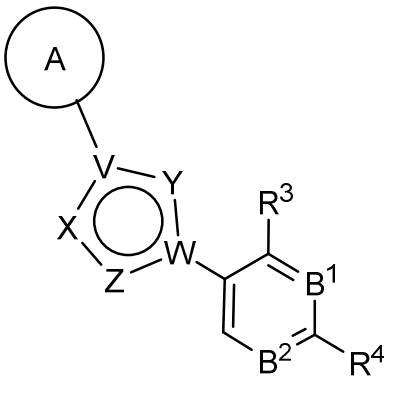
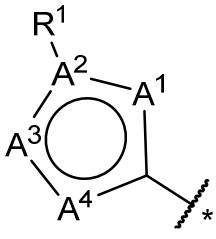
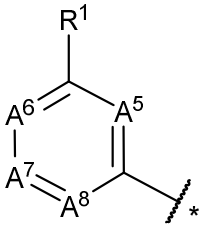
cells to KIF18A inhibitors. Ongoing in vivo mouse models using KIF18A inhibitor or knockdown demonstrated effect of inhibited tumor growth. Thus, there is a need for new compounds for use in treating diseases mediated by KIF18A.

BRIEF SUMMARY

[0004] The present disclosure provides compounds of Formula (I) and Formula (II), Formula (III), 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 are compounds of Formula (I):

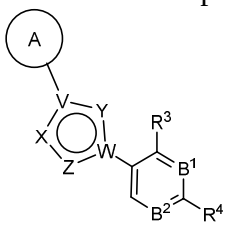


(I),

or a pharmaceutically acceptable salt thereof, wherein: X and Z are independently O, N, or CH; Y is NH, N, or CH; V and W are independently N or C; wherein at least one of X and Z is N or Y is NH; Ring A is  or , wherein one, two, or three of A^1, A^3, and A^4 are independently N, NR^{A1}, O, or S, and the remaining one or two of A^1, A^3, and A^4, if present, are independently CH or CR^2, wherein R^{A1} is H or C_{1-3} alkyl; A^2 is N or C; A^5-A^8 are independently CH, CR^2, N, or NR^{A2}, wherein at least two of A^5, A^6, A^7, and A^8 are CH or CR^2, and the remaining one or two of A^5, A^6, A^7, and A^8, if present, are N or NR^{A2}, wherein R^{A2} is =O; wherein "*" indicates the point of attachment to V; B^1 and B^2 are each independently N, CH or CR^B, wherein R^B is halogen; R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, or $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, wherein the C_1-C_6 alkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH,

$S(O)_2R^{c13}$, 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, wherein each C_1-C_6 alkyl of R^{c1}-R^{c13} is optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -C(O)-O-C_1-C_3 alkyl, and wherein each C_{3-10} cycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkylene-OH. In some examples, when X is N, Y is N, and Z is O, then R^4 is not H.

[0004a] In one aspect, the present disclosure provides a compound of Formula (I):



(I),

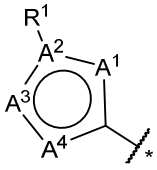
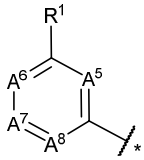
or a pharmaceutically acceptable salt thereof, wherein:

X and Z are independently O, N, or CH;

Y is NH, N, or CH;

V and W are independently N or C;

wherein at least one of X and Z is N or Y is NH;

Ring A is  or , wherein

one, two, or three of A^1, A^3, and A^4 are independently N, NR^{A1}, O, or S, and the remaining one or two of A^1, A^3, and A^4, if present, are independently CH or CR^2, wherein R^{A1} is H or C_{1-3} alkyl;

A^2 is N or C;

A^5-A^8 are independently CH, CR^2, N, or NR^{A2}, wherein at least two of A^5, A^6, A^7, and A^8 are CH or CR^2, and the remaining one or two of A^5, A^6, A^7, and A^8, if present, are N or NR^{A2}, wherein R^{A2} is =O;

wherein "*" indicates the point of attachment to V;

