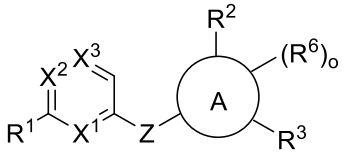
properties of these compounds, such as high cellular efflux, long pharmacokinetic terminal half-life and dose-limiting myelosuppression, specifically neutropenia and thrombocytopenia, as previously seen, for example, with the kinesin motor protein KIF11 (Eg-5) inhibitors, as discussed in P. Navais, et, al. Pharmaceutics 2021, 13, 1011.

Thus, there is a need for KIF18A inhibitors as potential therapeutic agents for treating diseases or disorders that are responsive to KIF18A inhibition, and specifically compounds which demonstrate improvements in the properties described above (i.e., better cellular efflux, different pharmacokinetic terminal half-life, and decreased myelosuppression, specifically neutropenia and thrombocytopenia).

SUMMARY

The present disclosure provides compounds that are KIF18A inhibitors.

In one aspect, the present disclosure provides a compound represented by Formula (I)



(I);

or a pharmaceutically acceptable salt thereof, wherein:

(i) X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

Ring A is phenyl, 6-membered heteroaryl, 6,5-bicyclic heteroaryl, or 4- to 10-membered monocyclic or bicyclic heterocyclyl;

Z is *-NHC(O)- or *-C(O)NH-, wherein *- represents the attachment to ring A;

o is an integer from 0 to 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, SO_2R^{1a}, $NR^{N1a}SO_2R^{1a}$, $NR^{N1a}R^{N1b}$, $-C(O)R^{1a}$, halo, cyano, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

R^{1a} is C_{1-6}alkyl, $NR^{N1a}R^{N1b}$, OR^{O1a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

each R^{1b} is independently selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{1-6}haloalkoxy;

or two R^{1b}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl;

R^{N1a} and R^{N1b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^{O1a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^2 is H, C_{1-6}alkyl, SO_2R^{2a}, $NR^{N2a}SO_2R^{2a}$, OR^{O2a}, $S(O)(NR^{N2c})R^{2a}$, halo, cyano, $-C(O)R^{2a}$, or $NR^{N2a}R^{N2b}$, wherein the C_{1-6}alkyl is optionally substituted with 1 or more R^{2b};

R^{2a} is C_{1-6}alkyl, $NR^{N2a}R^{N2b}$, OR^{O2a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and heterocyclyl are each optionally substituted with 1 or more R^{2b};

each R^{2b} is independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-N(R^{N2c})_2$, and $–C(O)OC_{1-6}$alkyl;

R^{N2a} and R^{N2b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{2b};

each R^{N2c} is independently H, C_{1-3}alkyl, $-C(O)(C_{1-3}$alkyl);

R^{O2a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with 1 or more halo, hydroxy, C_{1-6}alkoxy, or C_{1-6}haloalkoxy;

R^3 is C_{3-6}cycloalkyl, phenyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 or more R^{3a};

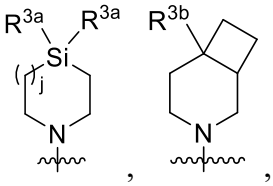
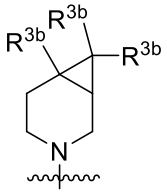
each R^{3a} is independently selected from halo, C_{1-6}haloalkyl, or C_{1-6}alkyl; or two R^{3a}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl substituted with 1 or more R^{3b};

each R^{3b} is independently selected from H, halo, C_{1-6}alkoxy, and C_{1-6}alkyl optionally substituted with one or more halo, OH, or C_{1-3}alkoxy;

R^4 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^5 is H, halo, or C_{1-6}alkyl;

each R^6 is independently C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

provided that if ring A is phenyl or 6-membered heteroaryl, then R^3 is , , 

or , where j is 0 or 1;

(ii) X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

Ring A is phenyl, 6-membered heteroaryl, 6,5-bicyclic heteroaryl, or 4- to 10-membered monocyclic or bicyclic heterocyclyl;

Z is *-NHC(O)- or *-C(O)NH-, wherein *- represents the attachment to ring A;

o is an integer from 0 to 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, SO_2R^{1a}, $NR^{N1a}SO_2R^{1a}$, $NR^{N1a}R^{N1b}$, $-C(O)R^{1a}$, halo, cyano, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

R^{1a} is C_{1-6}alkyl, $NR^{N1a}R^{N1b}$, OR^{O1a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

each R^{1b} is independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, and C_{1-6}haloalkoxy;

or two R^{1b}, together with the atom to which they are attached, form C_{3-6}cycloalkyl;

R^{N1a} and R^{N1b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^{O1a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^2 is H, C_{1-6}alkyl, SO_2R^{2a}, $NR^{N2a}SO_2R^{2a}$, OR^{O2a}, halo, cyano, $-C(O)R^{2a}$, or $NR^{N2a}R^{N2b}$, wherein the C_{1-6}alkyl is optionally substituted with 1 or more R^{2b};

R^{2a} is C_{1-6}alkyl, $NR^{N2a}R^{N2b}$, OR^{O2a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and heterocyclyl are each optionally substituted with 1 or more R^{2b};

each R^{2b} is independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, C_{1-6}haloalkoxy, and –C(O)OC_{1-6}alkyl;

R^{N2a} and R^{N2b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{2b};

R^{O2a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with 1 or more halo, hydroxy, C_{1-6}alkoxy, or C_{1-6}haloalkoxy;

R^3 is C_{3-6}cycloalkyl, phenyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 or more R^{3a};

each R^{3a} is independently selected from halo or C_{1-6}alkyl; or two R^{3a}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl substituted with 1 or more R^{3b};

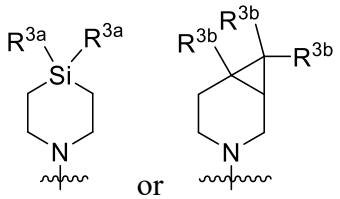
each R^{3b} is independently selected from H, halo, C_{1-6}alkoxy, and C_{1-6}alkyl optionally substituted with one or more halo or OH;

R^4 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^5 is H or C_{1-6}alkyl;

each R^6 is independently C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

provided that if ring A is phenyl or 6-membered heteroaryl, then R^3 is



or ; or

(iii) X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

Ring A is phenyl, 6-membered heteroaryl, 6,5-bicyclic heteroaryl, or 4- to 10-membered monocyclic or bicyclic heterocyclyl;

Z is *-NHC(O)- or *-C(O)NH-, wherein *- represents the attachment to ring A;

o is an integer from 0 to 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, SO_2R^{1a}, $NR^{N1a}SO_2R^{1a}$, $NR^{N1a}R^{N1b}$, -C(O)R^{1a}, halo, cyano, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

R^{1a} is C_{1-6}alkyl, $NR^{N1a}R^{N1b}$, OR^{O1a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

each R^{1b} is independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, and C_{1-6}haloalkoxy;

or two R^{1b}, together with the atom to which they are attached, form C_{3-6}cycloalkyl;

