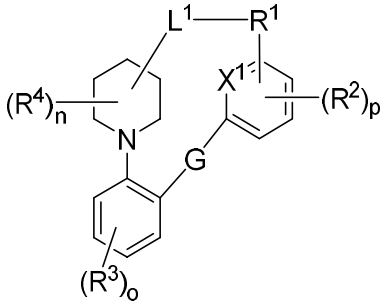
Q is optionally substituted C_1-C_6alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

[0006a] In one aspect, there is provided a compound having the structure of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein:

X^1 is N;

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond, -O-, -NL^{1a1}-, -S-, or -SO_2-;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is -NR^{1a}-;

R^{1a} is hydrogen, -C(=O)R^{1a1}, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or -SO_2-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl; each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, -$(CH_2)_m$-$N(R^{3a})_2$-, -OR^{3a}, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -SR^{3a}, -SO_2R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NH-S(O)(NH)-R^{3a}, -NH-S(O)(NH)-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)R^{3a}$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, -$B(R^{3a})_3$, -$P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl,

optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -$N(R^{3b})_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

k is 0 to 2;

l is 0 to 2 ;

m is 1 to 6;

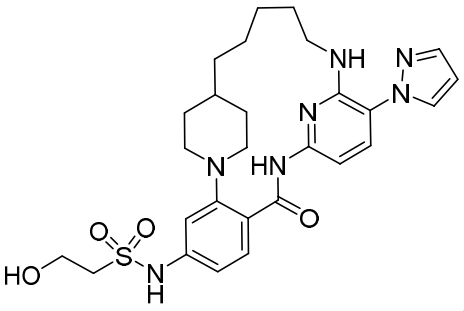
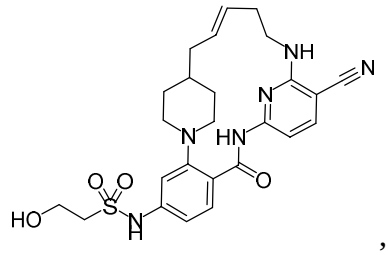
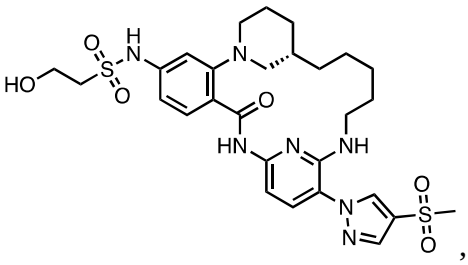
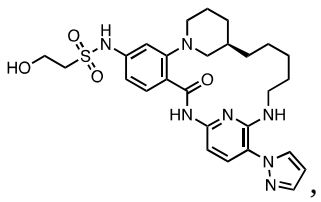
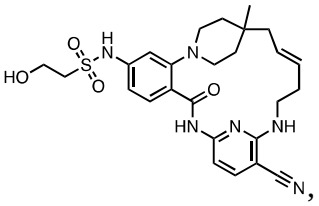
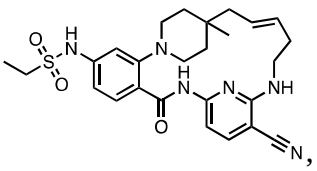
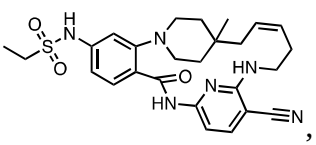
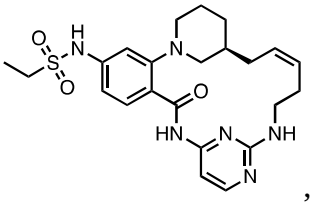
n is 0;