B^1 and B^2 are each independently N, CH or CR^B, wherein R^B is halogen;

R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, or $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$,

wherein the C_1-C_6 alkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, oxo, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo; wherein the C_{3-6} cycloalkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen; wherein the C_{3-10} cycloalkenyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen; and wherein the 3- to 10-membered heterocycloalkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

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; or

R^{a14} and R^{a15} are taken together with the nitrogen to which they are attached to form a 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

each R^2 is independently halogen, C_{1-3} alkyl, C_{3-5} cycloalkyl, cyano, C_{1-3} alkyloxy, C_{3-5} cycloalkyloxy, hydroxy, or $NR^{b1}R^{b2}$, wherein the C_{1-3} alkyl of R^2 is optionally substituted by one or more substituents selected from the group consisting of -OH and oxo, and wherein R^{b1} and R^{b2} are independently C_1-C_3 alkyl or R^{b1} and R^{b2} are taken together with the nitrogen to which they are attached to form a 3- to 6-membered ring; or

R^1 and the R^2 of A^5 are taken together with the carbon atoms to which they are attached to form a C_3-C_6 cycloalkyl or a 3- to 10-membered heterocycloalkyl;

R^3 is piperidinyl, pyrrolidinyl, or azepanyl, wherein the piperidinyl, the pyrrolidinyl, or the azepanyl is optionally substituted with a C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl, wherein the C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl forms a spirocyclic or fused bicyclic ring system with the piperidinyl, pyrrolidinyl, or azepanyl, or

wherein the piperidinyl, pyrrolidinyl, or azepanyl are optionally substituted with a C_{1-2} alkylene to form a bridged piperidinyl, pyrrolidinyl, or azepanyl ring system,

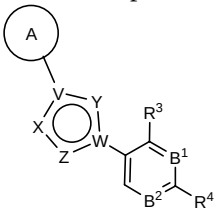
wherein the piperidinyl, the pyrrolidinyl, the azepanyl, or the spirocyclic, fused, or bridged bicyclic ring system formed by the C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, or C_{1-2} alkylene with piperidinyl, pyrrolidinyl, or azepanyl is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, and halo;

R^4 is H, 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,

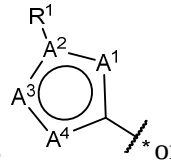
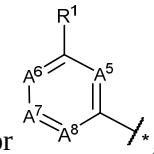
wherein R^4 is not H when X is N, Y is N, and Z is O; and

R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl, wherein each C_1-C_6 alkyl of R^{c1}-R^{c13} is optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -C(O)-O-C_1-C_3 alkyl, and wherein each C_{3-10} cycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkylene-OH.

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

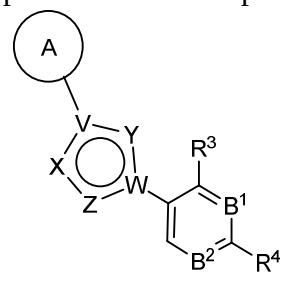


(II),

or a pharmaceutically acceptable salt thereof, wherein: X and Z are independently O, N, or CH; Y is NH or CH; V and W are independently N or C; wherein at least one of X and Z is N or Y is NH; Ring A is  or , wherein one or two of A^1, A^3, and A^4 are independently N, O, or S, and the remaining one or two of A^1, A^3, and A^4 are independently CH or CR^2; A^2 is N or C; A^5-A^8 are independently CH, CR^2 or N, wherein at least two of A^5, A^6, A^7, and A^8 are CH or CR^2, and the remaining one or two of A^5, A^6, A^7, and A^8, if present, are N; wherein "*" indicates the point of attachment to V; B^1 and B^2 are each independently N or CH; R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, or $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, wherein the C_1-C_6 alkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

