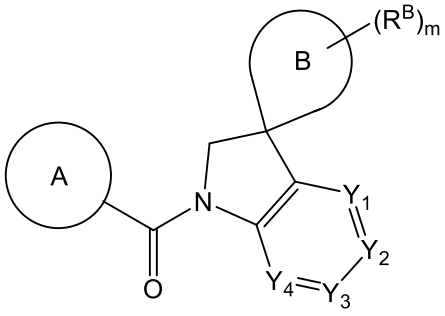
CIN-high (but not CIN-low), aneuploid and whole-genome doubled cells vulnerable to death. Cellular toxicity assay in isogenic cell lines confirmed the enhanced sensitivity of CIN-high cells to KIF18A inhibitors. Ongoing in vivo mouse models using KIF18A inhibitor or knockdown demonstrated effect of inhibited tumor growth. Thus, there is a need for new compounds for use in treating diseases mediated by KIF18A.

BRIEF SUMMARY

[0003a] In an aspect of the present disclosure, there is provided a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

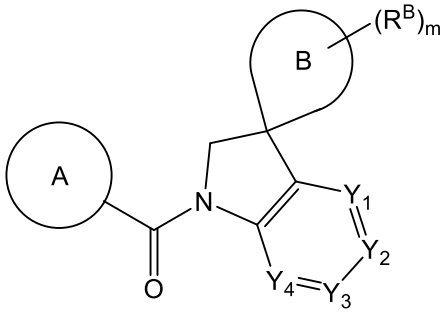
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18,}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0003b] In another aspect of the present disclosure, there is provided a compound of Formula (I-2):



(I-2),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

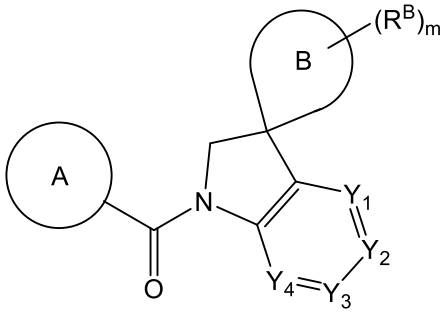
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0003c] In a further aspect of the present disclosure, there is provided a compound of Formula (I-1):



(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, and $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$;

R^{a1}-R^{a20} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10}

cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

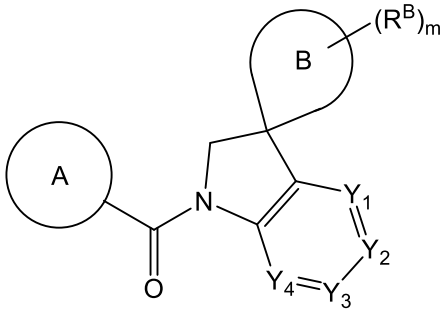
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0003d] In another aspect of the present disclosure, there is provided a compound of Formula (I-3):



(I-3),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10}

cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C_{3-7} cycloalkyl;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

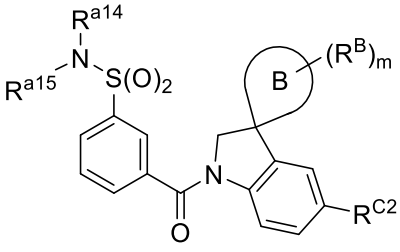
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18,}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0003e] In a further aspect of the present disclosure, there is provided a compound of Formula (Ia1):



(Ia1),

or a pharmaceutically acceptable salt thereof, wherein:

R^{a14} and R^{a15} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

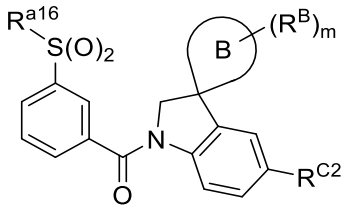
each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

R^{C2} is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

[0003f] In another aspect of the present disclosure, there is provided a compound of Formula (Ia2):



(Ia2),

or a pharmaceutically acceptable salt thereof, wherein:

R^{a16} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

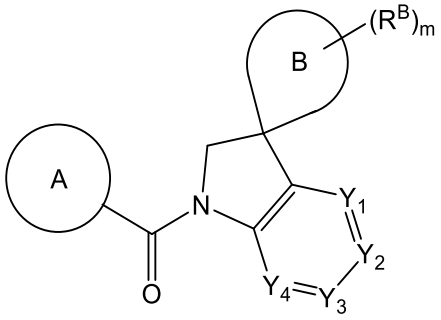
each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

R^{C2} is halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18,}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

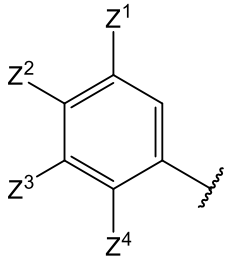
[0003g] In a further aspect of the present disclosure, there is provided a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is

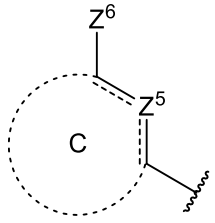
(i) 

, wherein Z^1, Z^2, Z^3, and Z^4 are each independently hydrogen or R^D, wherein R^D is halo, -OH, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, $-P(O)(R^{a23})(R^{a24})$, $-C=NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl,

provided that

(1) when Z^4 is hydrogen, then at least one of Z^1 and Z^3 is R^D; and

(2) when Z^4 is R^D, then Z^1 is R^D, or

(ii) 

, wherein


is a single bond or a double bond,

Z^5 is C-H, N, O, S, or N-X, wherein X is H or C_{1-6}alkyl;

Z^6 is $-NR^{a26}C(O)NR^{a27}R^{a28}$, $-NR^{a29}C(O)OR^{a30}$, $-N=S(O)R^{a31}R^{a32}$, $-S(O)R^{a33}$, $-S(O)(NR^{a34})R^{a35}$, $-S(O)_2NR^{a36}R^{a37}$, $-S(O)_2R^{a38}$, $-SR^{a39}$, 3- to 10-membered heterocycloalkyl, $-C(O)R^{a40}$, or $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo, and

ring C is 5- to 6-membered heteroaryl optionally substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl, or two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl;

R^{a4}-R^{a40} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo or C_{1-6} alkyl optionally substituted with one or more halo; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together to form a $=CR^{1a3}R^{1a4}$ group, wherein R^{1a3} and R^{1a4} are each independently hydrogen or C_{1-6} alkyl;

m is 0, 1, 2, 3, or 4;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

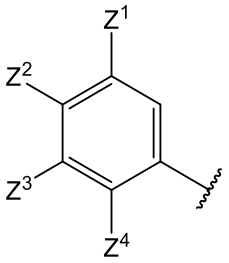
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

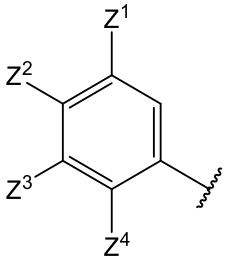
R^{C1}-R^{C4} are each independently hydrogen or R^F, wherein R^F is halo, cyano, -OH, -NO_2, -$C(O)NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -$P(O)R^{c7}R^{c8}$, -$N{=}S(O)R^{c9}R^{c10}$, -$S(O)(NR^{c11})R^{c12}$, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18,}$ -O-$S(O)_2R^{c19}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of halo and -OH, and

R^{c1}-R^{c19} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -O(C_{1-6} alkyl), - NHC(O)(C_{1-6} alkyl), and -OH;

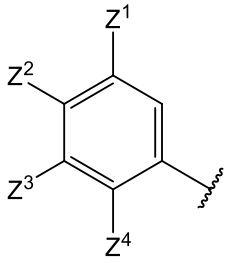
provided that

(1) when ring B is unsubstituted cyclopentyl, then ring A is 

, wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) substituted with one or more halo,

(2) when ring B is unsubstituted cyclohexyl and ring A is 

, then at least one of R^{C1}-R^{C4} is R^F, and

(3) when ring B is 5- to 7-membered heterocycloalkyl optionally substituted with 1-4 R^B, then ring A is 

, wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) optionally substituted with one or more halo.