R^{N1a} and R^{N1b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^{O1a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^2 is H, C_{1-6}alkyl, SO_2R^{2a}, $NR^{N2a}SO_2R^{2a}$, OR^{O2a}, halo, cyano, $-C(O)R^{2a}$, or $NR^{N2a}R^{N2b}$, wherein the C_{1-6}alkyl is optionally substituted with 1 or more R^{2b};

R^{2a} is C_{1-6}alkyl, $NR^{N2a}R^{N2b}$, OR^{O2a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and heterocyclyl are each optionally substituted with 1 or more R^{2b};

each R^{2b} is independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, C_{1-6}haloalkoxy, and $–C(O)OC_{1-6}$alkyl;

R^{N2a} and R^{N2b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{2b};

R^{O2a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with 1 or more halo, hydroxy, C_{1-6}alkoxy, or C_{1-6}haloalkoxy;

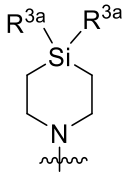
R^3 is C_{3-6}cycloalkyl, phenyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 or more R^{3a};

each R^{3a} is independently selected from halo or C_{1-6}alkyl; or two R^{3a}, together with the atom to which they are attached, form C_{3-6}cycloalkyl;

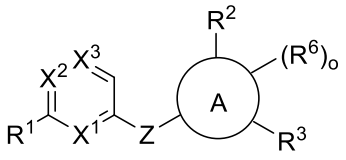
R^4 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^5 is H or C_{1-6}alkyl;

each R^6 is independently C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

provided that if ring A is phenyl or 6-membered heteroaryl, then R^3 is  .

In one example, the present disclosure relates to compounds having the Formula I:

 (I);

or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

Ring A is phenyl, 6-membered heteroaryl, 6,5-bicyclic heteroaryl, or 4- to 10-membered monocyclic or bicyclic heterocyclyl;

Z is *-NHC(O)- or *-C(O)NH-, wherein *- represents the attachment to ring A;

o is an integer from 0 to 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, SO_2R^{1a}, $NR^{N1a}SO_2R^{1a}$, $NR^{N1a}R^{N1b}$, $-C(O)R^{1a}$, halo, cyano, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

R^{1a} is C_{1-6}alkyl, $NR^{N1a}R^{N1b}$, OR^{O1a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

each R^{1b} is independently selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{1-6}haloalkoxy;

or two R^{1b}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl;

R^{N1a} and R^{N1b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^{O1a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^2 is H, C_{1-6}alkyl, SO_2R^{2a}, $NR^{N2a}SO_2R^{2a}$, OR^{O2a}, $S(O)(NR^{N2c})R^{2a}$, halo, cyano, $-C(O)R^{2a}$, or $NR^{N2a}R^{N2b}$, wherein the C_{1-6}alkyl is optionally substituted with 1 or more R^{2b};

R^{2a} is C_{1-6}alkyl, $NR^{N2a}R^{N2b}$, OR^{O2a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and heterocyclyl are each optionally substituted with 1 or more R^{2b};

each R^{2b} is independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-N(R^{N2c})_2$, and $–C(O)OC_{1-6}$alkyl;

R^{N2a} and R^{N2b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{2b};

each R^{N2c} is independently H, C_{1-3}alkyl, $-C(O)(C_{1-3}$alkyl);

R^{O2a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with 1 or more halo, hydroxy, C_{1-6}alkoxy, or C_{1-6}haloalkoxy;

R^3 is C_{3-6}cycloalkyl, phenyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 or more R^{3a};

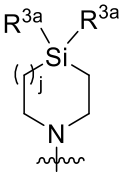
each R^{3a} is independently selected from halo, C_{1-6}haloalkyl, or C_{1-6}alkyl; or two R^{3a}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl substituted with 1 or more R^{3b};

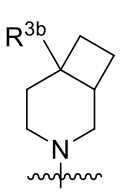
each R^{3b} is independently selected from H, halo, C_{1-6}alkoxy, and C_{1-6}alkyl optionally substituted with one or more halo, OH, or C_{1-3}alkoxy;

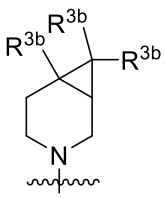
R^4 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^5 is H, halo, or C_{1-6}alkyl;

each R^6 is independently C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

provided that if ring A is phenyl or 6-membered heteroaryl, then R^3 is 

, 

, or 

, where j is 0 or 1. In some examples, R^2 is C_{1-6}alkyl, SO_2R^{2a},

$NR^{N2a}SO_2R^{2a}$, OR^{O2a}, halo, cyano, $-C(O)R^{2a}$, or $NR^{N2a}R^{N2b}$, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{2b}; and the remaining variables are as described above.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

One example of the disclosure relates to pharmaceutical compositions comprising compounds of Formula (I) or pharmaceutically acceptable salts thereof, and a pharmaceutical carrier.

In another example, the present disclosure relates to a method of treating a disease or disorder that is responsive to inhibition of KIF18A in a subject comprising administering to said subject an effective amount of at least one compound described herein or a pharmaceutically acceptable salt thereof. In some examples, the method is for the treatment of cancer.

In yet another aspect, the present disclosure provides use of the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating a KIF18A mediated disease or disorder.

One example of the present disclosure relates to the use of at least one compound described herein or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease or disorder responsive to inhibition of KIF18A. Also provided is a compound described herein or a pharmaceutically acceptable salt thereof for use in treating a disease or disorder responsive to inhibition of KIF18A.

In yet another aspect, the present disclosure provides the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, for use in treating a KIF18A mediated disease or disorder.

In yet another aspect, the present disclosure provides the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, for use in therapy.

In some examples, the compounds of the present disclosure have low efflux, especially in comparison to similar compounds known in the art. The benefits of compounds with low efflux are well known, such as overcoming resistance of cells with increased efflux pump prevalence, greater disease scope and targeting abilities, and higher cellular concentration.

In some examples, the compounds of the present disclosure are less cytotoxic against bone marrow cells, especially in comparison to similar compounds known in the art. In some examples, the compounds have a faster terminal half-life and/or clearance which allows for less systemic exposure and reduced potential for toxicity to bone-marrow cells. The benefits of compounds with low reactivity against bone marrow cells are well known, such as low risk of cytopenia, such as neutropenia or thrombocytopenia, for patients treated with the compounds.

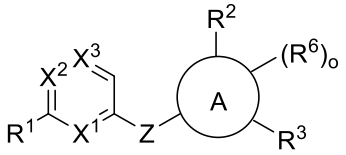
DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides compounds and pharmaceutical compositions thereof that may be useful in the treatment of diseases or disorders through mediation of KIF18A function/activity. In some embodiments, the compounds of present disclosure are KIF18A inhibitors.