wherein the C_{3-6} cycloalkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen; and wherein the 3- to 10-membered heterocycloalkyl of R^1 is optionally substituted with one or more halogens; 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; or R^{a14} and R^{a15} are taken together with the nitrogen to which they are attached to form a 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo; each R^2 is independently halogen, C_{1-3} alkyl, C_{3-5} cycloalkyl, cyano, C_{1-3} alkyloxy, C_{3-5} cycloalkyloxy, hydroxy, or $NR^{b1}R^{b2}$, wherein R^{b1} and R^{b2} are independently optionally substituted with C_1-C_3 alkyl or R^{b1} and R^{b2} are taken together with the nitrogen to which they are attached to form a 3- to 6-membered ring; or R^1 and the R^2 of A^5 are taken together with the carbon atoms to which they are attached to form a C_3-C_6 cycloalkyl or a 3- to 6-membered heterocycloalkyl; R^3 is piperidinyl, pyrrolidinyl, or azepanyl, wherein the piperidinyl, the pyrrolidinyl, or the azepanyl is optionally substituted with a C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl, wherein the C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl forms a spirocyclic or fused bicyclic ring system with the piperidinyl, pyrrolidinyl, or the azepanyl, and wherein the piperidinyl, the pyrrolidinyl, the azepanyl or the spirocyclic or fused bicyclic ring system formed by the C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl with piperidinyl, pyrrolidinyl, or azepanyl is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl; R^4 is H, 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, wherein each C_1-C_6 alkyl of R^{c1}-R^{c13} is optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -C(O)-O-C_1-C_3 alkyl.

[0005a] In another aspect, the present disclosure provides a compound of Formula (II):



(II),

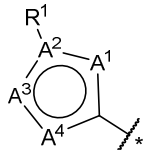
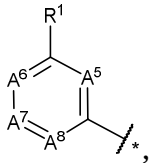
or a pharmaceutically acceptable salt thereof, wherein:

X and Z are independently O, N, or CH;

Y is NH or CH;

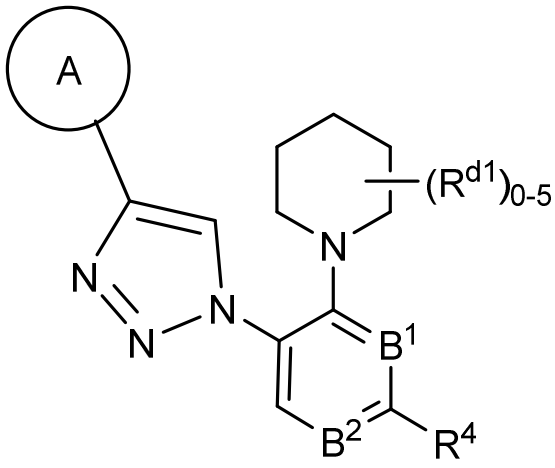
V and W are independently N or C;

wherein at least one of X and Z is N or Y is NH;

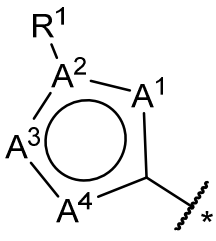
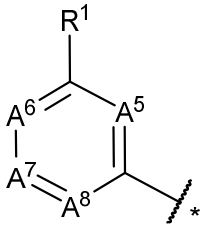
Ring A is  or , wherein