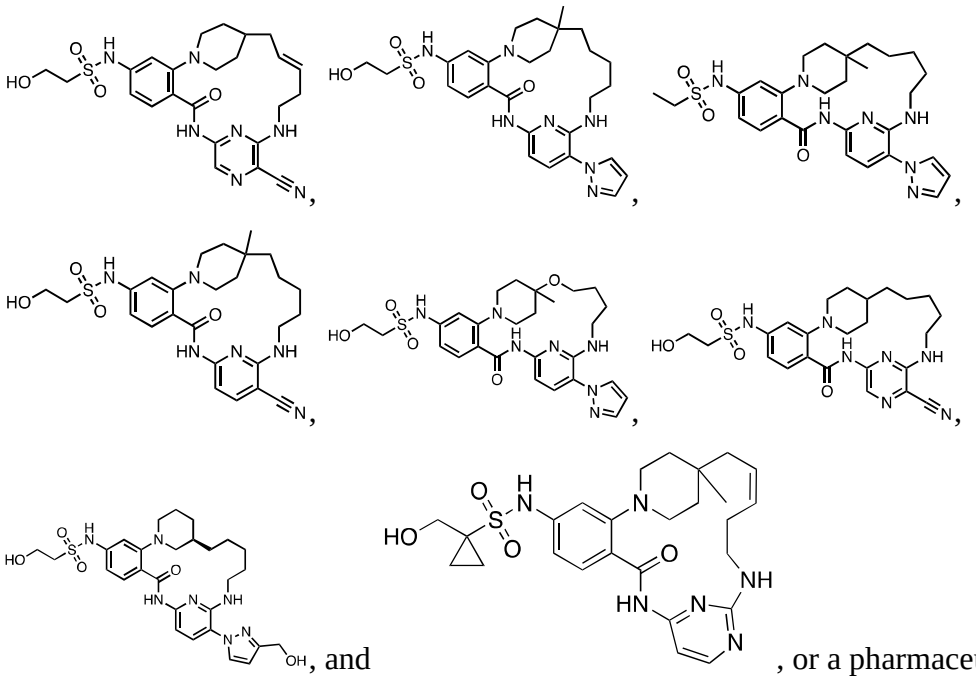
o is 0 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

[0006b] In another aspect, the present disclosure provides a compound selected from:


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, and , or a pharmaceutically acceptable salt or solvate thereof.

[0006c] In yet another aspect, there is provided a pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt or solvate thereof, as described herein, and a pharmaceutically acceptable excipient.

[0006d] In another aspect, the present disclosure provides a use of a compound as described herein in the manufacture of a medicament for treating cancer in a patient in need thereof.

[0007] Provided in some embodiments herein is a composition comprising a protein and a compound, wherein the protein is KIF18A, the compound is a compound of Formula (B), and the protein and the compound form the adduct described herein.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The KIF18A gene is part of the Kinesin-8 subfamily. KIF18A is a plus-end-directed motor. In some instances, KIF18A influences dynamics at the plus end of kinetochore microtubules, such as controlling chromosomal positioning and spindle tension. In some instances, depletion of KIF18A leads to longer spindles, increased chromosome oscillation at metaphase, and activation of the mitotic spindle assembly checkpoint.

[0009] KIF18A is a potential target for treating cancer, such as cancers where KIF18A is overexpressed and/or that depend on KIF18A for cell division and survival. For example, such cancers include colon, breast, lung, pancreas, prostate, bladder, head, neck, cervix, and ovarian cancers. In some instances, genetic deletion, knockdown, or inhibition of KIF18A affects mitotic spindle apparatus. In some instances, inhibition of KIF18A induces mitotic cell arrest.

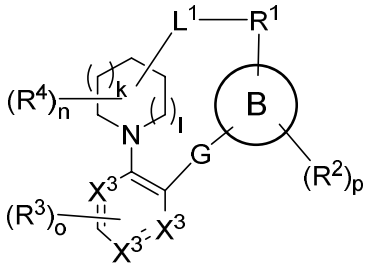
In some instances, mitotic cell arrest is a vulnerability that can promote cell death in mitosis via apoptosis, mitotic catastrophe, or multipolarity driven lethality or death after mitotic slippage in interphase.

[00010] Provided in some embodiments herein are KIF18A modulators.

Compounds

[00011] The compounds described herein can be useful as KIF18A modulators. In some embodiments, the compounds described herein are KIF18A inhibitors.

