the carbon atom attached to each of them form a cyclopropyl, cyclobutyl, or cyclopentyl ring spiro to the R^x ring.

7. The compound of any one of claims 1 to 6, or the pharmaceutically-acceptable salt thereof, wherein the group  is selected from:



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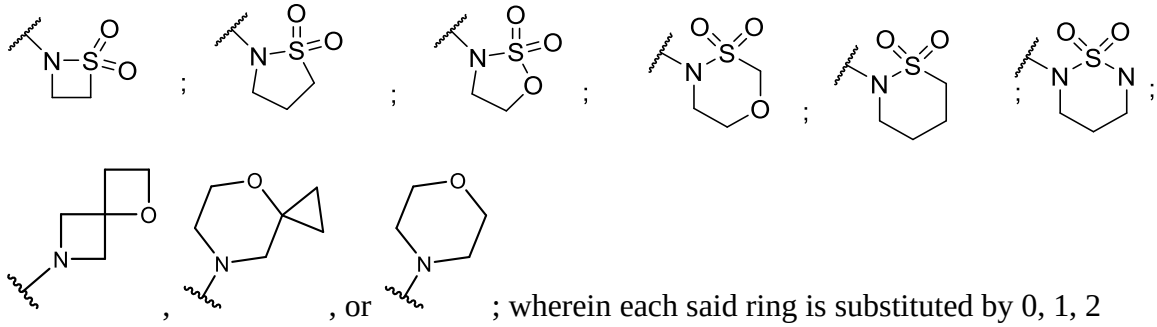
8. The compound of any one of claims 1 to 7, or the pharmaceutically-acceptable salt thereof, wherein the group  is .

9. The compound of any one of claims 1 to 8, or the pharmaceutically-acceptable salt thereof, wherein R^1 is -CN, or a group -Z-R^{12}, wherein Z is a bond, -NH-, -$NHSO_2$-, -SO_2NH-,
-S(=O)(=NH)-, -S-, -S(=O)-, -SO_2-, -(C=O)-, -(C=O)NH-, or -NH(C=O)-; and

R^{12} is selected from:

(a) H;

(b) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxiranyl, oxetanyl, tetrahydrofuranyl, azetidinyl, imidazolyl, morpholinyl, pyrrolidinyl, piperazinyl,



; wherein each said ring is substituted by 0, 1, 2 or 3 group(s) selected from wherein each ring is substituted by 0, 1, 2 or 3 OH, F,

methyl, -CH_2OH, ~~-C(=O)OCH_3,~~

-C(=O)$OC(CH_3)_3$, ~~NH_2,~~ and CN~~, and oxo~~; or

(c) C_{1-6}alk substituted by 0, 1, 2 or 3 OH, or F~~, -C(=O)OCH_3, -NH_2, -$NH(CH_3)$, or -$N(CH_3)_2$~~.

10. The compound of any one of claims 1 to 9, or the pharmaceutically-acceptable salt thereof, wherein R^1 is -CN, or a group -Z-R^{12}, wherein Z is a bond, -NH-, -$NHSO_2$-, -SO_2NH-,

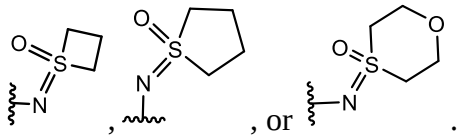
-S(=O)(=NH)-, -S-, -S(=O)-, -SO_2-, -(C=O)-, -(C=O)NH-, or -NH(C=O)-; and

(a) R^{12} is H;

(b) R^{12} is oxetanyl, cyclopropyl; or

(c) R^{12} is C_{1-6}alk substituted by 0, 1, 2 or 3 OH group(s).

11. The compound of any one of claims 1 to 8, or the pharmaceutically-acceptable salt thereof, wherein the group -Z-R^{12} is -N=S(=O)-$(R^{12})_2$, wherein the two R^{12} pair can alternatively combine with the sulfur atom attached to each of them to form a saturated or partially-saturated 3-, 4-, 5-, or 6-membered monocyclic ring containing 0, 1, 2 or 3 N atoms and 0, 1, or 2 atoms selected from O and S; which is selected from:



, , or .