CLAIMS

What is claimed is:

1. A compound represented by Formula (I)



(I);

or a pharmaceutically acceptable salt thereof, wherein:

(i) X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

Ring A is phenyl, 6-membered heteroaryl, 6,5-bicyclic heteroaryl, or 4- to 10-membered monocyclic or bicyclic heterocyclyl;

Z is *-NHC(O)- or *-C(O)NH-, wherein *- represents the attachment to ring A;

o is an integer from 0 to 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, SO_2R^{1a}, $NR^{N1a}SO_2R^{1a}$, $NR^{N1a}R^{N1b}$, $-C(O)R^{1a}$, halo, cyano, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

R^{1a} is C_{1-6}alkyl, $NR^{N1a}R^{N1b}$, OR^{O1a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

each R^{1b} is independently selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, and C_{1-6}haloalkoxy;

or two R^{1b}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl;

R^{N1a} and R^{N1b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^{O1a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^2 is H, C_{1-6}alkyl, SO_2R^{2a}, $NR^{N2a}SO_2R^{2a}$, OR^{O2a}, $S(O)(NR^{N2c})R^{2a}$, halo, cyano, $-C(O)R^{2a}$, or $NR^{N2a}R^{N2b}$, wherein the C_{1-6}alkyl is optionally substituted with 1 or more R^{2b};

R^{2a} is C_{1-6}alkyl, $NR^{N2a}R^{N2b}$, OR^{O2a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and heterocyclyl are each optionally substituted with 1 or more R^{2b};

each R^{2b} is independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, C_{1-6}haloalkoxy, $-N(R^{N2c})_2$, and $-C(O)OC_{1-6}$alkyl;

R^{N2a} and R^{N2b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{2b};

each R^{N2c} is independently H, C_{1-3}alkyl, $-C(O)(C_{1-3}$alkyl);

R^{O2a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with 1 or more halo, hydroxy, C_{1-6}alkoxy, or C_{1-6}haloalkoxy;

R^3 is C_{3-6}cycloalkyl, phenyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 or more R^{3a};

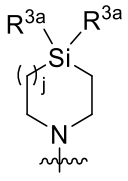
each R^{3a} is independently selected from halo, C_{1-6}haloalkyl, or C_{1-6}alkyl; or two R^{3a}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl substituted with 1 or more R^{3b};

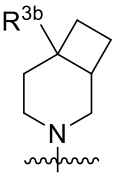
each R^{3b} is independently selected from H, halo, C_{1-6}alkoxy, and C_{1-6}alkyl optionally substituted with one or more halo, OH, or C_{1-3}alkoxy;

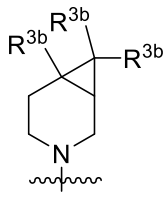
R^4 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^5 is H, halo, or C_{1-6}alkyl;

each R^6 is independently C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

provided that if ring A is phenyl or 6-membered heteroaryl, then R^3 is 

, 

, 

or , where j is 0 or 1;

(ii) X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

Ring A is phenyl, 6-membered heteroaryl, 6,5-bicyclic heteroaryl, or 4- to 10-membered monocyclic or bicyclic heterocyclyl;

Z is *-NHC(O)- or *-C(O)NH-, wherein *- represents the attachment to ring A;

o is an integer from 0 to 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, SO_2R^{1a}, $NR^{N1a}SO_2R^{1a}$, $NR^{N1a}R^{N1b}$, $-C(O)R^{1a}$, halo, cyano, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

R^{1a} is C_{1-6}alkyl, $NR^{N1a}R^{N1b}$, OR^{O1a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

each R^{1b} is independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, and C_{1-6}haloalkoxy;

or two R^{1b}, together with the atom to which they are attached, form C_{3-6}cycloalkyl;

R^{N1a} and R^{N1b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^{O1a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^2 is H, C_{1-6}alkyl, SO_2R^{2a}, $NR^{N2a}SO_2R^{2a}$, OR^{O2a}, halo, cyano, $-C(O)R^{2a}$, or $NR^{N2a}R^{N2b}$, wherein the C_{1-6}alkyl is optionally substituted with 1 or more R^{2b};

R^{2a} is C_{1-6}alkyl, $NR^{N2a}R^{N2b}$, OR^{O2a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and heterocyclyl are each optionally substituted with 1 or more R^{2b};

each R^{2b} is independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, C_{1-6}haloalkoxy, and $–C(O)OC_{1-6}$alkyl;

R^{N2a} and R^{N2b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{2b};

R^{O2a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with 1 or more halo, hydroxy, C_{1-6}alkoxy, or C_{1-6}haloalkoxy;

R^3 is C_{3-6}cycloalkyl, phenyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 or more R^{3a};

each R^{3a} is independently selected from halo or C_{1-6}alkyl; or two R^{3a}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl substituted with 1 or more R^{3b};

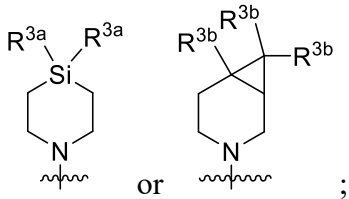
each R^{3b} is independently selected from H, halo, C_{1-6}alkoxy, and C_{1-6}alkyl optionally substituted with one or more halo or OH;

R^4 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^5 is H or C_{1-6}alkyl;

each R^6 is independently C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

provided that if ring A is phenyl or 6-membered heteroaryl, then R^3 is



or ; or

(iii) X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

Ring A is phenyl, 6-membered heteroaryl, 6,5-bicyclic heteroaryl, or 4- to 10-membered monocyclic or bicyclic heterocyclyl;

Z is *-NHC(O)- or *-C(O)NH-, wherein *- represents the attachment to ring A;

o is an integer from 0 to 3;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, SO_2R^{1a}, $NR^{N1a}SO_2R^{1a}$, $NR^{N1a}R^{N1b}$, -C(O)R^{1a}, halo, cyano, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

R^{1a} is C_{1-6}alkyl, $NR^{N1a}R^{N1b}$, OR^{O1a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with one or more R^{1b};

each R^{1b} is independently selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, and C_{1-6}haloalkoxy;

or two R^{1b}, together with the atom to which they are attached, form C_{3-6}cycloalkyl;

R^{N1a} and R^{N1b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^{O1a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{1b};

R^2 is H, C_{1-6}alkyl, SO_2R^{2a}, $NR^{N2a}SO_2R^{2a}$, OR^{O2a}, halo, cyano, -C(O)R^{2a}, or $NR^{N2a}R^{N2b}$, wherein the C_{1-6}alkyl is optionally substituted with 1 or more R^{2b};

R^{2a} is C_{1-6}alkyl, $NR^{N2a}R^{N2b}$, OR^{O2a}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the C_{1-6}alkyl, C_{3-6}cycloalkyl, and heterocyclyl are each optionally substituted with 1 or more R^{2b};

each R^{2b} is independently selected from C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, C_{1-6}haloalkoxy, and –C(O)OC_{1-6}alkyl;

R^{N2a} and R^{N2b} are each independently selected from H and C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more R^{2b};

R^{O2a} is H or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with 1 or more halo, hydroxy, C_{1-6}alkoxy, or C_{1-6}haloalkoxy;

R^3 is C_{3-6}cycloalkyl, phenyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 or more R^{3a};