one or two of A^1, A^3, and A^4 are independently N, O, or S, and the remaining one or two of A^1, A^3, and A^4 are independently CH or CR^2;
A^2 is N or C;
A^5-A^8 are independently CH, CR^2 or N, wherein at least two of A^5, A^6, A^7, and A^8 are CH or CR^2, and the remaining one or two of A^5, A^6, A^7, and A^8, if present, are N;
wherein "*" indicates the point of attachment to V;
B^1 and B^2 are each independently N or CH;
R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, 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}, -$S(O)R^{a11}$, -$S(O)(NR^{a12})R^{a13}$, -$S(O)_2NR^{a14}R^{a15}$, -$S(O)_2R^{a16}$, or -$(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$,
wherein the C_1-C_6 alkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;
wherein the C_{3-6} cycloalkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen; and wherein the 3- to 10-membered heterocycloalkyl of R^1 is optionally substituted with one or more halogens;
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;
or R^{a14} and R^{a15} are taken together with the nitrogen to which they are attached to form a 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;
each R^2 is independently halogen, C_{1-3} alkyl, C_{3-5} cycloalkyl, cyano, C_{1-3} alkyloxy, C_{3-5} cycloalkyloxy, hydroxy, or $NR^{b1}R^{b2}$, wherein R^{b1} and R^{b2} are independently C_1-C_3 alkyl or R^{b1} and R^{b2} are taken together with the nitrogen to which they are attached to form a 3- to 6-membered ring; or
R^1 and the R^2 of A^5 are taken together with the carbon atoms to which they are attached to form a C_3-C_6 cycloalkyl or a 3- to 6-membered heterocycloalkyl;
R^3 is piperidinyl, pyrrolidinyl, or azepanyl, wherein the piperidinyl, the pyrrolidinyl, or the azepanyl is optionally substituted with a C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl, wherein the C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl forms a spirocyclic or fused bicyclic ring system with the piperidinyl, pyrrolidinyl, or the azepanyl, and
wherein the piperidinyl, the pyrrolidinyl, the azepanyl or the spirocyclic or fused bicyclic ring system formed by the C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl with piperidinyl, pyrrolidinyl, or azepanyl is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_3 alkyl and C_1-C_3 haloalkyl;
R^4 is 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; and
R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl, wherein each C_1-C_6 alkyl of R^{c1}-R^{c13} is optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -C(O)-O-C_1-C_3 alkyl.

[0006] In yet another example, provided herein is a compound of Formula (III)

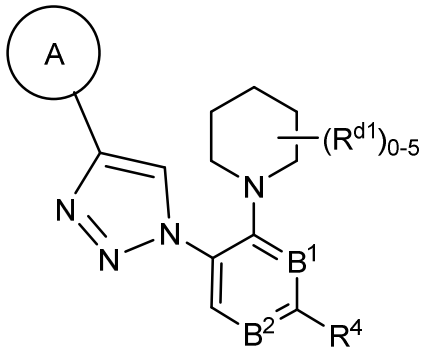


(III),

or a pharmaceutically acceptable salt thereof, wherein: Ring A is  or , wherein one, two, or three of A^1, A^3, and A^4 are independently N, NR^{A1}, O, or S, and the remaining one or two of A^1, A^3, and A^4, if present, are independently CH or CR^2, wherein R^{A1} is H or C_{1-3} alkyl; A^2 is N or C; A^5-A^8 are independently CH, CR^2, N, or NR^{A2}, wherein at least two of A^5, A^6, A^7, and A^8 are CH or CR^2, and the remaining one or two of A^5, A^6, A^7, and A^8, if present, are N or NR^{A2}, wherein R^{A2} is =O; wherein "*" indicates the point of attachment to V; B^1 and B^2 are each independently N, CH or CR^B, wherein R^B is halogen; R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, or $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$, wherein the C_1-C_6 alkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, oxo, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo; wherein the C_{3-6} cycloalkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen; wherein the C_{3-10}

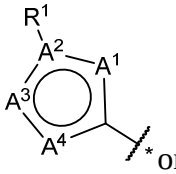
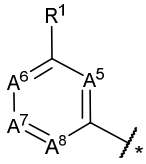
C_3 alkyl, and wherein each C_{3-10} cycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkylene-OH.