12. The compound of any one of claims 1 to 10, or the pharmaceutically-acceptable salt thereof, wherein R^1 is a group -Z-R^{12}, wherein Z is -$NHSO_2$- or -SO_2NH-; and R^{12} is oxetanyl, cyclopropyl, or R^{12} is C_{1-6}alk substituted by 0, 1, 2 or 3 OH group(s).

13. The compound of any one of claims 1 to 10 or 12, or the pharmaceutically-acceptable salt thereof, wherein R^1 is a group -Z-R^{12}, wherein Z is -$NHSO_2$- and R^{12} is –CH_2-CH_2-OH.

14. The compound of any one of claims 1 to 13, or the pharmaceutically-acceptable salt thereof, wherein R^2 is halo or a group –Y-R^{13}, wherein Y is a bond, -NH-, -NH-$(CH_2)_{0-4}$-, or -O-$(CH_2)_{0-4}$; and

R^{13} is a saturated, partially-saturated or unsaturated 3-, 4-, 5-, 6-, or 7-membered monocyclic or

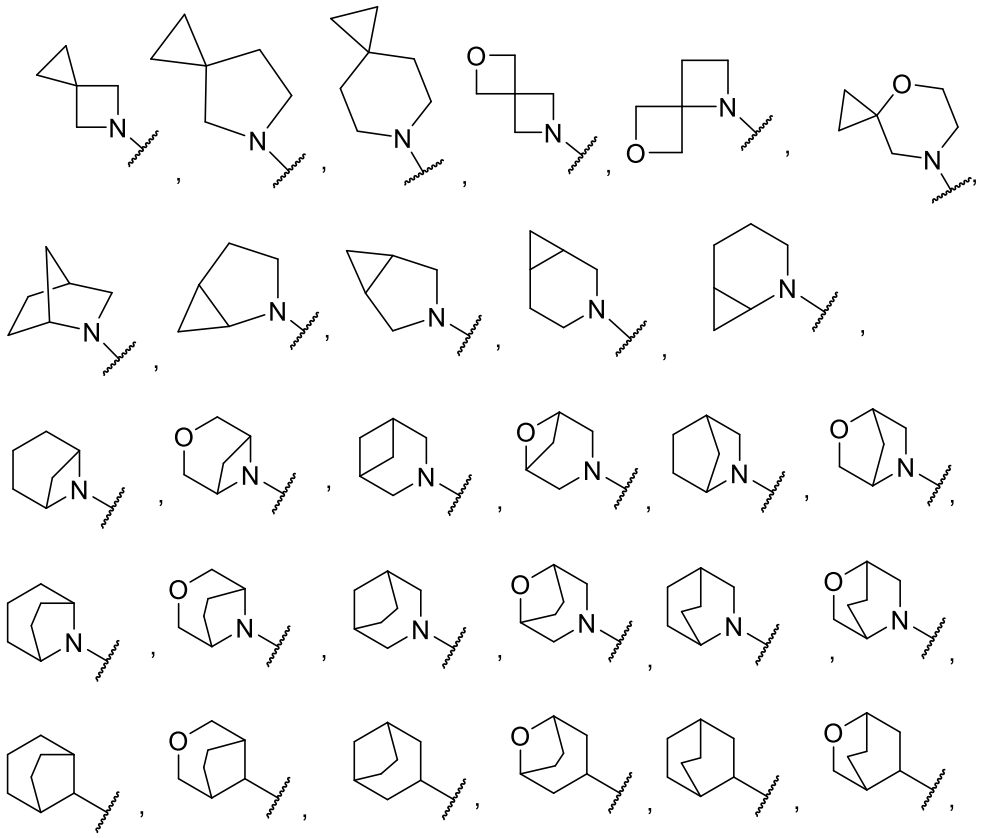
4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic ring containing 0, 1, 2 or 3 N atoms and 0 or 1 atoms selected from O and S, which is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, -OH, -OC_{1-4}haloalk, CN, R^{14}, and oxo; or

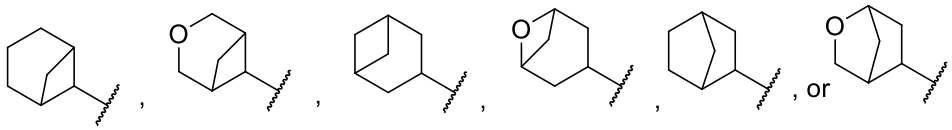
R^{13} is C_{1-6}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, -OH, -OC_{1-4}haloalk, or CN.