[0003h] In another aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of compounds of **Table 1**.

[0003i] In a further aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of compounds of **Table 2**.

[0003j] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

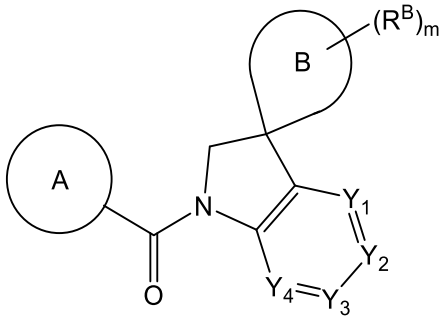
[0003k] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting KIF18A, wherein a cell is to be contacted with the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition.

[0003l] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease or condition mediated by KIF18A in a subject in need thereof.

[0003m] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0003n] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in therapy.

[0004] The present disclosure provides compounds of Formula (I), compositions thereof, and methods of using said compounds and compositions thereof for the treatment of diseases or conditions associated with KIF18a. In one example, provided is a compound of Formula (I):

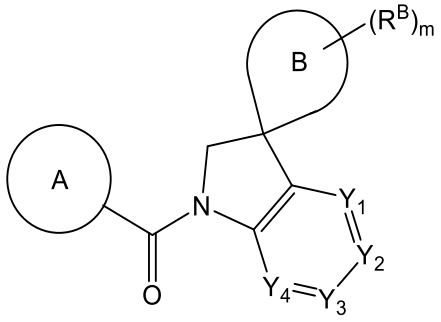


(I),

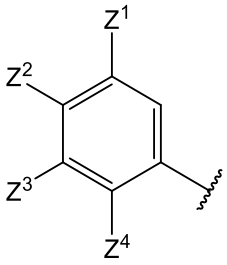
or a pharmaceutically acceptable salt thereof, wherein: ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo; R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, $-O(C_{1-6}$ alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, $-S(C_{1-6}$ alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and $-O(C_{1-6}$ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon; each R^B

group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl; m is 0, 1, 2, 3, or 4; Y^1 is N or CR^{C1}; Y^2 is N or CR^{C2}; Y^3 is N or CR^{C3}; Y^4 is N or CR^{C4}; wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N; R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH; R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

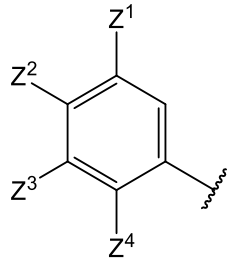
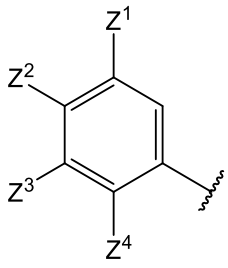
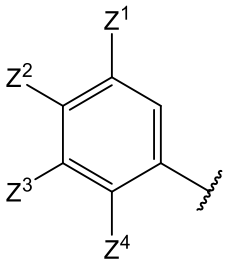
[0005] In another example, provided is a compound of Formula (II):



(II),



or a pharmaceutically acceptable salt thereof, wherein: ring A is (i) , wherein Z^1, Z^2, Z^3, and Z^4 are each independently hydrogen or R^D, wherein R^D is halo, -OH, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, $-P(O)(R^{a23})(R^{a24})$, $-C=NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl, provided that (1) when Z^4 is hydrogen, then at least one of Z^1 and Z^3 is R^D; and (2) when Z^4

with one or more substituents independently selected from the group consisting of halo and -OH, and R^{c1}-R^{c19} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -O(C_{1-6} alkyl), -NHC(O)(C_{1-6} alkyl), and -OH; provided that (1) when ring B is unsubstituted cyclopentyl, then ring A is , wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) substituted with one or more halo, (2) when ring B is unsubstituted cyclohexyl and ring A is , then at least one of R^{C1}-R^{C4} is R^F, and (3) when ring B is 5- to 7-membered heterocycloalkyl optionally substituted with 1-4 R^B, then ring A is , wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) optionally substituted with one or more halo.

[0006] In another example, provided is pharmaceutical composition comprising a compound of Formula (I), Formula (I-1), Formula (Ia1), Formula (Ia2), Formula (I-3), Formula (Ia1), Formula (Ia2), or Formula (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0007] In another example, provided herein is a method of inhibiting KIF18A comprising contacting a cell with an effective amount of a compound or a pharmaceutical composition as described herein.

[0008] In another example, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically

effective amount of a compound or a pharmaceutical composition as described herein. In some examples, the disease or condition is mediated by KIF18A. In some examples, the disease or condition is cancer. In some examples, the disease or condition is a cellular proliferation disorder.

DESCRIPTION OF FIGURES

[0009] **Figures 1A-1E** show graphs of tumor volume of vehicle- and compound-treated mice plotted as a function of time after start of treatment.

[0010] **Figure 1A** shows Compound **22** (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of HCC15 implanted SCID Beige mice.

[0011] **Figure 1B** shows Compound **22** (10 mg/kg QD, 30 mg/kg QD, 60 mg/kg QD) treatment of OVCAR-3 implanted Balb/C nude mice.

[0012] **Figure 1C** shows Compound **134** (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of HCC15 implanted SCID Beige mice.

[0013] **Figure 1D** shows Compound **134** (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of OVCAR-3 implanted Balb/C nude mice.

[0014] **Figure 1E** shows Compound **134** (30 mg/kg BID, 30 mg/kg QD, 60 mg/kg QD) treatment of OVCAR-3 implanted Balb/C nude mice.