[00012] Provided in some embodiments herein is a compound having the structure of Formula (I-1), or a pharmaceutically acceptable salt or solvate thereof:



(I-0)

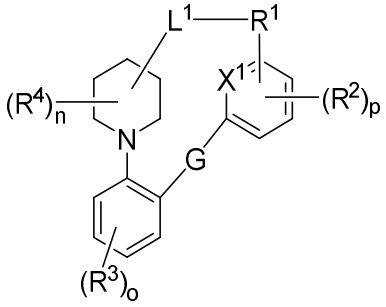
wherein:

each X^3 is independently CH or N;

ring B is a 5- or 6- membered heteroaryl or phenyl;

CLAIMS

1. A compound having the structure of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein:

X^1 is N;

L^1 is a linker comprising the structure $-L^{1a}-L^{1b}-$;

L^{1a} is a bond, -O-, $-NL^{1a1}-$, -S-, or $-SO_2-$;

L^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2$-C_1-C_6 alkyl;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

G is -(C=O)-NH- or -NH-(C=O)-;

R^1 is $-NR^{1a}-$;

R^{1a} is hydrogen, $-C(=O)R^{1a1}$, optionally substituted C_1-C_6 alkyl, C_1-C_6alkylene-C_3-C_6 cycloalkyl, or $-SO_2$-C_1-C_6 alkyl;

R^{1a1} is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

each R^2 is independently halogen, $-OR^{2a}$, $-N(R^{2a})_2$, $-S(O)_2N(R^{2a})_2$, $-SO_2$-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl; each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently halogen, -CN, $-(CH_2)_m-N(R^{3a})_2-$, $-OR^{3a}$, $-N(R^{3a})_2$, $-N(SO_2R^{3b})R^{3a}$, $-SR^{3a}$, $-SO_2R^{3a}$, $-NR^{3a}-S(O)_2-(CH_2)_m-R^{3a}$, $-NH-S(O)(NH)-R^{3a}$, $-NH-S(O)(NH)-(CH_2)_m-R^{3a}$, $-NR^{3a}-S(O)_2-(CH_2)_m-OR^{3b}$, $-NH-S(O)R^{3a}-(CH_2)_m-OR^{3b}$, $-NH-S(O)_2-R^{3c}$, $-B(R^{3a})_3$, $-P(R^{3a})_3$, optionally substituted C_3-C_8 cycloalkyl,

optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{3a} is independently hydrogen, -C(O)OR^{3b}, optionally substituted C_1-C_6 alkyl, or -N(R^{3b})$_2$;

R^{3b} is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_2-C_6 alkenyl;

R^{3c} is C_3-C_8 cycloalkyl or 3- to 8- membered heterocycle;

k is 0 to 2;

l is 0 to 2 ;

m is 1 to 6;

n is 0;

o is 0 to 4;

p is 0 to 4; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

2. The compound of claim 1, wherein

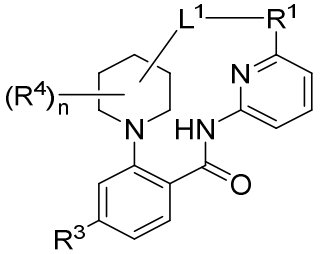
k is 0 or 1;

l is 0 or 1;

o is 1; and

p is 0 to 2.

3. The compound of claim 1, wherein the compound has the structure of Formula (III-A), or a pharmaceutical salt or solvate thereof:



(III-A),

wherein:

L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene;

R^1 is -NR^{1a}-;

R^{1a} is hydrogen, -C(=O)H, optionally substituted C_1-C_6 alkyl, or C_1-C_6alkylene-C_3-C_6 cycloalkyl;

R^3 is halogen, -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

R^{3a} is C_1-C_6 alkyl;

R^{3b} is hydrogen or C_1-C_6 alkyl;

m is 1 to 3; and

n is 0.

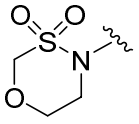
4. The compound of any one of claims 1 to 3, wherein R^2 is halogen, -OR^{2a}, -$N(R^{2a})_2$, optionally substituted C_1-C_6 alkyl, or -$S(O)_2N(R^{2a})_2$.

5. The compound of any one of claims 1 to 4, wherein L^{1a} is a bond or -O-.

6. The compound of any one of claims 1 to 5, wherein R^{1a} is hydrogen.

7. The compound of any one of claims 1 to 5, wherein L^1-R^1 is –$(CH_2)_4NH$–, –cyclopropyl-$(CH_2)_3NH$–, –$(CH_2)_3NH$–, –$(CH_2)_3NCH_3$–, –$(CH_2)_2NH$–, or –$O(CH_2)_2NH$–.