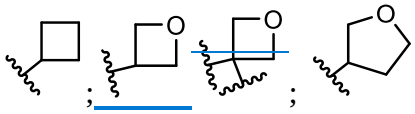
15. The compound of any one of claims 1 to 14, or the pharmaceutically-acceptable salt thereof, wherein R^2 is a saturated 5- or 6-membered monocyclic ring wherein each said ring contains 0, 1, or 2 N atoms and 0 or 1 O atom, and wherein each said ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, C_{1-6}alk, C_{1-4}haloalk, -OH, -OC_{1-4}haloalk, CN, R^{14}, and oxo.

16. The compound of any one of claims 1 to 15, or the pharmaceutically-acceptable salt thereof, wherein

R^2 is (a) halo; (b) a group –Y-R^{13}, wherein Y is a bond; and R^{13} is morpholinyl, piperidinyl, azetidinyl, pyrrolidinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperazinyl, tetrahydrofuranyl,




; wherein each said ring is substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, ~~methyl, CF_3,~~ -OH, $-OCHF_2$, CN, and oxo; or

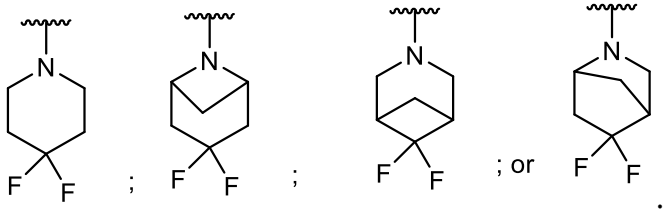
(c) a group –Y-R^{13}, wherein Y is NH, -O-, $-O-(CH_2)-$, $-O-(CH_2)-(CH_2)-$, or $-O-(CH_2)-(CH_2)-(CH_2)-$, and wherein R^{13} is 
; or R^{13} is C_{1-6}alk substituted by 0, 1, 2, 3, 4, or 5 group(s) selected from F, Cl, Br, ~~methyl, CF_3,~~ -OH, or CN.

17. The compound of any one of claims 1 to 16, or the pharmaceutically-acceptable salt thereof, wherein R^2 is morpholinyl or piperidinyl substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, methyl, CF_3, -OH, $-OCHF_2$, CN, or oxo.

18. The compound of any one of claims 1 to 17, or the pharmaceutically-acceptable salt thereof, of any one of claims 1-4, or the pharmaceutically-acceptable salt thereof, wherein R^2 is morpholinyl substituted by 1, 2 or 3 methyl group(s).

19. The compound of any one of claims 1 to 17, or the pharmaceutically-acceptable salt thereof, wherein R^2 is piperidinyl substituted by 1, 2 or 3 fluoro group(s).

20. The compound of any one of claims 1 to 16, or the pharmaceutically-acceptable salt thereof, wherein R^2 is


.

21. The compound of any one of claims 1 to 13, or the pharmaceutically-acceptable salt thereof, wherein Z is a bond, -NH-, $-NHSO_2-$, $-SO_2NH-$, -S(=O)(=NH)-, -S-, -S(=O)-, $-SO_2-$, -(C=O)-, -(C=O)NH-, or -NH(C=O)-.

22. The compound of any one of claims 1 to 13 or 21, or the pharmaceutically-acceptable salt thereof, wherein R^{12} is selected from (a) H; (b) C_{1-6}alk substituted by 0, 1, 2 or 3 group(s) selected from F, Cl, Br, -OH, or $-OCH_3$, ~~or cyclopropyl~~; 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, $C_{1\text{-}6}$alk, $C_{1\text{-}4}$haloalk, -$C_{1\text{-}6}$alkOH,
-OH, -OCH_3, -NH_2, or oxo.