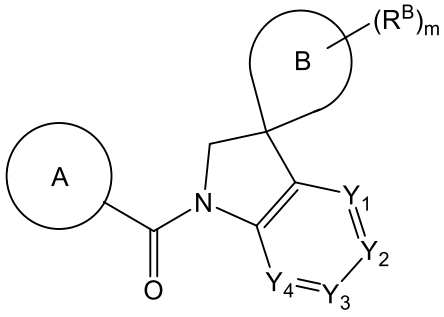
DETAILED DESCRIPTION

[0015] The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles defined herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Thus, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms

to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

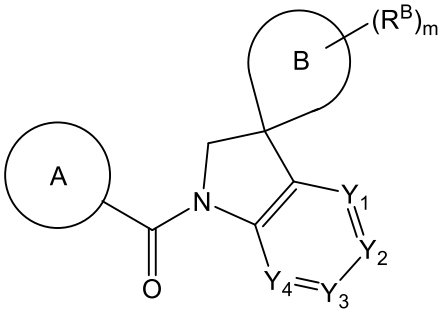
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N{=}S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

2. A compound of Formula (I-2):



(I-2),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10}

cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

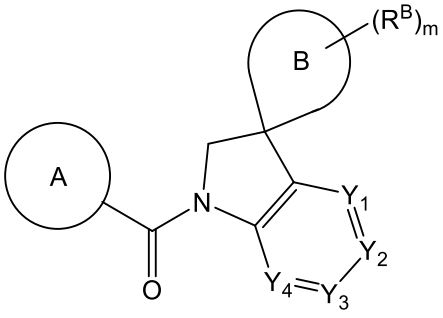
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c15} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

3. A compound of Formula (I-1):



(I-1),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, and $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$;

R^{a1}-R^{a20} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

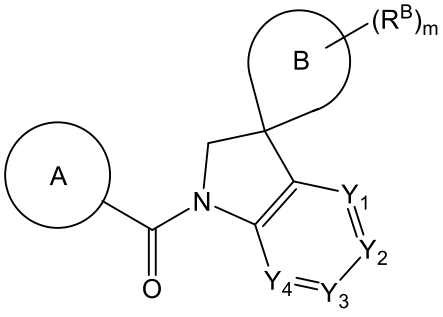
wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein the compound is not 4'-fluoro-1'-[3-(piperidine-1-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; 3-cyclopropyl-1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; 1-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]-3-(propan-2-yl)urea; [4-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]methanol; 4'-fluoro-1'-(1H-indole-5-carbonyl)-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; N-[3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]pyrimidin-2-amine; 4'-fluoro-1'-[3-(morpholine-4-sulfonyl)benzoyl]-1',2'-dihydrospiro[cyclopentane-1,3'-indole]; [3-({4'-fluoro-1',2'-dihydrospiro[cyclopentane-1,3'-indol]-1'-yl}carbonyl)phenyl]urea; or salt of any of the foregoing.

5. A compound of Formula (I-3):



(I-3),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{6-14} aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C_{1-6} alkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, and C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C_{3-7} cycloalkyl;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

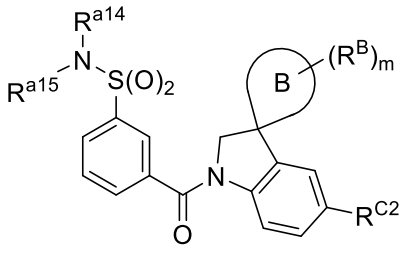
R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, $-NO_2$, $-C(O)NR^{c1}R^{c2}$, $-NR^{c3}R^{c4}$, $-NR^{c5}S(O)_2R^{c6}$, $-P(O)R^{c7}R^{c8}$, $-N=S(O)R^{c9}R^{c10}$, $-S(O)(NR^{c11})R^{c12}$, $-S(O)_2R^{c13}$, $-NR^{c14}C(O)OR^{c15}$, $-NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18,}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted C_{6-14} aryl.

7. The compound of any one of the claims 1-6, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted phenyl.

8. A compound of Formula (Ia1):



(Ia1),

or a pharmaceutically acceptable salt thereof, wherein:

R^{a14} and R^{a15} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), =$CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

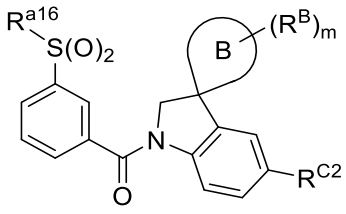
R^{C2} is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH; and R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

10. The compound of claim 8 or claim 9, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is -$NR^{c5}S(O)_2R^{c6}$, and R^{c5} and R^{c6} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

11. A compound of Formula (Ia2):



(Ia2),

or a pharmaceutically acceptable salt thereof, wherein:

R^{a16} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents

independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), =$CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

each R^B group is independently halo, C_{1-6} alkyl optionally substituted with one or more halo, or C_{2-6} alkenyl; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl;

m is 0, 1, 2, 3, or 4;

R^{C2} is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18,}$ or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is halo, cyano, -OH, -NO_2, -C(O)$NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -P(O)$R^{c7}R^{c8}$, -N=S(O)$R^{c9}R^{c10}$, -S(O)(NR^{c11})R^{c12}, -$S(O)_2R^{c13}$, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH, and R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

13. The compound of claim 11 or claim 12, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is -$NR^{c5}S(O)_2R^{c6}$, and R^{c5} and R^{c6} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

14. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein ring A is optionally substituted 5- to 10-membered heteroaryl.

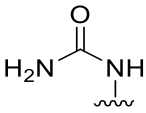
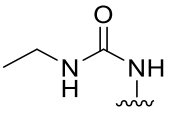
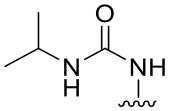
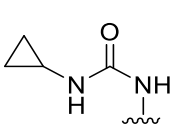
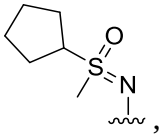
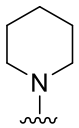
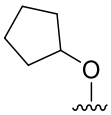
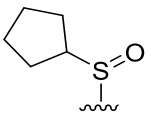
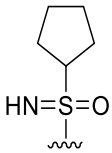
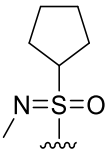
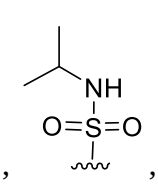
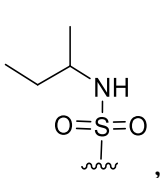
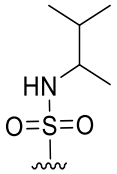
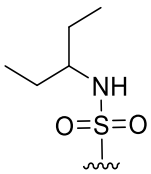
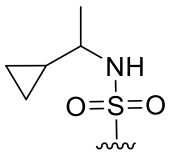
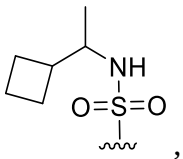
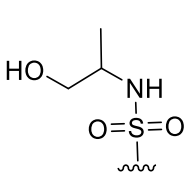
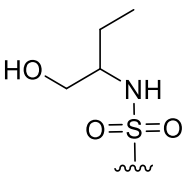
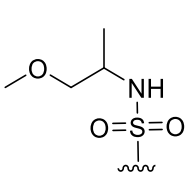
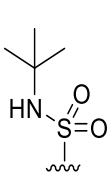
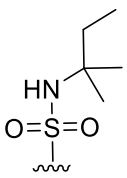
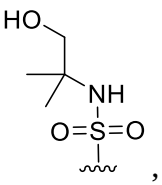
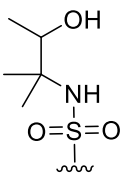
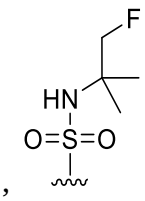
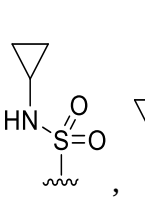
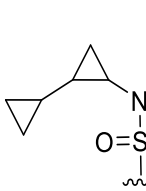
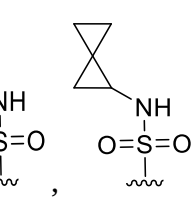
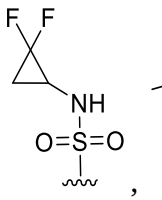
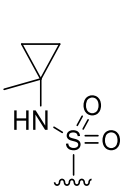
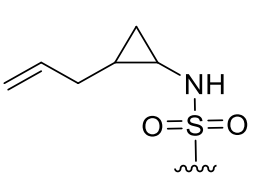
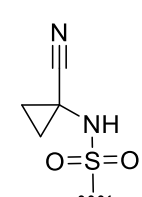
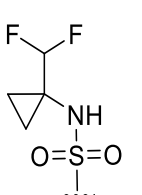
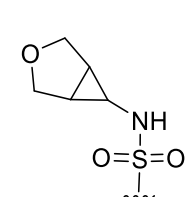
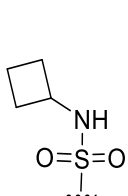
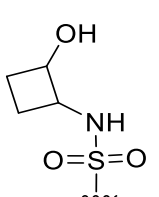
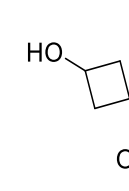
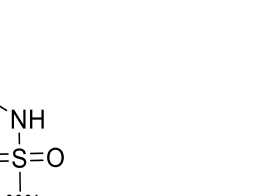
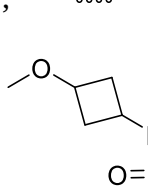
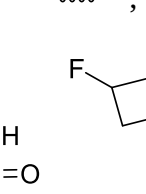
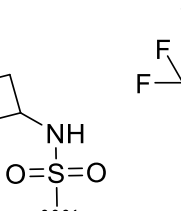
15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein ring A is indolyl, indazolyl, pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl, chromanyl, or quinolinyl, each optionally substituted.