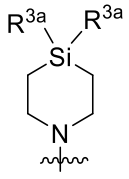
each R^{3a} is independently selected from halo or C_{1-6}alkyl; or two R^{3a}, together with the atom to which they are attached, form C_{3-6}cycloalkyl;

R^4 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^5 is H or C_{1-6}alkyl;

each R^6 is independently C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

provided that if ring A is phenyl or 6-membered heteroaryl, then R^3 is

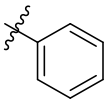
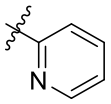
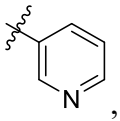
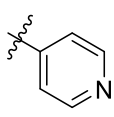
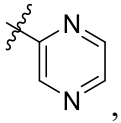
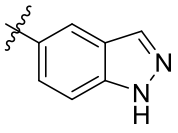


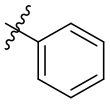
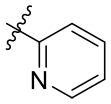
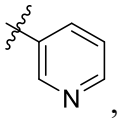
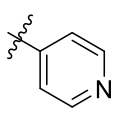
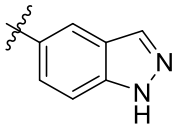
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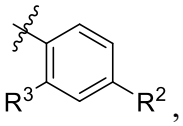
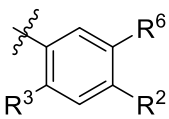
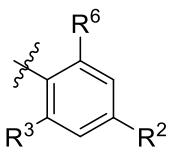
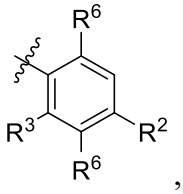
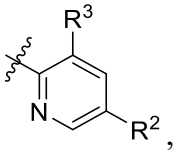
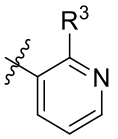
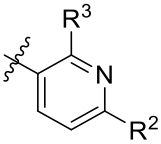
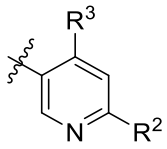
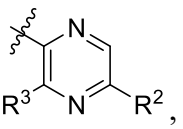
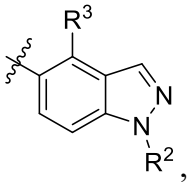
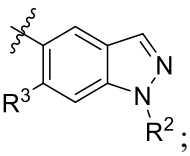
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z is *-C(O)NH-, wherein *- represents the attachment to ring A.

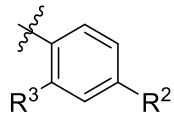
3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:
(i) Ring A is phenyl, 6-membered heteroaryl, or a 6,5-bicyclic heteroaryl, each of which is substituted with R^2, R^3, and 0 to 2 R^6;
(ii) Ring A is phenyl, 6-membered heteroaryl, or a 6,5-bicyclic heteroaryl, each of which is substituted with R^2, R^3, and 0 to 1 R^6;
(iii) Ring A is phenyl, pyridinyl, pyrazinyl, or indazolyl, each of which is substituted with R^2, R^3, and 0 to 2 R^6;

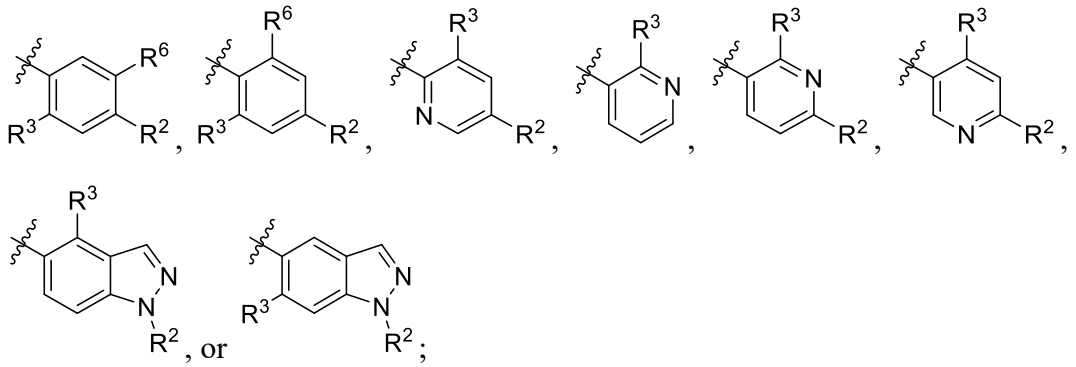
(iv) Ring A is phenyl, pyridinyl, or indazolyl, each of which is substituted with R^2, R^3, and 0 to 1 R^6;

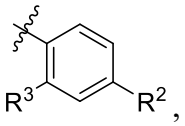
(v) Ring A is represented by the following structural formula: , , , , , or ; each of which is substituted with R^2, R^3, and 0 to 2 R^6;

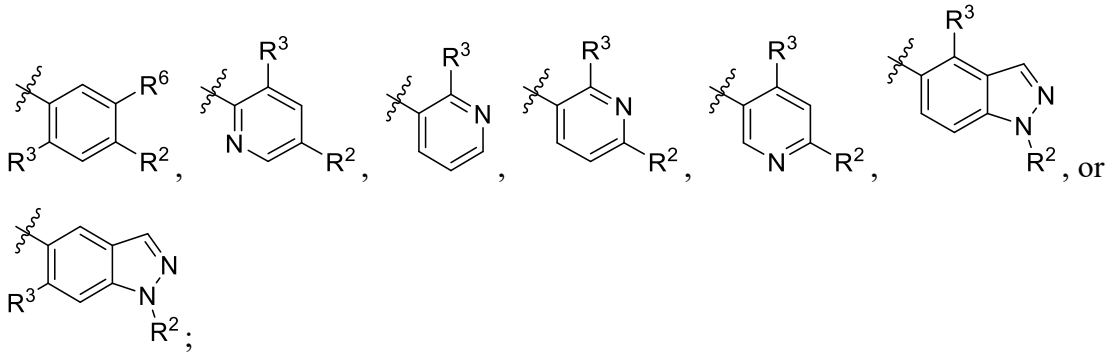
(vi) Ring A is represented by the following structural formula: , , , , or ; each of which is substituted with R^2, R^3, and 0 to 1 R^6;

(vii) Ring A is represented by the following structural formula: , , , , , , , , , , or ;

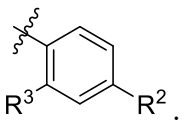
(viii) Ring A is represented by the following structural formula: ,



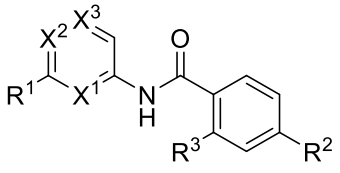
(ix) Ring A is represented by the following structural formula: ,



(x) Ring A is phenyl substituted with R^2 and R^3; or

(xi) Ring A is represented by the following structural formula: .

4. The compound of any one of claims 1 to 3, wherein the compound is represented by Formula (IA):

 (IA),

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are both N and X^3 is CR^4; or

X^1 and X^3 are both N and X^2 is CR^5.

6. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein:

(i) X^3 is CR^4, one of X^1 or X^2 is N, and the other is CR^5; or

(ii) X^3 is CR^4, and X^1 and X^2 are both CR^5.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^4 is H or $–CH_3$ and R^5 is H, -F, or $–CH_3$;

(ii) R^4 is H or $–CH_3$ and R^5 is H or $–CH_3$; or

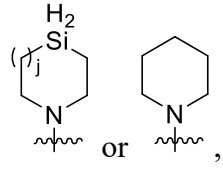
(iii) R^4 is H and R^5 is H or $–CH_3$.

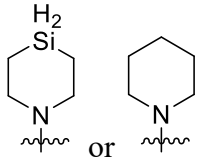
8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein:

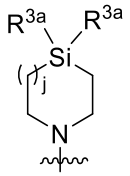
(i) R^3 is a 5- or 6-membered monocyclic heterocyclyl optionally substituted with 1 to 3 R^{3a};

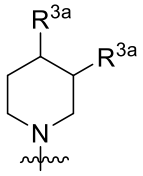
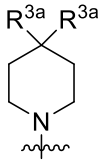
(ii) R^3 is a 6-membered monocyclic heterocyclyl optionally substituted with 1 to 3 R^{3a};

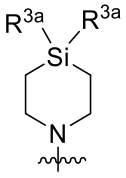
(iii) R^3 is piperdinyl, 1,3-azasilolidinyl, or 1,4-azasilinanyl, each of which is optionally substituted with 1 to 3 R^{3a}; or

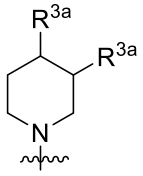
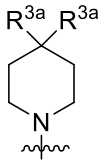
(iv) R^3 is represented by the following structural formula:  or , wherein j is 0 or 1, each of which is optionally substituted with 1 to 3 R^{3a};

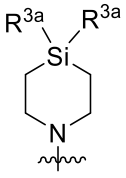
(v) R^3 is represented by the following structural formula:  or , each of which is optionally substituted with 1 to 3 R^{3a};

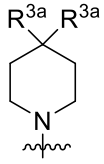
(vi) R^3 is represented by the following structural formula: ,

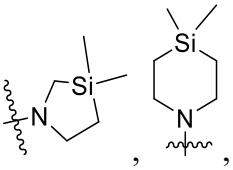
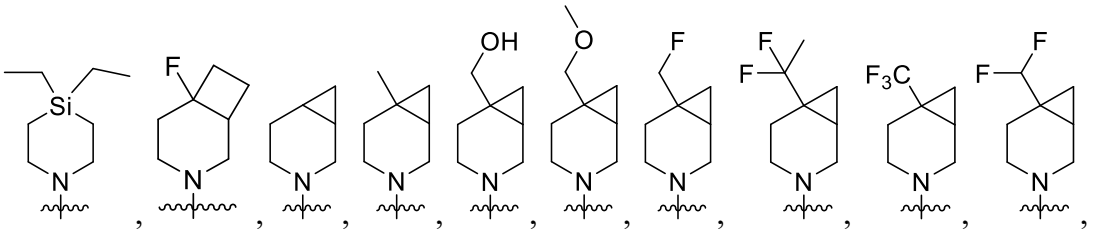
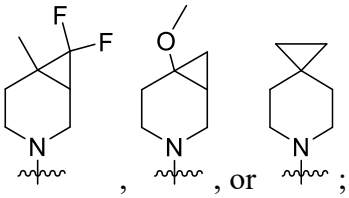
, or ; and each R^{3a} is $C_{1\text{-}3}$alkyl, or two R^{3a}, together with the atom or atoms to which they are attached, form $C_{3\text{-}6}$cycloalkyl substituted with 1 to 3 R^{3b};

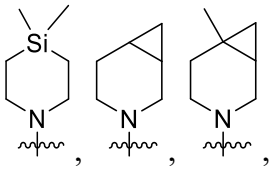
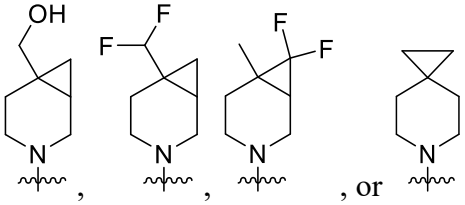
(vii) R^3 is represented by the following structural formula: ,

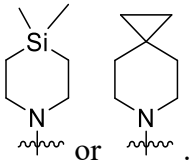
, or ; and each R^{3a} is $C_{1\text{-}3}$alkyl, or two R^{3a}, together with the atom or atoms to which they are attached, form $C_{3\text{-}6}$cycloalkyl substituted with 1 to 3 R^{3b};

(viii) R^3 is represented by the following structural formula:  or

; and each R^{3a} is $C_{1\text{-}3}$alkyl, or two R^{3a}, together with the atom to which they are attached, form $C_{3\text{-}6}$cycloalkyl;

(ix) R^3 is represented by the following structural formula: , , , or ;

(x) R^3 is represented by the following structural formula: , , or ; or

(xi) R^3 is represented by the following structural formula: .

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein:

(i) each R^{3a} is $–CH_3$ or $-CH_2CH_3$, or two R^{3a}, together with the atom or atoms to which they are attached, form cyclopropyl or cyclobutyl substituted with 1 to 3 R^{3b}, and each R^{3b} is independently H, halo, $-CH_3$, $-OCH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CF_2CH_3$, $-CH_2OCH_3$, or $-CH_2OH$;

(ii) each R^{3a} is $–CH_3$, or two R^{3a}, together with the atom or atoms to which they are attached, form cyclopropyl substituted with 1 to 3 R^{3b}, and each R^{3b} is independently H, halo, $-CH_3$, $-CHF_2$, or $-CH_2OH$;

(iii) each R^{3a} is $–CH_3$, or two R^{3a}, together with the atom to which they are attached, form cyclopropyl; or

(iv) R^{3a} is $–CH_3$.

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^1 is C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, or SO_2R^{1a}, wherein the C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{1b};

R^{1a} is -NHR^{N1b}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 to 3 halo;

R^{N1b} is C_{1-4}alkyl optionally substituted with 1 or 2 R^{1b};

R^{O1a} is C_{1-3}alkyl optionally substituted with 1 to 3 R^{1b};

each R^{1b} is independently selected from halo, cyano, C_{1-3}haloalkyl, and C_{1-3}alkyl;

or two R^{1b}, together with the atom or atoms to which they are attached, form C_{3-6}cycloalkyl;

(ii) R^1 is C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, or SO_2R^{1a}, wherein the C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{1b};

R^{1a} is -NHR^{N1b}, C_{3-6}cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1 to 3 halo;

R^{N1b} is C_{1-4}alkyl optionally substituted with 1 or 2 R^{1b};

R^{O1a} is C_{1-3}alkyl optionally substituted with 1 to 3 R^{1b};

each R^{1b} is independently selected from halo and C_{1-3}alkyl;

or two R^{1b}, together with the atom to which they are attached, form C_{3-6}cycloalkyl;

(iii) R^1 is C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, OR^{O1a}, or SO_2R^{1a}, wherein the C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{1b};

R^{1a} is -NHR^{N1b} or C_{3-6}cycloalky;