23. The compound of any one of claims 1 to 13 or 21 to 22, or the pharmaceutically-acceptable salt thereof, wherein R^{12} is selected from cyclopropyl, cyclobutyl, cyclopentyl, oxetanyl, azetidinyl, tetrahydrofuranyl, or 1,3,4-oxathiazinanyl.

24. The compound of any one of claims 1 to 23, or the pharmaceutically-acceptable salt thereof, wherein R^4 is selected from (a) H; (b) $C_{1\text{-}6}$alk substituted by 0, 1, 2 or 3 OH group(s); or (c) cyclopropyl.

25. The compound of any one of claims 1 to 24, or the pharmaceutically-acceptable salt thereof, wherein R^4 is H or methyl.

26. The compound of any one of claims 1 to 25, or the pharmaceutically-acceptable salt thereof, wherein R^5 is H.

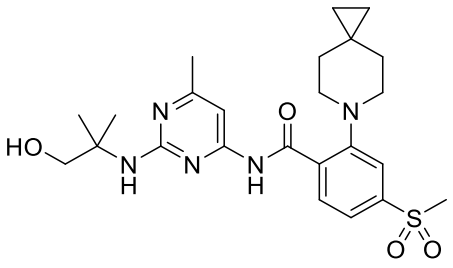
27. The compound of any one of claims 1 or 3 to 26, or the pharmaceutically-acceptable salt thereof, wherein R^6 is H or F.

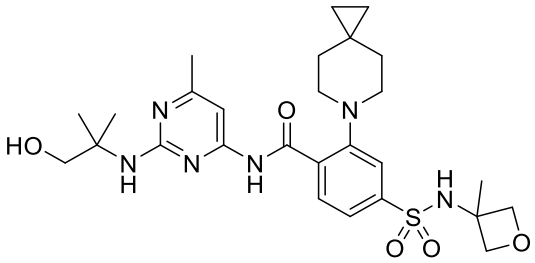
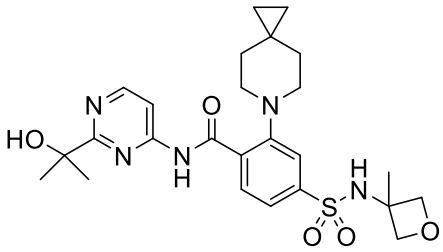
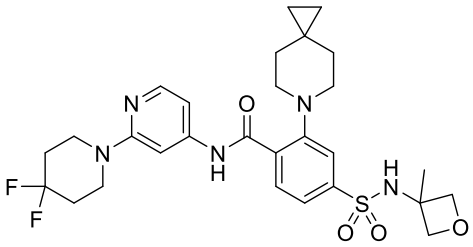
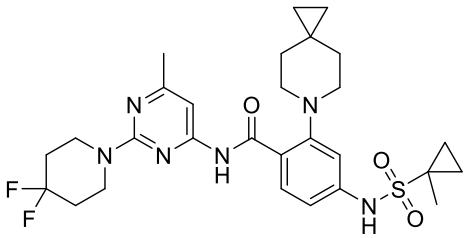
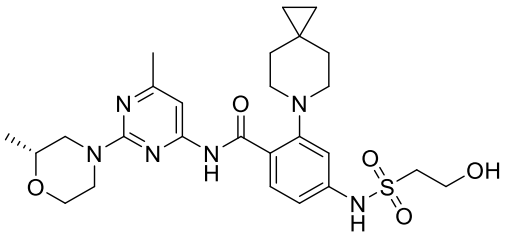
28. The compound of any one of claims 1 to 27, or the pharmaceutically-acceptable salt thereof, wherein R^7 is H or F.