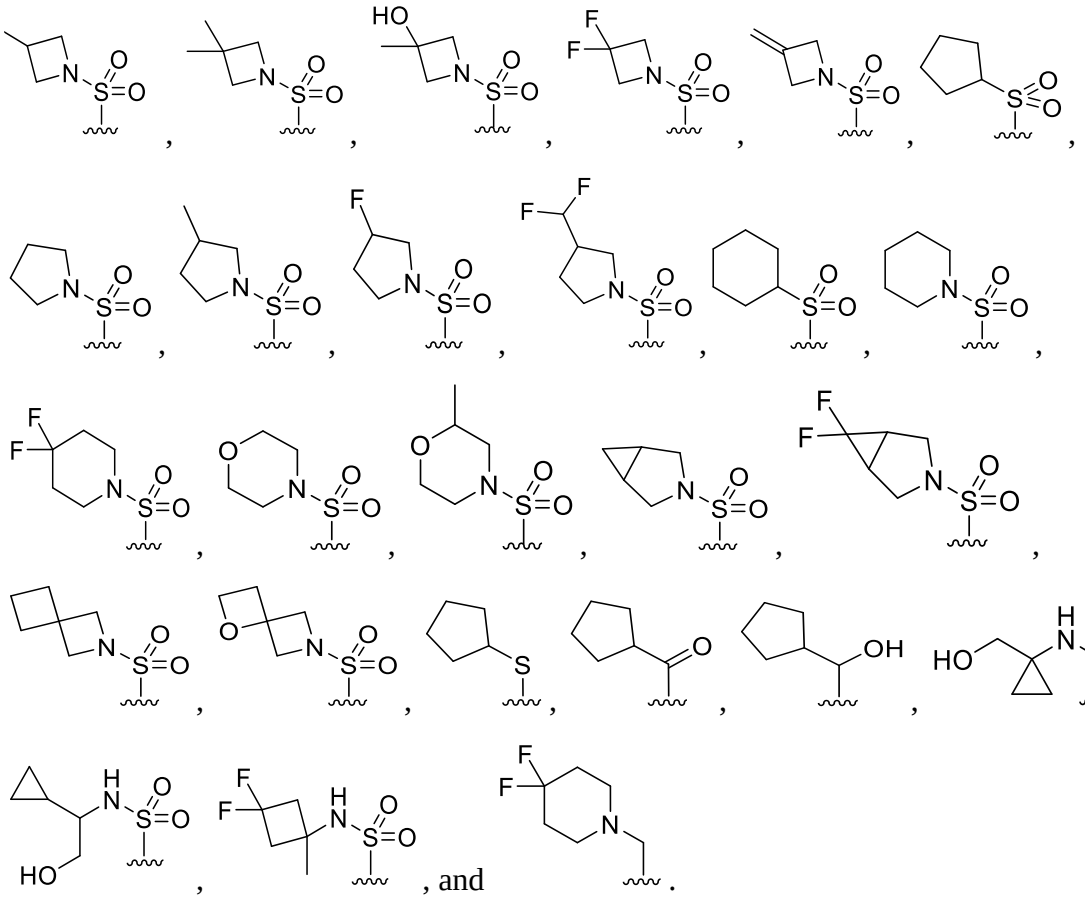
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein R^{a1} is hydrogen or C_{1-6} alkyl; R^{a2} and R^{a3} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a4} is hydrogen or C_{1-6} alkyl; R^{a5} is hydrogen or C_{1-6} alkyl; R^{a6} and R^{a7} are each independently hydrogen, C_{1-6} alkyl, or 5- to 12-membered heteroaryl optionally substituted with C_{1-6} alkyl; R^{a8} and R^{a9} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a10} is C_{3-10} cycloalkyl; R^{a11} is C_{3-10} cycloalkyl; R^{a12} is hydrogen or C_{1-6} alkyl; R^{a13} is C_{3-10} cycloalkyl; R^{a16} is C_{3-10} cycloalkyl or 3- to 12-membered heterocycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl or halo; R^{a17} and R^{a18} are each independently hydrogen or C_{1-6} alkyl; R^{a19} and R^{a20} are each independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl; R^{a21} is C_{3-10} cycloalkyl; and R^{a22} is C_{3-10} cycloalkyl.

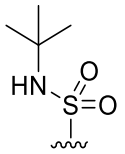
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, wherein R^{a14} and R^{a15} are each independently hydrogen; C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, -OH, -O(C_{1-6} alkyl), -S(C_{1-6} alkyl), and halo; C_{2-6} alkenyl; C_{3-10} cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of C_{2-6} alkenyl, C_{3-10} cycloalkyl, halo, cyano, -OH, -O(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of -OH, -O(C_{1-6} alkyl), and halo, wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl; C_{3-10} cycloalkenyl; or 3- to 12-membered heterocycloalkyl optionally substituted with one or more C_{1-6} alkyl.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein R^{a14} is hydrogen and R^{a15} is *tert*-butyl.