8. The compound of any one of claims 1 to 7, wherein each R^3 is independently -$N(R^{3a})_2$, -$N(SO_2R^{3b})R^{3a}$, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-R^{3a}, -NR^{3a}-$S(O)_2$-$(CH_2)_m$-OR^{3b}, -NH-$S(O)_2$-R^{3c}, or optionally substituted 5- to 8- membered heterocycle.

9. The compound of claim 8, wherein each R^3 is independently -$NHSO_2(CH_2)_2OH$, -$NHSO_2C(CH_3)_2CH_2OH$, -$NHSO_2C$(cyclopropyl)CH_2OH, -$NHSO_2CH(CH_3)CH_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2CHCH_2$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or .

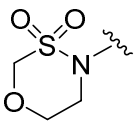
10. A compound having the structure of a compound of Table 1 or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein:

L^{1a} is a bond or -O-;

G is -(C=O)-NH-;

R^{1a} is hydrogen;

each R^3 is independently -$NHSO_2(CH_2)_2OH$, -$NHSO_2C(CH_3)_2CH_2OH$, -$NHSO_2C$(cyclopropyl)CH_2OH, -$NHSO_2CH(CH_3)CH_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2CHCH_2$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or ;

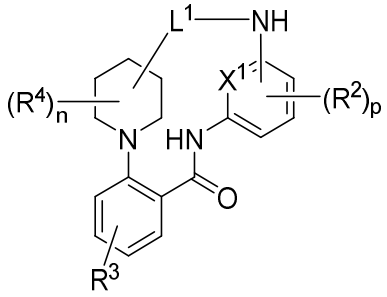
k is 0 or 1;

l is 0 or 1;

o is 1; and

p is 0 or 1.

12. The compound of claim 11, wherein the compound has the structure of Formula (I-a):



(I-a),

or a pharmaceutical salt or solvate thereof, wherein:

X^1 is N;

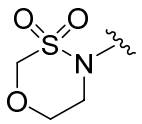
L^1 is a linker comprising the structure -L^{1a}-L^{1b}-;

L^{1a} is a bond or -O-;

L^{1b} is optionally substituted C_1-C_8 alkylene, optionally substituted C_2-C_8 alkenylene, or optionally substituted C_2-C_8 alkynylene;

each R^2 is independently halogen, -OR^{2a}, -$N(R^{2a})_2$, -$S(O)_2N(R^{2a})_2$, -SO_2-C_1-C_6 alkyl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl, or two R^2 are taken together to form an oxo, an optionally substituted C_3-C_8 cycloalkyl, an optionally substituted 5- to 8- membered heterocycle, or optionally substituted 5- to 8- membered heteroaryl;

each R^{2a} is independently hydrogen or optionally substituted C_1-C_6 alkyl;

each R^3 is independently -$NHSO_2(CH_2)_2OH$, -$NHSO_2C(CH_3)_2CH_2OH$, -$NHSO_2C$(cyclopropyl)CH_2OH, -$NHSO_2CH(CH_3)CH_2OH$, -$NMeSO_2(CH_2)_2OH$, -$NHSO_2CH_2CH_3$, -$NHSO_2CHCH_2$, -$NHSO_2$-oxetanyl, -$NMeSO_2CH_3$, -$N(SO_2Me)(CH_2)_2OH$, or ;

k is 0 or 1;

l is 0 or 1;

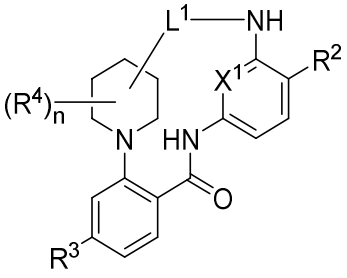
n is 0;

o is 1;

p is 0 or 1; and

wherein when any one of variable G, L^1, R^1, R^2, R^3, or R^4 are present, the bond to variable G, L^1, R^1, R^2, R^3 or R^4 replaces a hydrogen on a carbon or nitrogen atom.

13. The compound of claim 11 or claim 12, wherein the compound has the structure of Formula (II-a):

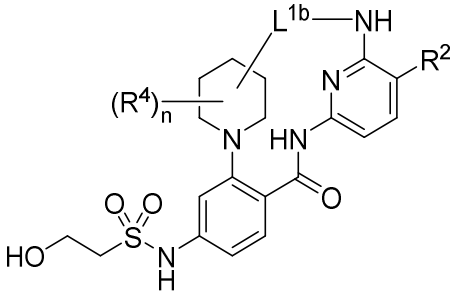


(II-a),

or a pharmaceutical salt or solvate thereof.