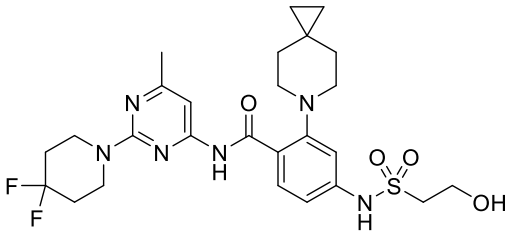
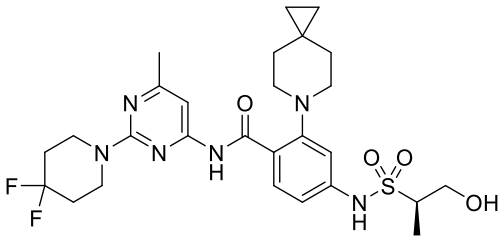
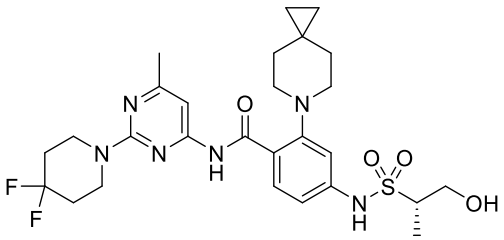
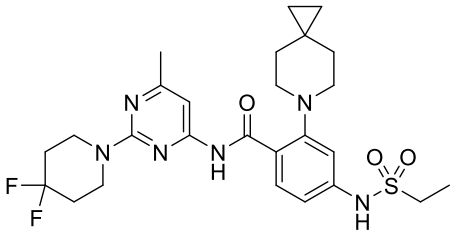
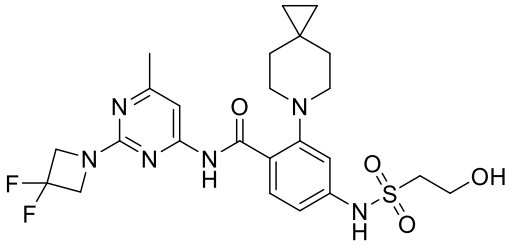
29. The compound of any one of claims 1 to 28, or the pharmaceutically-acceptable salt thereof, wherein R^8 is H.

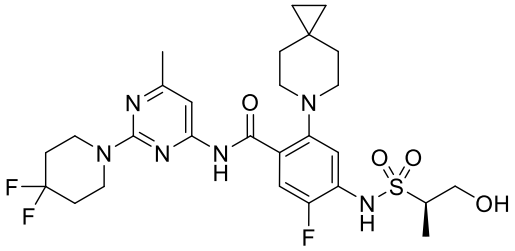
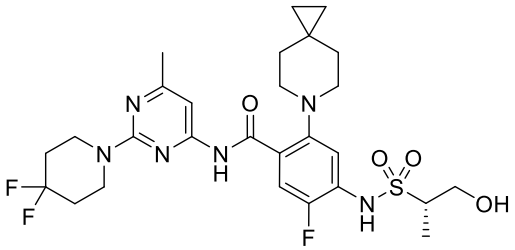
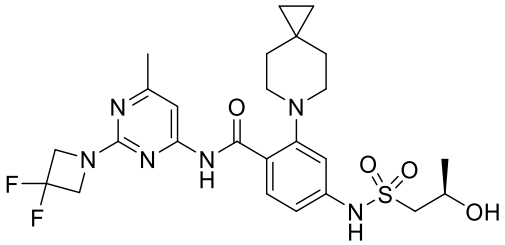
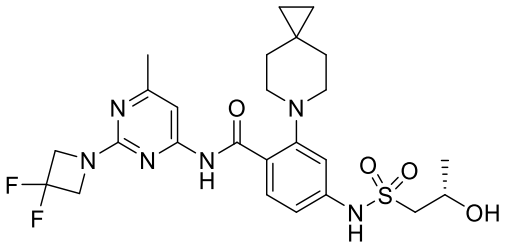
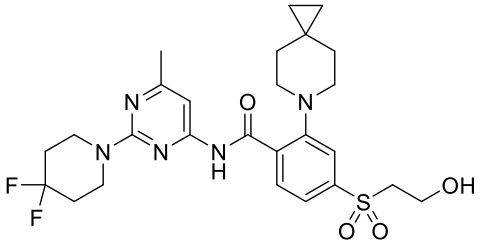
30. The compound of any one of claims 1 to 29, or the pharmaceutically-acceptable salt thereof, wherein R^9 is H.