[0006a] In another aspect, the present disclosure provides a compound of Formula (III)



(III),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  or , wherein

one, two, or three of A^1, A^3, and A^4 are independently N, NR^{A1}, O, or S, and the remaining one or two of A^1, A^3, and A^4, if present, are independently CH or CR^2, wherein R^{A1} is H or C_{1-3} alkyl;

A^2 is N or C;

A^5-A^8 are independently CH, CR^2, N, or NR^{A2}, wherein at least two of A^5, A^6, A^7, and A^8 are CH or CR^2, and the remaining one or two of A^5, A^6, A^7, and A^8, if present, are N or NR^{A2}, wherein R^{A2} is =O;

wherein "*" indicates the point of attachment to V;

B^1 and B^2 are each independently N, CH or CR^B, wherein R^B is halogen;

R^1 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, $-NR^{a1}C(O)NR^{a2}R^{a3}$, $-NR^{a4}C(O)OR^{a5}$, $-NR^{a6}R^{a7}$, $-N{=}S(O)R^{a8}R^{a9}$, $-OR^{a10}$, $-S(O)R^{a11}$, $-S(O)(NR^{a12})R^{a13}$, $-S(O)_2NR^{a14}R^{a15}$, $-S(O)_2R^{a16}$, or $-(CR^{a17}R^{a18})_{0-1}C(O)NR^{a19}R^{a20}$,

wherein the C_1-C_6 alkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, oxo, cyano, C_{3-10} cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo; wherein the C_{3-6} cycloalkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen; wherein the C_{3-10} cycloalkenyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen; and wherein the 3- to 10-membered heterocycloalkyl of R^1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

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; or

R^{a14} and R^{a15} are taken together with the nitrogen to which they are attached to form a 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

each R^2 is independently halogen, C_{1-3} alkyl, C_{3-5} cycloalkyl, cyano, C_{1-3} alkyloxy, C_{3-5} cycloalkyloxy, hydroxy, or $NR^{b1}R^{b2}$, wherein the C_{1-3} alkyl of R^2 is optionally substituted by one or more substituents selected from the group consisting of -OH and oxo, and wherein R^{b1} and R^{b2} are independently C_1-C_3 alkyl or R^{b1} and R^{b2} are taken together with the nitrogen to which they are attached to form a 3- to 6-membered ring; or

R^1 and the R^2 of A^5 are taken together with the carbon atoms to which they are attached to form a C_3-C_6 cycloalkyl or a 3- to 10-membered heterocycloalkyl;

wherein each R^{d1} is independently selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, and halo; or wherein two R^{d1} are taken together to form a C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl, wherein the C_{3-10} cycloalkyl or 3- to 10-membered heterocycloalkyl forms a spirocyclic or fused bicyclic ring system with the piperidinyl; or wherein two R^{d1} are taken together to form a C_{1-2} alkylene, wherein the C_{1-2} alkylene forms a bridged piperidinyl ring system,

wherein the spirocyclic, fused, or bridged bicyclic ring system formed by the C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, or C_1-$_2$ alkylene with the piperidinyl is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, and halo;

R^4 is H, 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

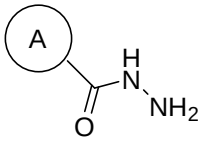
R^{c1}-R^{c13} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl, wherein each C_1-C_6 alkyl of R^{c1}-R^{c13} is optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, an d-C(O)-O-C_1-C_3 alkyl, and wherein each C_{3-10} cycloalkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_1-C_6 alkylene-OH.

[0007] In another example, provided is pharmaceutical composition comprising a compound of Formula (I), a compound of Formula (II), a compound of Formula (III), or a compound of Table 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. In one aspect, provided is a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0008] 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. In one aspect, provided herein is an *in vitro* method of inhibiting KIF18A comprising contacting a cell with (i) an effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or with (ii) a pharmaceutical composition comprising said (i) and a pharmaceutically acceptable carrier or excipient

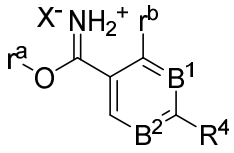
[0009] In another example, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition as described herein. In some examples, the disease or condition 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. In one aspect, provided herein is use of a composition comprising (i) a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or comprising (ii) said (i) and a pharmaceutically acceptable carrier or excipient, in the manufacture of a medicament for treating a disease or condition mediated by KIF18A in a subject in need thereof. In another aspect, provided herein is use of a composition comprising (i) a therapeutically effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or comprising (ii) said (i) and a pharmaceutically acceptable carrier or excipient, in the manufacture of a medicament for treating cancer in a subject in need thereof. In another aspect, provided is a composition comprising (i) a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt thereof, or comprising (ii) said (i) and a pharmaceutically acceptable carrier or excipient, for use as a medicament.