R^{N1b} is C_{1-4}alkyl optionally substituted with 1 or 2 R^{1b};

R^{O1a} is C_{1-3}alkyl optionally substituted with 1 to 3 R^{1b};

each R^{1b} is independently selected from halo and C_{1-3}alkyl;

or two R^{1b}, together with the atom to which they are attached, form C_{3-6}cycloalkyl;

(iv) R^1 is $–S(O)_2NHC(CH_3)_3$, $-SO_2$-cyclopentyl, $-SO_2$-piperdinyl, $-OCH_2CH_2CF_3$, $-OCH_2CH(OH)CF_3$, cyclopropyl, cyclohexyl, morpholinyl, piperdinyl, azetidinyl, 3H-diazirinyl, or pyrrolidinyl, wherein the cyclopropyl, cyclohexyl, morpholinyl, piperdinyl, piperdinyl of the $–SO_2$-piperdinyl, azetidinyl, 3H-diazirinyl, and pyrrolidinyl are each optionally substituted with 1 to 3 R^{1b}; and

each R^{1b} is –F -CN, $-CF_3$, or $–CH_3$;

or two R^{1b}, together with the atom to which they are attached, form cyclopropyl;

(v) R^1 is $–S(O)_2NHC(CH_3)_3$, $-SO_2$-cyclopentyl, $-SO_2$-piperdinyl, $-OCH_2CH_2CF_3$, cyclopropyl, cyclohexyl, morpholinyl, piperdinyl, azetidinyl, or pyrrolidinyl, wherein the cyclopropyl, cyclohexyl, morpholinyl, piperdinyl, piperdinyl of the $–SO_2$-piperdinyl, azetidinyl, and pyrrolidinyl are each optionally substituted with 1 to 3 R^{1b}; and

each R^{1b} is –F or $–CH_3$;

or two R^{1b}, together with the atom to which they are attached, form cyclopropyl;

(vi) R^1 is $–S(O)_2NHC(CH_3)_3$, $-SO_2$-cyclopentyl, $-OCH_2CH_2CF_3$, cyclopropyl, cyclohexyl, morpholinyl, piperdinyl, azetidinyl, or pyrrolidinyl, wherein the cyclopropyl, cyclohexyl, morpholinyl, piperdinyl, azetidinyl, and pyrrolidinyl are each optionally substituted with 1 to 3 R^{1b}; and

each R^{1b} is –F or $–CH_3$;

or two R^{1b}, together with the atom to which they are attached, form cyclopropyl;

(vii) R^1 is C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, or SO_2R^{1a}, wherein the C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{1b};

R^{1a} is $-NHR^{N1b}$;

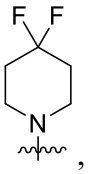
R^{N1b} is C_{1-4}alkyl;

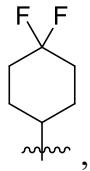
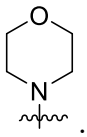
each R^{1b} is independently halo;

(viii) R^1 is $–S(O)_2NHC(CH_3)_3$, cyclohexyl, morpholinyl, or piperdinyl, wherein the cyclohexyl, morpholinyl, and piperdinyl are each optionally substituted with 1 to 3 R^{1b}; and

each R^{1b} is –F; or

(ix) R^1 is



$–S(O)_2NHC(CH_3)_3$, or R^1 is represented by the following structural formula: ,  , or  .

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^2 is H, $C_{1\text{-}3}$alkyl, $NR^{N2a}R^{N2b}$, SO_2R^{2a}, $S(O)(NH)R^{2a}$, or $NHSO_2R^{2a}$, wherein the $C_{1\text{-}3}$alkyl is optionally substituted with 1 to 3 R^{2b};

R^{2a} is $C_{1\text{-}4}$alkyl, $-NHR^{N2b}$, $C_{3\text{-}4}$cycloalkyl, or 3- to 6-membered monocyclic heterocyclyl, wherein the $C_{1\text{-}3}$ alkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{2b};

R^{N2a} and R^{N2b} are each independently H or $C_{1\text{-}3}$alkyl optionally substituted with 1 to 3 R^{2b};

each R^{2b} is independently selected from hydroxy, $-N(R^{N2c})_2$ and $C_{1\text{-}3}$alkyl;

each R^{N2c} is independently H, $C_{1\text{-}3}$alkyl, $-C(O)(C_{1\text{-}3}$alkyl);

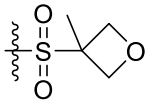
(ii) R^2 is H, $C_{1\text{-}3}$alkyl, SO_2R^{2a}, or $NHSO_2R^{2a}$, wherein the $C_{1\text{-}3}$alkyl is optionally substituted with 1 to 3 R^{2b};

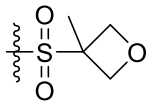
R^{2a} is $C_{1\text{-}4}$alkyl, $-NHR^{N2b}$, or 3- to 6-membered monocyclic heterocyclyl, wherein the $C_{1\text{-}3}$ alkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{2b};

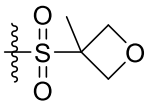
R^{N2b} is $C_{1\text{-}3}$alkyl optionally substituted with 1 to 3 R^{2b};

each R^{2b} is independently selected from hydroxy and $C_{1\text{-}3}$alkyl;

(iii) R^2 is H, $–NHS(O)_2CH_3$, $–NHS(O)_2CH_2CH_2OH$, $–NHS(O)_2CH_2CH_2NH_2$, $–NHS(O)_2CH_2CH_2NHCH_3$, $NHS(O)_2CH_2CH_2NHC(O)CH_3$, $–NHS(O)_2C(CH_3)_3$, $-NHS(O)_2NHCH_3$, $-NHS(O)_2NHCH_2CH_2OH$, $-NHS(O)_2N(CH_3)CH_2CH_2OH$, $-S(O)_2NHCH_2CH_2OH$, $-NHC(CH_3)_2CH_2OH$, -S(O)(NH)-cyclopropyl, -

$S(O)_2CH_2CH_2OH$, $-CH_2CH_2OH$, $-N(CH_3)CH_2CH_2OH$, or R^2 is represented by the following formula: ;

(iv) R^2 is H, $–NHS(O)_2CH_3$, $–NHS(O)_2CH_2CH_2OH$, $–NHS(O)_2C(CH_3)_3$, $-NHS(O)_2NHCH_2CH_2OH$, $-S(O)_2NHCH_2CH_2OH$, $-CH_2CH_2OH$, or R^2 is represented by the following formula: ;

(v) R^2 is H, $–NHS(O)_2CH_3$, $–NHS(O)_2CH_2CH_2OH$, $–NHS(O)_2C(CH_3)_3$, $-S(O)_2NHCH_2CH_2OH$, $-CH_2CH_2OH$, or R^2 is represented by the following formula: ;

(vi) R^2 is $NHSO_2R^{2a}$;

R^{2a} is $C_{1\text{-}4}$alkyl optionally substituted with 1 to 3 R^{2b};

each R^{2b} is hydroxyl; or

(vii) R^2 is $–NHS(O)_2CH_2CH_2OH$ or $–NHS(O)_2C(CH_3)_3$.