19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein ring A is substituted with one or more substituents independently selected from the

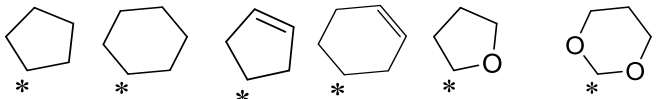
group consisting of fluoro, chloro, -OH, methyl, amino, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , .

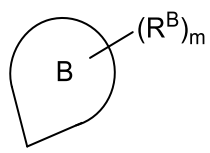


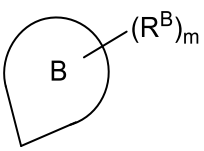
20. The compound of any one of claims 1-13 and 16-19, or a pharmaceutically acceptable salt thereof, wherein ring A is phenyl substituted with .

21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein ring B is C_{5-7} cycloalkyl.

22. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 7-membered heterocycloalkyl.

23. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein ring B is , wherein * denotes the point of attachment to the rest of Formula (I).

24. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein  of Formula (I) is , or wherein * denotes the point of attachment to the rest of Formula (I).

25. The compound of claim 21, or a pharmaceutically acceptable salt thereof, wherein  of Formula (I) is .

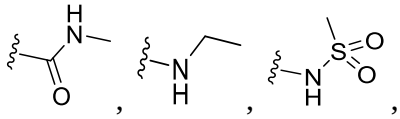
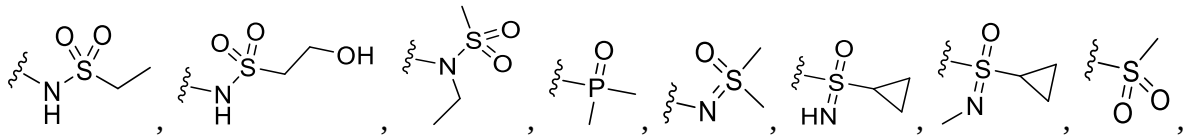
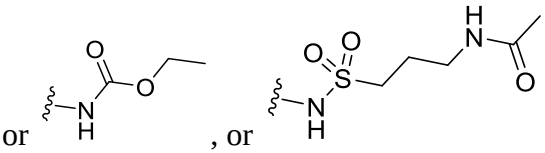
26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

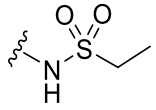
27. The compound of claim 26, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or $-NH_2$.

28. The compound of claim 26 or claim 27, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each hydrogen.

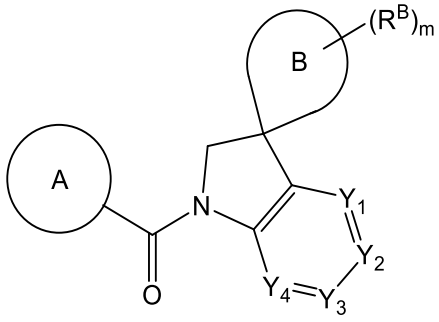
29. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

30. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

31. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is cyano, -OH, -CH_2OH, bromo, -NO_2, , , or .

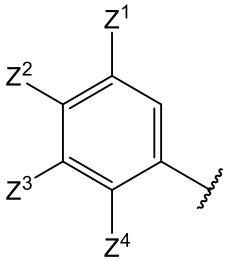
32. The compound of claim 31, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is .

33. A compound of Formula (II):


(II),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is

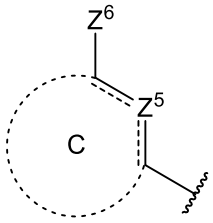
(i) , wherein Z^1, Z^2, Z^3, and Z^4 are each independently hydrogen or R^D, wherein R^D is halo, -OH, -$NR^{a4}C(O)OR^{a5}$, -$NR^{a6}R^{a7}$, -

$N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, $-P(O)(R^{a23})(R^{a24})$, $-C=NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl,

provided that

(1) when Z^4 is hydrogen, then at least one of Z^1 and Z^3 is R^D; and

(2) when Z^4 is R^D, then Z^1 is R^D, or

(ii) 

, wherein

 is a single bond or a double bond,

Z^5 is C-H, N, O, S, or N-X, wherein X is H or C_{1-6}alkyl;

Z^6 is $-NR^{a26}C(O)NR^{a27}R^{a28}$, $-NR^{a29}C(O)OR^{a30}$, $-N=S(O)R^{a31}R^{a32}$, $-S(O)R^{a33}$, $-S(O)(NR^{a34})R^{a35}$, $-S(O)_2NR^{a36}R^{a37}$, $-S(O)_2R^{a38}$, $-SR^{a39}$, 3- to 10-membered heterocycloalkyl, $-C(O)R^{a40}$, or $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo, and

ring C is 5- to 6-membered heteroaryl optionally substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl, or two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl;

R^{a4}-R^{a40} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), $=CR^{1a1}R^{1a2}$, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the

group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

each R^B group is independently halo or C_{1-6} alkyl optionally substituted with one or more halo; or two vicinal R^B groups are taken together with the carbon atoms to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together with the carbon atom to which they are attached to form C_{3-10} cycloalkyl; or two geminal R^B groups are taken together to form a $=CR^{1a3}R^{1a4}$ group, wherein R^{1a3} and R^{1a4} are each independently hydrogen or C_{1-6} alkyl;

m is 0, 1, 2, 3, or 4;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

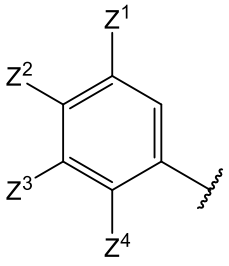
Y^4 is N or CR^{C4};

wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

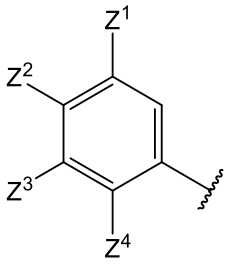
R^{C1}-R^{C4} are each independently hydrogen or R^F, wherein R^F is halo, cyano, -OH, -NO_2, -$C(O)NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -$P(O)R^{c7}R^{c8}$, -$N{=}S(O)R^{c9}R^{c10}$, -$S(O)(NR^{c11})R^{c12}$, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, -$NR^{c16}S(O)_2(CH_2)_{1-6}NR^{c17}C(O)R^{c18,}$ -O-$S(O)_2R^{c19}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of halo and -OH, and

R^{c1}-R^{c19} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -O(C_{1-6} alkyl), - NHC(O)(C_{1-6} alkyl), and -OH;

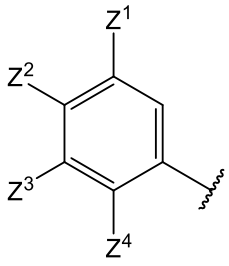
provided that

(1) when ring B is unsubstituted cyclopentyl, then ring A is 

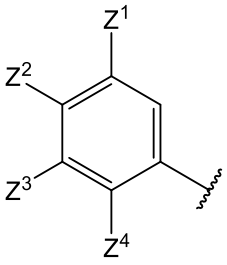
, wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) substituted with one or more halo,

(2) when ring B is unsubstituted cyclohexyl and ring A is 

, then at least one of R^{C1}-R^{C4} is R^F, and

(3) when ring B is 5- to 7-membered heterocycloalkyl optionally substituted with 1-4 R^B, then ring A is 

, wherein at least one of Z^1-Z^4 is -$S(O)_2$-(3- to 10-membered heterocycloalkyl) optionally substituted with one or more halo.