[0009a] In another aspect, provided herein is a method of synthesizing the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, the method comprising:



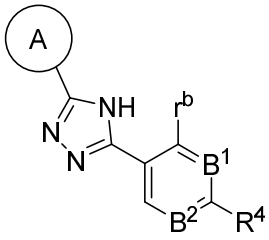
A

(1) contacting a compound of Formula (A) with a compound of



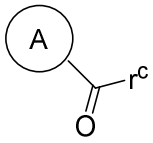
B

Formula (B) to produce a compound of Formula (C) or (I)



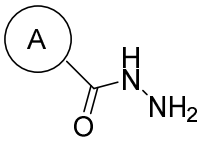
C or **I**

wherein Y is NH, X is N, and Z is N;



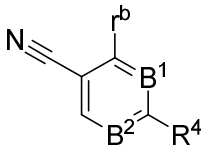
D

(2) converting a compound of Formula (D) to compound of Formula (A)



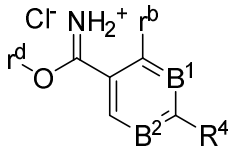
A

;

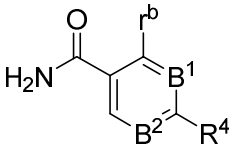


E

(3) converting a compound of Formula (E) to a compound of

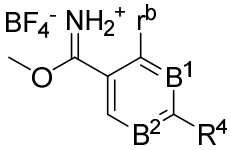


Formula (B^a) **B^a** ;

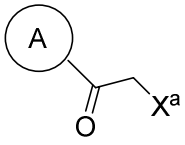


F

(4) converting a compound of Formula (F) to a compound of

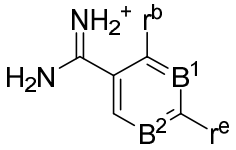


Formula (B^b) **B^b** ;

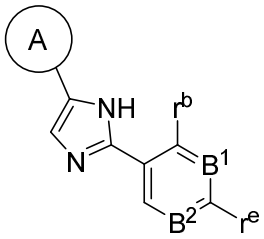


G

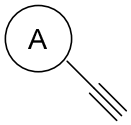
(5) contacting a compound of Formula (G) with a compound of



Formula (H) **H** to produce a compound of Formula (J) or (I)

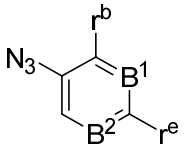


J or **I**, wherein Y is NH and Z is N;

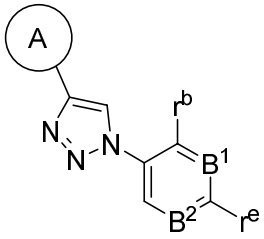


K

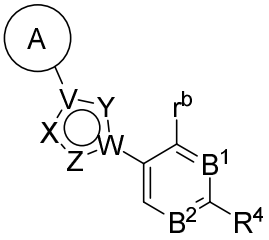
(6) contacting a compound of Formula (K) with a compound of Formula



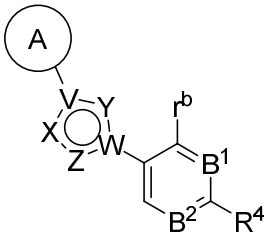
(L) **L** to produce a compound of Formula (M) or (I)



