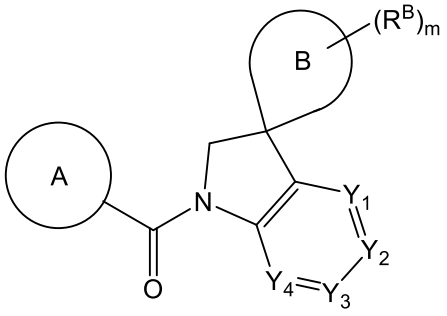
CIN-high (but not CIN-low), aneuploid and whole-genome doubled cells vulnerable to death. Cellular toxicity assay in isogenic cell lines confirmed the enhanced sensitivity of CIN-high cells to KIF18A inhibitors. Ongoing in vivo mouse models using KIF18A inhibitor or knockdown demonstrated effect of inhibited 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 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};

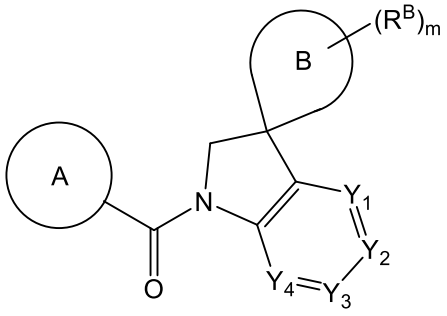
wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}, R^{C3}, and 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^{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; and

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 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};

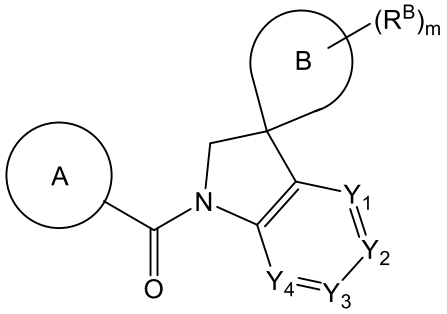
wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}, R^{C3}, and 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^{C2} is halo, cyano, -OH, -NO_2, -$C(O)NR^{c1}R^{c2}$, -$NR^{c3}R^{c4}$, -$NR^{c5}S(O)_2R^{c6}$, -$P(O)R^{c7}R^{c8}$, -$N{=}S(O)R^{c9}R^{c10}$, -$S(O)(NR^{c11})R^{c12}$, -$S(O)_2R^{c13}$, -$NR^{c14}C(O)OR^{c15}$, 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^{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 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};

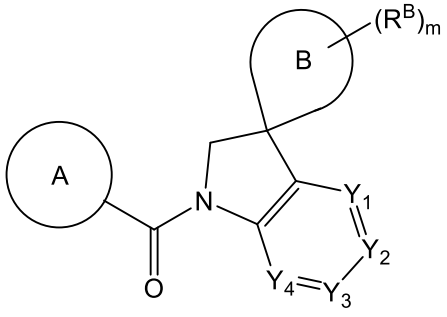
wherein no more than three of Y^1, Y^2, Y^3, and Y^4 are N;

R^{C1}, R^{C3}, and 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^{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.

[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 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^{C2}, and 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^{2C} 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^{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):

[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 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.

[0003j] 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.

[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):