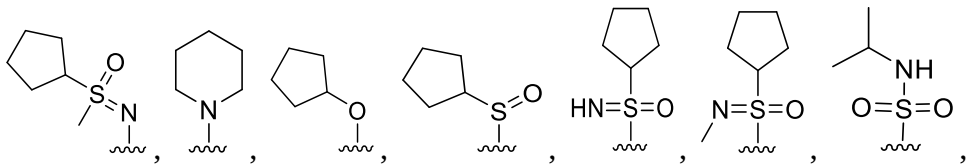
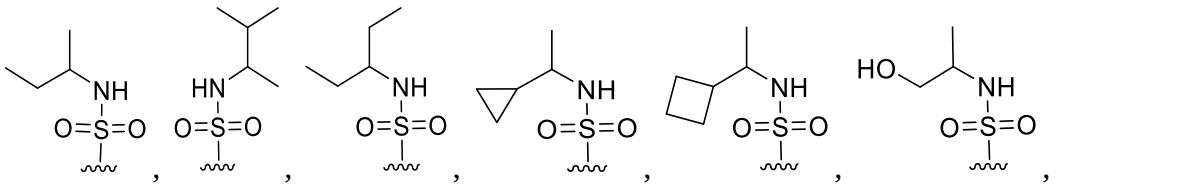
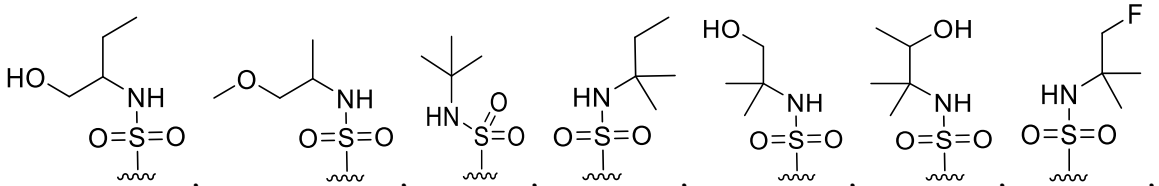
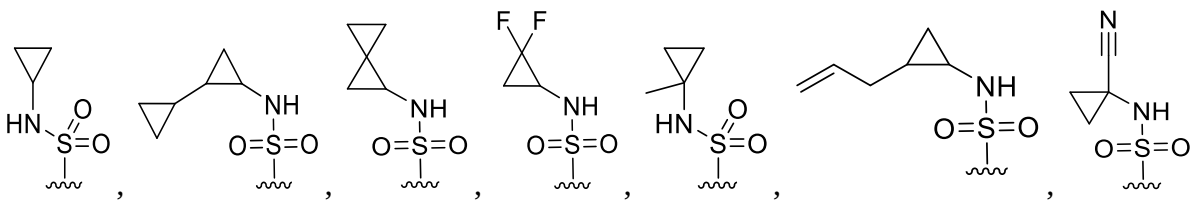
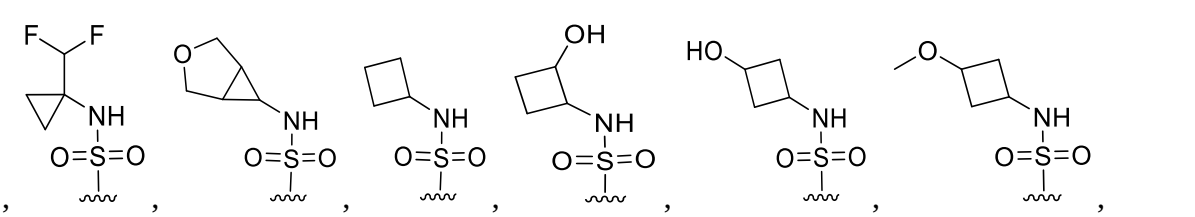
34. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein ring A is 

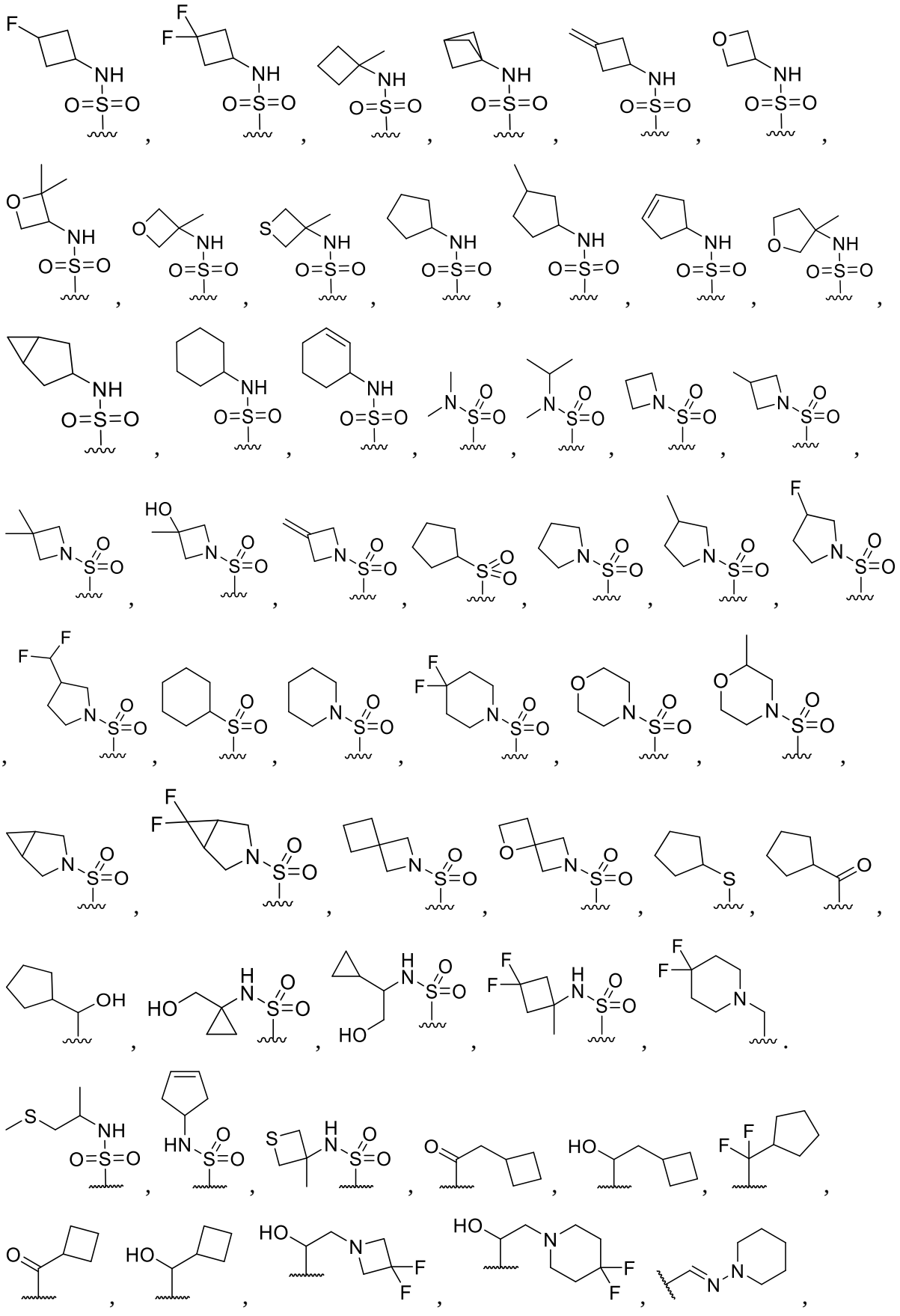
.