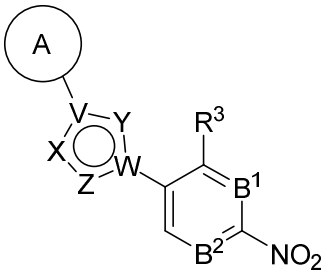
M or **I**, wherein Y is CH, X is N, Z is N, and W is N;



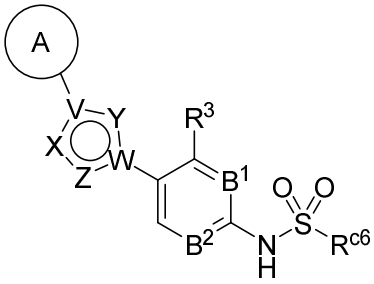
(7) converting a compound of Formula (C), (J), or (M) **C, J, or M** to a



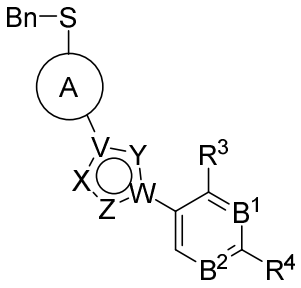
compound of Formula (I) **I** ;



(8) converting a compound of Formula (C), (J), or (M) **C, J, or M** to a

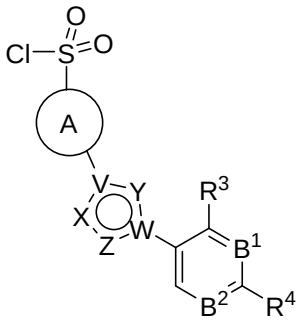


compound of Formula (I) **I** ;



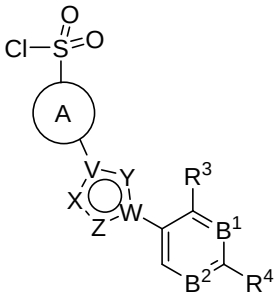
N

(9) converting a compound of Formula (N) to a compound of



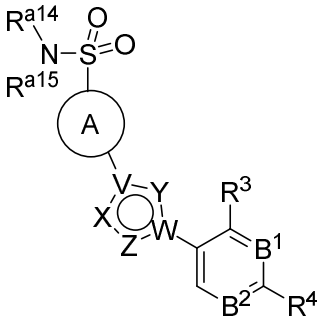
O

Formula (O) ;



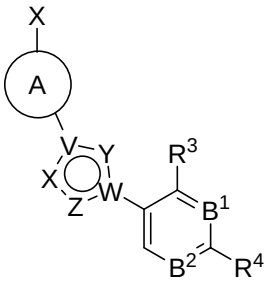
O

(10) converting a compound of Formula (O) to a compound of



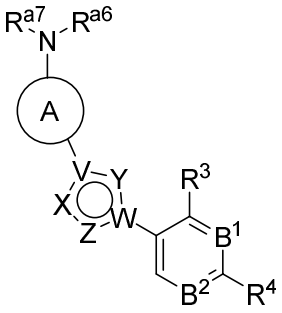
I

Formula (I) ; or



P

(11) converting a compound of Formula (P) to a compound of



I

Formula (I) ;

or any combination of (1) to (11).

DESCRIPTION OF THE FIGURES

[0010] The drawings illustrate certain features and advantages of this disclosure. These embodiments are not intended to limit the scope of the appended claims in any manner.

[0011] Figure 1 depicts a plot of tumor volume over time in an *in vivo* xenograft ovarian cancer cell line model (OVCAR3) in Balb/c mice treated with Compound 47 (at doses of 3, 10 and 30 mg/kg QD PO) as compared to vehicle control.

[0012] Figure 2 depicts a plot of tumor volume over time in an *in vivo* xenograft non-small cell lung carcinoma cell line model (HCC15) in Balb/c mice treated with Compound 47 (at doses of 3, 10 and 30 mg/kg QD PO) as compared to vehicle control.

DETAILED DESCRIPTION

[0013] 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