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein:

(i) R^4 is H or $C_{1\text{-}3}$alkyl; or

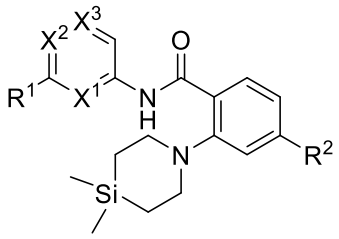
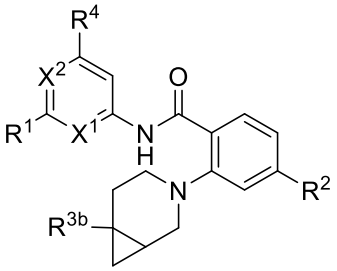
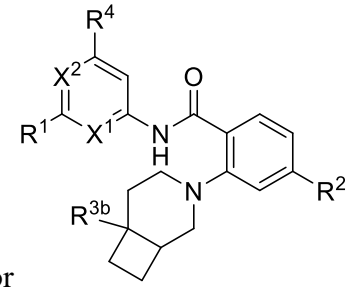
(ii) R^4 is H or $–CH_3$.

13. The compound of any one of claims 1 to 3 and 7 to 12, or a pharmaceutically acceptable salt thereof, wherein each R^6 is halo, preferably wherein R^6 is -F.

14. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein o is 0.

15. The compound of claim 1, wherein:

(i) the compound is represented by Formula (II), (III), or (IV):


(II),

(III),

or (IV),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

R^1 is C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, or SO_2R^{1a}, wherein the C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{1b};

R^{1a} is $-NHR^{N1b}$;

R^{N1b} is C_{1-4}alkyl;

each R^{1b} is independently halo;

R^2 is $NHSO_2R^{2a}$;

R^{2a} is C_{1-4}alkyl optionally substituted with 1 or 2 R^{2b};

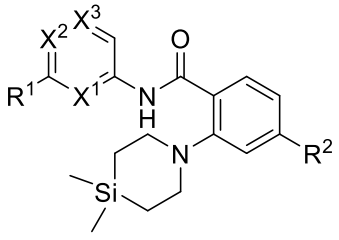
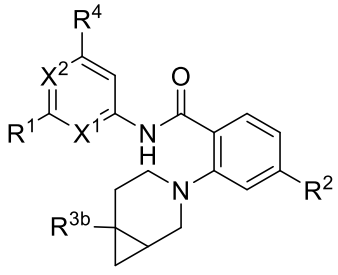
each R^{2b} is hydroxy;

R^{3b} is H, halo, C_{1-3}alkyl, or C_{1-3}haloalkyl;

R^4 is H or C_{1-3}alkyl;

R^5 is H or C_{1-3}alkyl;

(ii) the compound is represented by Formula (II) or (III):


(II) or

(III),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

R^1 is C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, or SO_2R^{1a}, wherein the C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{1b};

R^{1a} is -NHR^{N1b};

R^{N1b} is C_{1-4}alkyl;

each R^{1b} is independently halo;

R^2 is $NHSO_2R^{2a}$;

R^{2a} is C_{1-4}alkyl optionally substituted with 1 or 2 R^{2b};

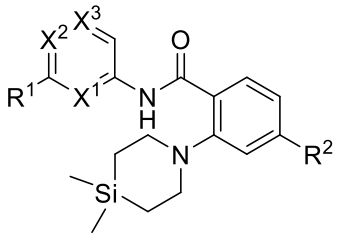
each R^{2b} is hydroxy;

R^{3b} is H, C_{1-3}alkyl, or C_{1-3}haloalkyl;

R^4 is H or C_{1-3}alkyl;

R^5 is H or C_{1-3}alkyl;

(iii) the compound is represented by Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are each independently CR^5 or N, and X^3 is CR^4 or N;

R^1 is C_{3-6}cycloalkyl, 3- to 6-membered monocyclic heterocyclyl, or SO_2R^{1a}, wherein the C_{3-6}cycloalkyl and 3- to 6-membered monocyclic heterocyclyl are each optionally substituted with 1 to 3 R^{1b};

R^{1a} is -NHR^{N1b};

R^{N1b} is C_{1-4}alkyl;

each R^{1b} is independently halo;

R^2 is $NHSO_2R^{2a}$;

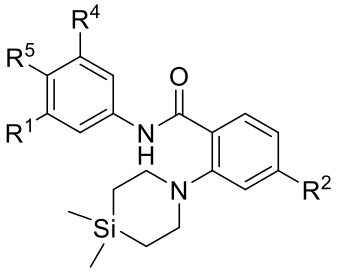
R^{2a} is C_{1-4}alkyl optionally substituted with 1 or 2 R^{2b};

each R^{2b} is hydroxy;

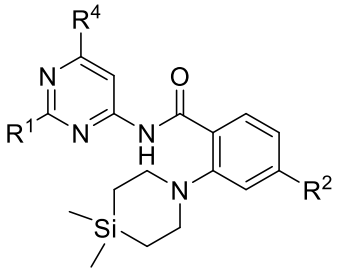
R^4 is H or C_{1-3}alkyl;

R^5 is H or C_{1-3}alkyl;

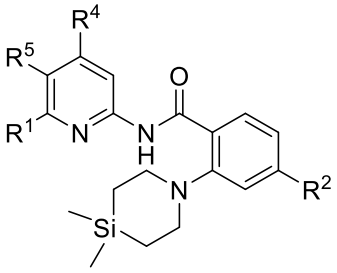
(iv) the compound is represented by Formula (IIA), (IIB), (IIC), (IID) (IIE), (IIIA), or (IVA):