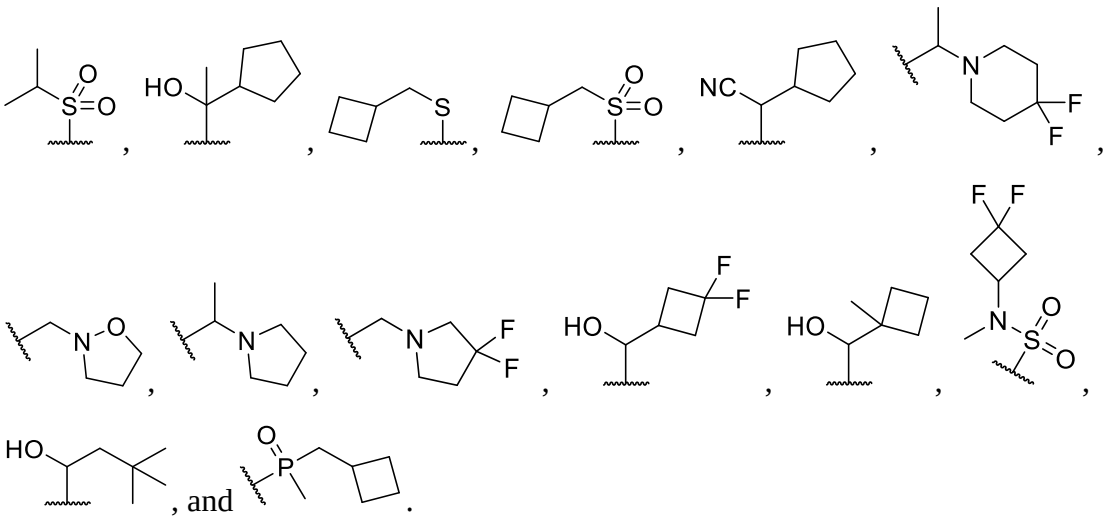
35. The compound of claim 34, or a pharmaceutically acceptable salt thereof, wherein Z^4 is hydrogen, and at least one of Z^1 and Z^3 is R^D, wherein R^D is halo, -OH, -$NR^{a4}C(O)OR^{a5}$, -$NR^{a6}R^{a7}$, -$N{=}S(O)R^{a8}R^{a9}$, -OR^{a10}, -$S(O)R^{a11}$, -$S(O)(NR^{a12})R^{a13}$, -$S(O)_2NR^{a14}R^{a15}$, -$S(O)_2R^{a16}$, -$(CR^{a17}R^{a18})_{0\text{-}1}C(O)NR^{a19}R^{a20}$, -$SR^{a21}$, -$C(O)R^{a22}$, -$P(O)(R^{a23})(R^{a24})$, -$C{=}NR^{a25}$, or $C_{1\text{-}6}$ alkyl

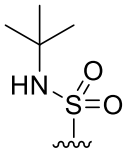
substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl.

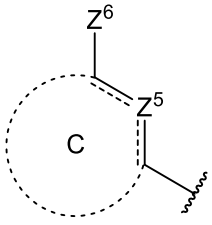
36. The compound of claim 34, or a pharmaceutically acceptable salt thereof, wherein Z^4 is R^D and Z^1 is R^D, wherein R^D is independently halo, -OH, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N=S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, $-SR^{a21}$, $-C(O)R^{a22}$, $-P(O)(R^{a23})(R^{a24})$, $-C=NR^{a25}$, or C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo or C_{1-3} alkyl.

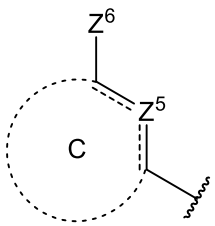
37. The compound of any one of claims 33-36, or a pharmaceutically acceptable salt thereof, wherein one or more of Z^1-Z^4 is selected from the group consisting of fluoro, chloro, -OH, -NH_2, -CH_2OH, , , , , .





38. The compound of any one of claims 33-37, or a pharmaceutically acceptable salt thereof, wherein one of Z^1-Z^4 is .

39. The compound of claim 33, or a pharmaceutically acceptable salt thereof, wherein ring A is  and ring C is 5- to 6-membered heteroaryl optionally substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl, or two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl.

40. The compound of claim 33 or claim 39, or a pharmaceutically acceptable salt thereof, wherein ring A is  and ring C is 5- to 6-membered heteroaryl optionally

substituted with one or more R^E substituents, wherein each R^E substituent is independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl.

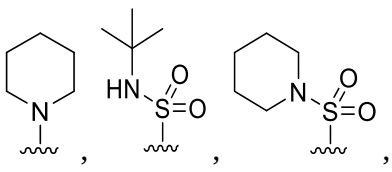
41. The compound of claim 39 or claim 40, or a pharmaceutically acceptable salt thereof, wherein ring C is pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, or oxazolyl, each optionally substituted.

42. The compound of any one of claims 39-41, or a pharmaceutically acceptable salt thereof, wherein the one or more R^E substituents are independently selected from the group consisting of halo, -OH, and C_{1-6} alkyl.

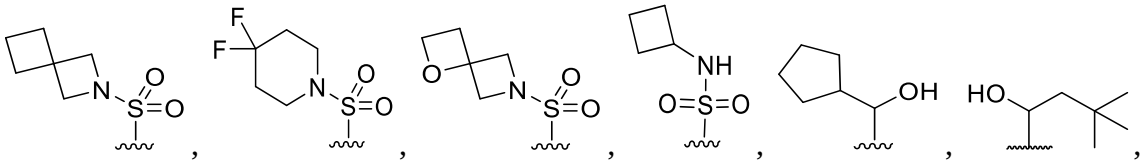
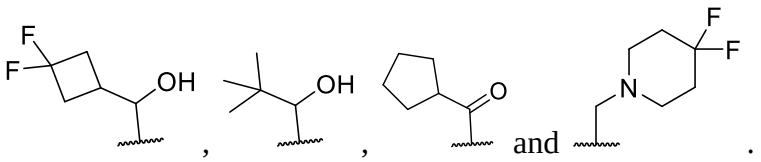
43. The compound of claim 42, or a pharmaceutically acceptable salt thereof, wherein the one or more R^E substituent is methyl.