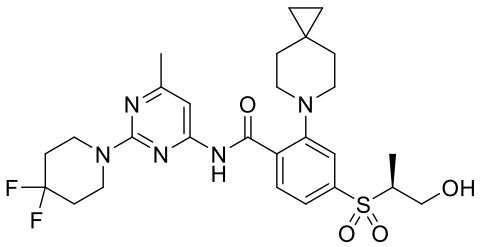
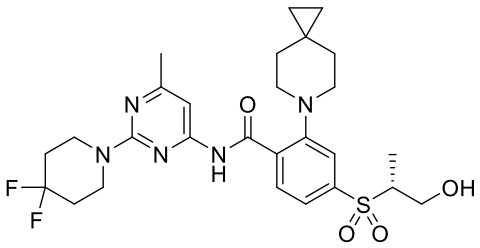
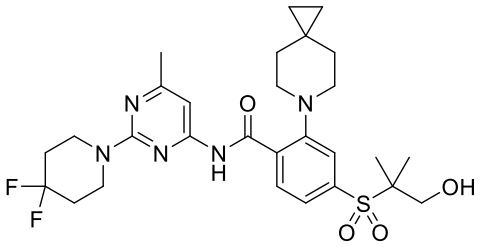
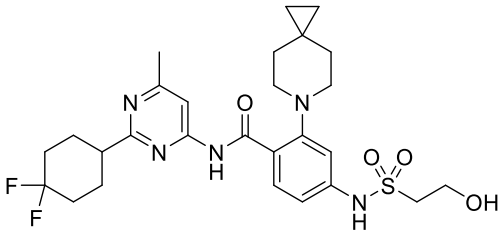
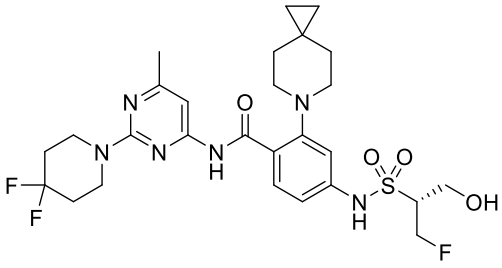
31. The compound of any one of claims 1 to 30, selected from:

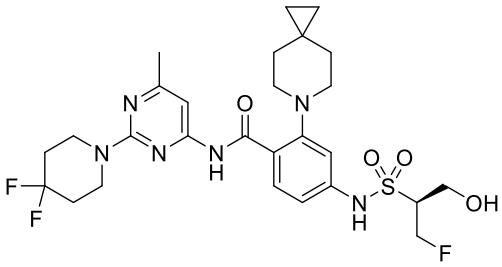
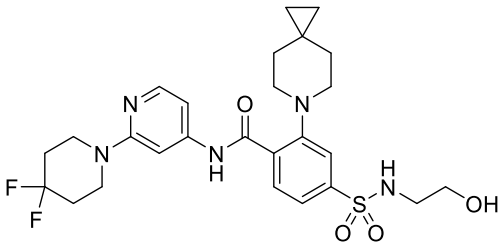
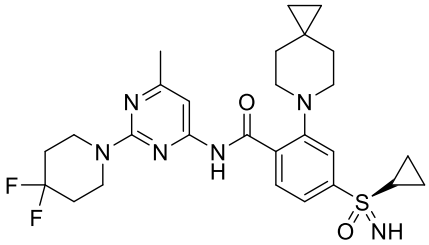
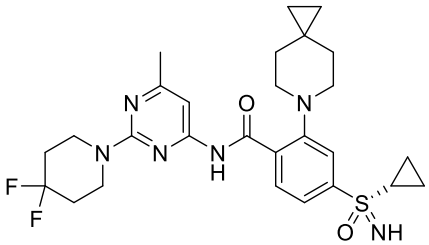
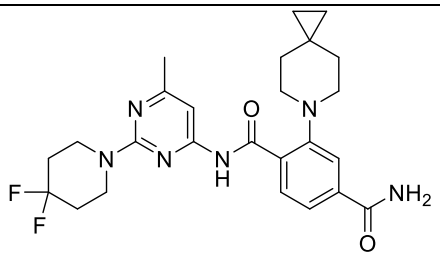
Ex. #	Chemical Structure	Name
1		*N*-(2-((1-Hydroxy-2-methylpropan-2-yl)amino)-6-methylpyrimidin-4-yl)-4-(methylsulfonyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