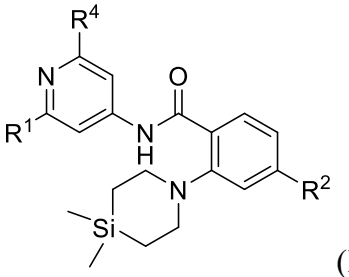
(IIA),



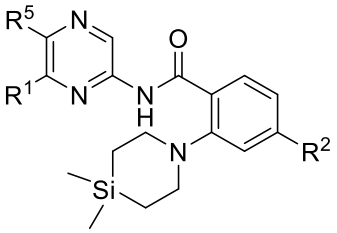
(IIB),



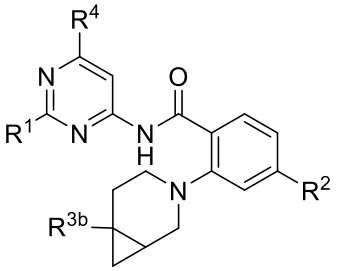
(IIC),



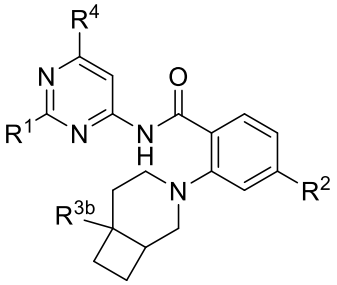
(IID),



(IIE),



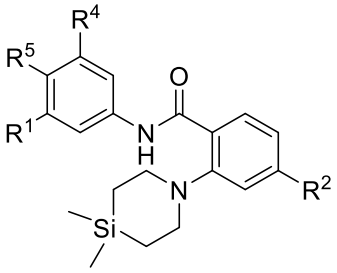
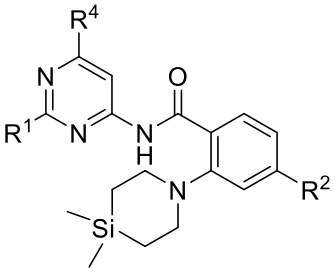
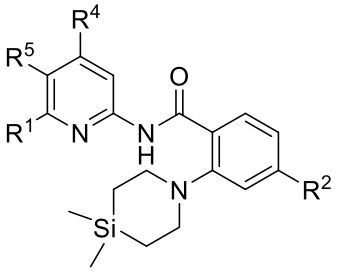
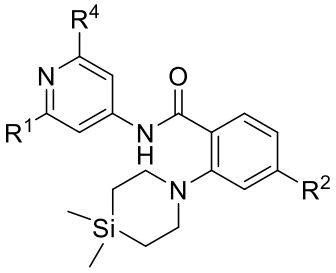
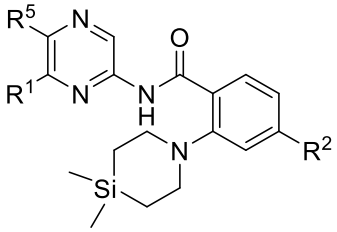
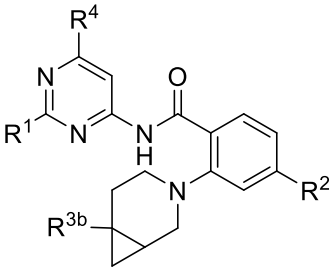
(IIIA), or



(IVA);

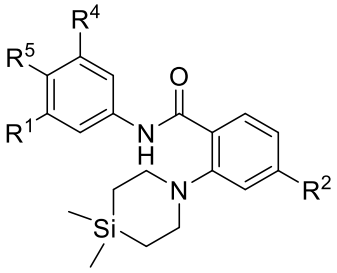
or a pharmaceutically acceptable salt thereof;

(v) the compound is represented by Formula (IIA), (IIB), (IIC), (IID) (IIE), or (IIIA):

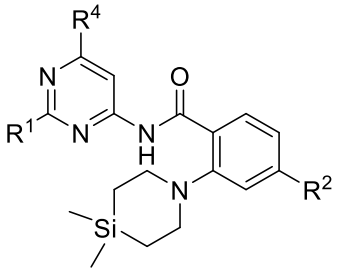

(IIA),

(IIB),

(IIC),

(IID),

(IIE), or

(IIIA);

or a pharmaceutically acceptable salt thereof;

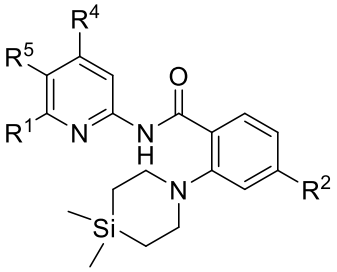
(vi) the compound is represented by Formula (IIA), (IIB), (IIC), (IID) or (IIE):



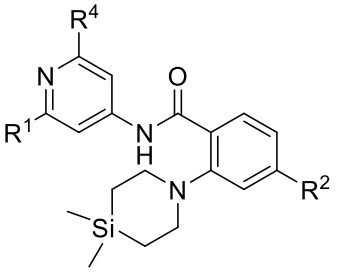
(IIA),



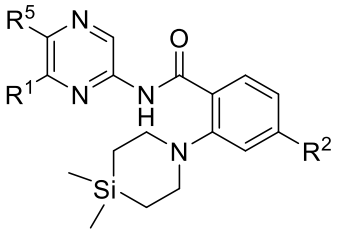
(IIB),



(IIC),



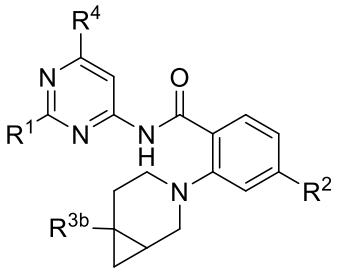
(IID), or



(IIE);

or a pharmaceutically acceptable salt thereof;

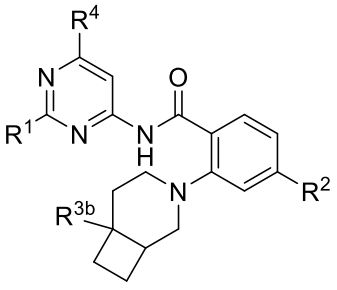
(vii) the compound is represented by Formula (IIIA):



(IIIA),

or a pharmaceutically acceptable salt thereof; or

(viii) the compound is represented by Formula (IVA):



(IVA);

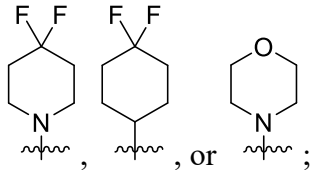
or a pharmaceutically acceptable salt thereof.

16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein:

(a)

(i) R^1 is $–S(O)_2NHC(CH_3)_3$, cyclohexyl, morpholinyl, or piperdinyl, wherein the cyclohexyl, morpholinyl, and piperdinyl are each optionally substituted with 1 to 2 R^{1b}; and

each R^{1b} is –F; or

(ii) R^1 is $–S(O)_2NHC(CH_3)_3$, or R^1 is represented by the following structural formula: 

, , or ;

(b) R^2 is $–NHS(O)_2CH_2CH_2OH$ or $–NHS(O)_2C(CH_3)_3$;

(c) R^4 and R^5 are each H or $–CH_3$; and/or

(d)

(i) R^{3b} is H, -F, $-CH_3$, $-CH_2F$, or $–CHF_2$; or

(ii) R^{3b} is H, $-CH_3$, or $–CHF_2$.

17. The compound of claim 1, wherein the compound is selected from any one of Examples 1-134, or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

19. Use of the compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for treating a KIF18A mediated disease or disorder.

20. The use of claim 19, wherein the disease or disorder is:

(i) a cancer;

(ii) a chromosomally unstable cancer;

(iii) a cancer that displays whole-genome doubling;

(iv) a cancer that has a mutation in TP53, BRCA1, BRCA2, RB1, and/or an amplification in CCNE1;

(v) small-cell lung cancer, non-small cell lung cancer, pancreatic cancer, triple-negative breast cancer, colorectal cancer, hepatobiliary cancer, esophagogastric cancer, endometrial cancer, head and neck squamous cell carcinoma, ovarian cancer, platinum resistant ovarian cancer, bladder cancer, soft-tissue sarcoma, renal cell cancer, uterine cancer, cervical cancer, or bone cancer; and/or

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

21. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 18, for use in treating a KIF18A mediated disease or disorder.

22. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 18, for use in therapy.