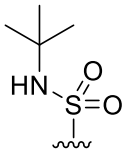
44. The compound of claim 39 or claim 40, or a pharmaceutically acceptable salt thereof, wherein two R^E substituents are taken, together with the atoms to which they are attached, to form C_{5-6} cycloalkyl, C_{5-6} cycloalkenyl, 5- to 6-membered heterocycloalkyl, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heteroaryl.

45. The compound of any one of claims 39-44, or a pharmaceutically acceptable salt thereof, wherein Z^6 is $-CH(Z^7)(Z^8)$, wherein Z^7 is hydrogen or -OH, and Z^8 is C_{1-6} alkyl, C_{3-10} cycloalkyl optionally substituted with one or more halo, or 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo.

46. The compound of any one of claims 39-44, or a pharmaceutically acceptable salt thereof, wherein Z^6 is selected from the group consisting of 

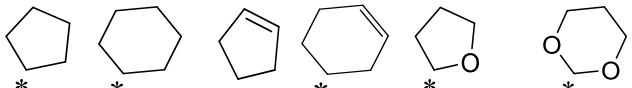
,
,
,

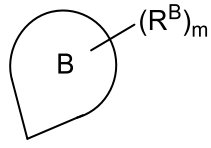
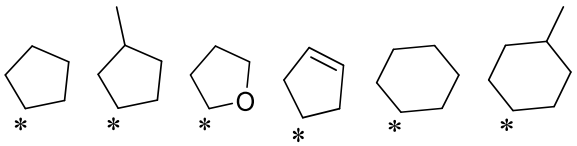
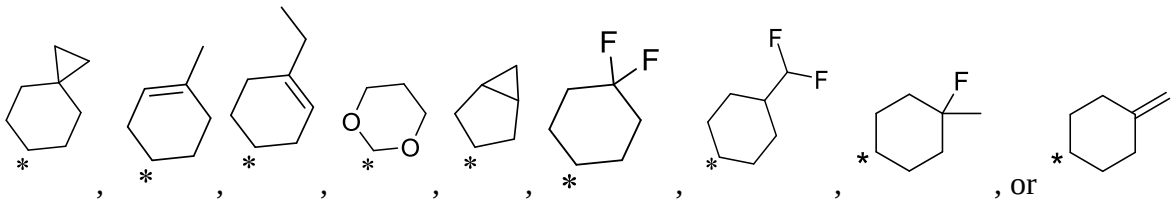


and .

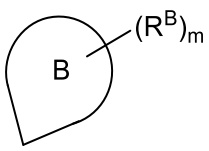
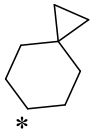
47. The compound of claim 46, wherein Z^6 is .

48. The compound of any one of claims 33-47, or a pharmaceutically acceptable salt thereof, wherein ring B is C_{5-7} cycloalkyl.

49. The compound of any one of claims 33-47, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 7-membered heterocycloalkyl.

50. The compound of any one of claims 33-47, or a pharmaceutically acceptable salt thereof, wherein ring B is , wherein * denotes the point of attachment to the rest of Formula (II).

51. The compound of any one of claims 33-47, or a pharmaceutically acceptable salt thereof, wherein  of Formula (II) is ,
, or
wherein * denotes the point of attachment to the rest of Formula (II).

52. The compound of claim 51, or a pharmaceutically acceptable salt thereof, wherein  of Formula (II) is .

53. The compound of any one of claims 33-52, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

54. The compound of claim 53, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each independently hydrogen, halo, or $-NH_2$.

55. The compound of claim 54, or a pharmaceutically acceptable salt thereof, wherein R^{C1}, R^{C3}, and R^{C4} are each hydrogen.

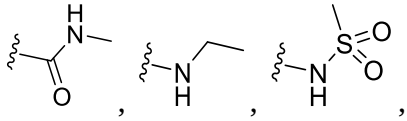
56. The compound of any one of claims 33-52, or a pharmaceutically acceptable salt thereof, wherein Y^1 is N; Y^2 is CR^{C2}; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

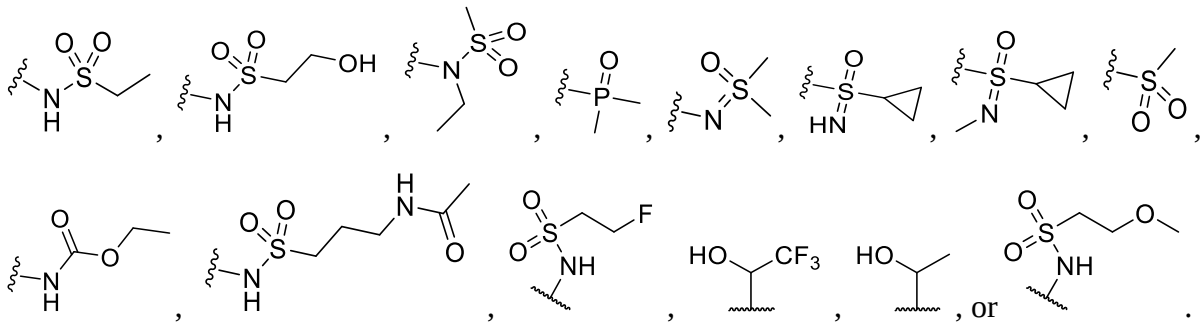
57. The compound of any one of claims 33-52, or a pharmaceutically acceptable salt thereof, wherein Y^1 is CR^{C1}; Y^2 is N; Y^3 is CR^{C3}; and Y^4 is CR^{C4}.

58. The compound of claim 53 or claim 57, or a pharmaceutically acceptable salt thereof, wherein R^{C1} is halo.

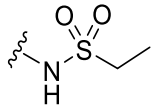
59. The compound of any one of claims 53, 56, or 57, or a pharmaceutically acceptable salt thereof, wherein R^{C3} is halo.

60. The compound of any one of claims 53, 56, or 57, or a pharmaceutically acceptable salt thereof, wherein R^{C4} is halo or $-NH_2$.

61. The compound of any one of claims 33-56, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is cyano, -OH, $-CH_2OH$, fluro, bromo, $-NO_2$, ,



62. The compound of claim 61, or a pharmaceutically acceptable salt thereof, wherein R^{C2} is



63. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of compounds of **Table 1**.

64. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of compounds of **Table 2**.

65. A pharmaceutical composition comprising a compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

66. Use of a compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 65, in the manufacture of a medicament for inhibiting KIF18A, wherein a cell is to be contacted with the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition.

67. Use of a compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 65, in the manufacture of a medicament for treating a disease or condition mediated by KIF18A in a subject in need thereof.

68. Use of a compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 65, in the manufacture of a medicament for treating cancer in a subject in need thereof.

69. The use of claim 68, wherein the cancer is selected from the group consisting of carcinomas, cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung, pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, or skin, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin including sarcomas, tumors of the central and peripheral nervous system, tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors comprising retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, and other cancer-related disorders that are a consequence of cancer presence or progression.

70. A compound of any one of claims 1-64, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 65, for use in therapy.