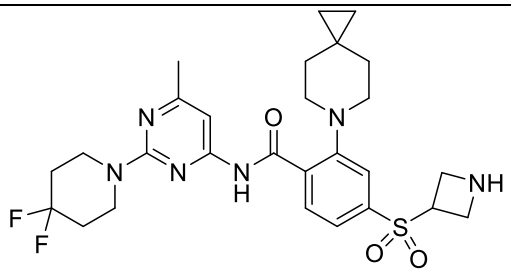
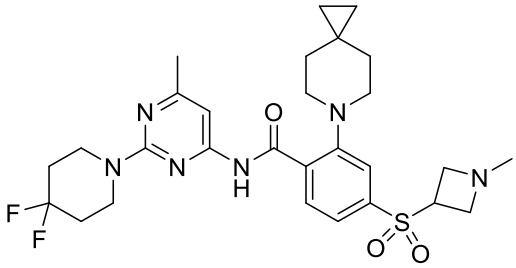
Ex. #	Chemical Structure	Name
1-7		N-(2-((1-hydroxy-2-methylpropan-2-yl)amino)-6-methylpyrimidin-4-yl)-4-(N-(3-methyloxetan-3-yl)sulfamoyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
2		*N*-(2-(2-Hydroxypropan-2-yl)pyrimidin-4-yl)-4-(*N*-(3-methyloxetan-3-yl)sulfamoyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
2-4		*N*-(2-(4,4-Difluoropiperidin-1-yl)pyridin-4-yl)-4-(*N*-(3-methyloxetan-3-yl)sulfamoyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
2-8		*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((1-methylcyclopropane)-1-sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
3		(*R*)-4-((2-Hydroxyethyl)sulfonamido)-*N*-(6-methyl-2-(2-methylmorpholino)pyrimidin-4-yl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

Ex. #	Chemical Structure	Name
4		*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
5-1		(*R*)-*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxy-1-methylethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
5-2		(*S*)-*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxy-1-methylethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
6-7		*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-(ethylsulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
7		*N*-(2-(3,3-Difluoroazetidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

Ex. #	Chemical Structure	Name
8-1		(*R*)-*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-5-fluoro-4-((2-hydroxy-1-methylethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
8-2		(*S*)-*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-5-fluoro-4-((2-hydroxy-1-methylethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
10-1		(*R*)-*N*-(2-(3,3-Difluoroazetidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxypropyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
10-2		(*S*)-*N*-(2-(3,3-Difluoroazetidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxypropyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
12		*N*-(2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxyethyl)sulfonyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

Ex. #	Chemical Structure	Name
13-1		(*S*)-*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((1-hydroxypropan-2-yl)sulfonyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
13-2		(*R*)-*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((1-hydroxypropan-2-yl)sulfonyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
14		*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((1-hydroxy-2-methylpropan-2-yl)sulfonyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
15		*N*-(2-(4,4-Difluorocyclohexyl)-6-methylpyrimidin-4-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
16-1		(*R*)-*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-fluoro-1-(hydroxymethyl)ethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

Ex. #	Chemical Structure	Name
16-2		(*S*)-*N*-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-fluoro-1-(hydroxymethyl)ethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
17		*N*-(2-(4,4-Difluoropiperidin-1-yl)pyridin-4-yl)-4-(N-(2-hydroxyethyl)sulfamoyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
18-1		2-(6-Azaspiro[2.5]octan-6-yl)-4-(*R*-cyclopropylsulfonimidoyl)-*N*-(2-(4,4-difluoro-1-piperidinyl)-6-methyl-4-pyrimidinyl)benzamide
18-2		2-(6-Azaspiro[2.5]octan-6-yl)-4-(*S*-cyclopropylsulfonimidoyl)-*N*-(2-(4,4-difluoro-1-piperidinyl)-6-methyl-4-pyrimidinyl)benzamide
20		(N^1-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-2-(6-azaspiro[2.5]octan-6-yl)terephthalamide

Ex. #	Chemical Structure	Name
21		4-(Azetidin-3-ylsulfonyl)-*N*-(2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide
22		*N*-(2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((1-methylazetidin-3-yl)sulfonyl)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

; or any pharmaceutically-acceptable salt thereof.

32. A pharmaceutical composition comprising the compound according to any one of claims 1 to 31, or the pharmaceutically acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

33. Use of a ~~KIF18a inhibitors~~compound in accordance with any one of claims 1 to 31, or the pharmaceutical composition according to claim 32 in the preparation of a medicament for treating a condition, 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~~ and (f) a melanoma,

seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer or Kaposi's sarcoma.

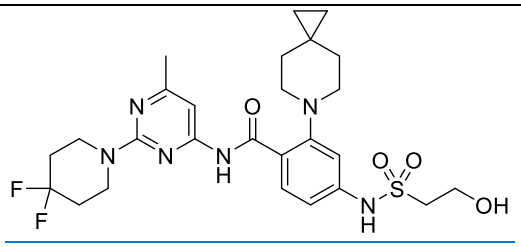
34. Use of the compound in accordance with any one of claims 1 to 31, or the pharmaceutically acceptable salt thereof, or the composition according to claim 32 in the manufacture of a medicament for reducing the size of a solid tumor in a subject.

35. Use of the compound in accordance with any one of claims 1 to 31, or the pharmaceutically acceptable salt thereof, or the composition according to claim 32 in the manufacture of a medicament for treating a cell proliferation disorder in a subject.

36. ~~Use of a~~A compound, or pharmaceutically acceptable salts thereof, in accordance with any one of claims 1 to 31, or the pharmaceutically acceptable salt thereof, or the composition according to claim 32 ~~in the manufacture of a medicament for inhibiting KIF18A in a cell~~for use in therapy.

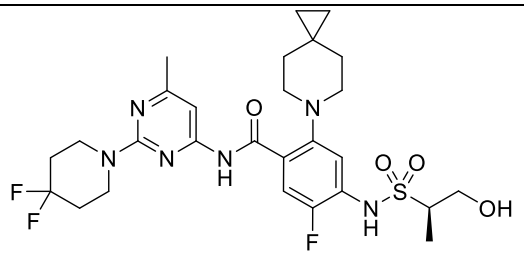
~~37. Use of the compound or the pharmaceutically acceptable salt of said compound according to any one of claims 1 to 31, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to Claim 32, in the preparation of a medicament for treating a condition that may be treated with KIF18a inhibitors; wherein the 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.~~

37. The compound of claim 1, which is:

4		N-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

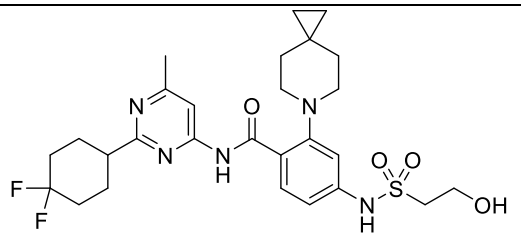
or the pharmaceutically acceptable salt thereof.

38. The compound of claim 1, which is:

8-1		(R)-N-(2-(4,4-Difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl)-5-fluoro-4-((2-hydroxy-1-methylethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

or the pharmaceutically acceptable salt thereof.

39. The compound of claim 1, which is:

15		N-(2-(4,4-Difluorocyclohexyl)-6-methylpyrimidin-4-yl)-4-((2-hydroxyethyl)sulfonamido)-2-(6-azaspiro[2.5]octan-6-yl)benzamide

or the pharmaceutically acceptable salt thereof.