14. The compound of any one of claims 11 to 13, or a pharmaceutical salt or solvate thereof, wherein L^{1a} is a bond; and R^3 is $-NHS(O)_2-(CH_2)_2-OH$.

15. The compound of any one of claims 11 to 14, wherein the compound has the structure of Formula (V), or a pharmaceutical salt or solvate thereof:



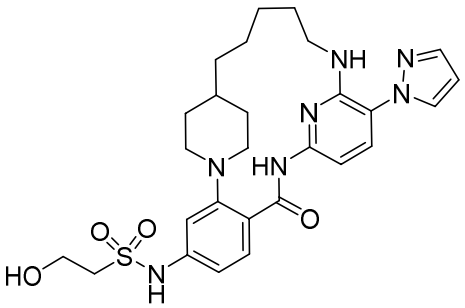
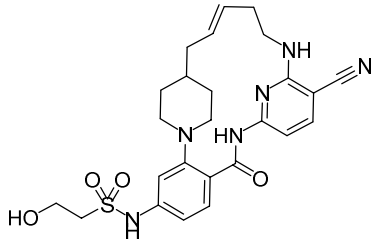
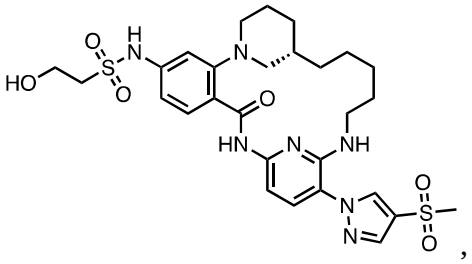
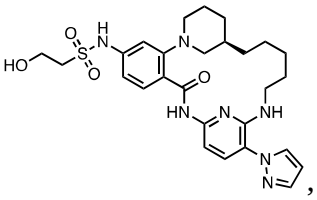
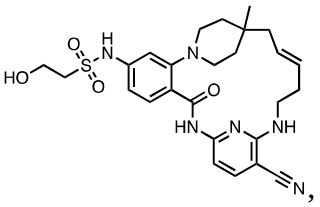
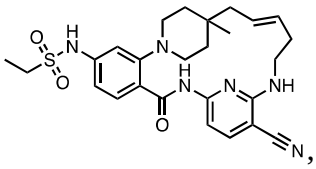
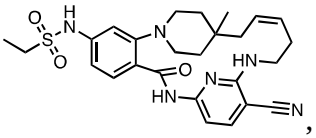
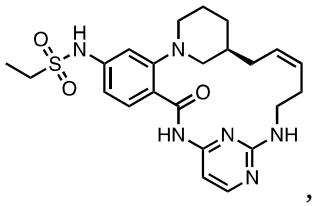
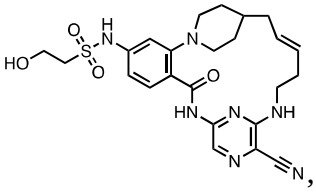
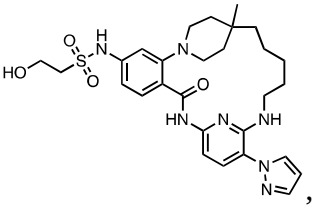
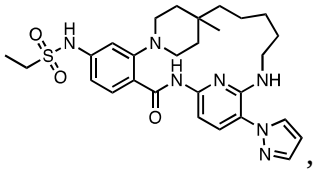
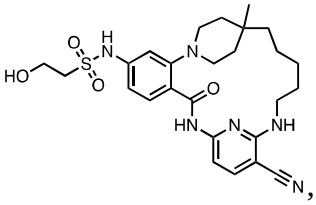
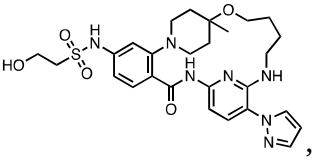
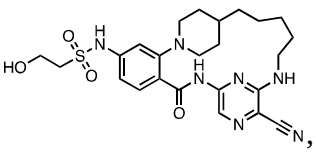
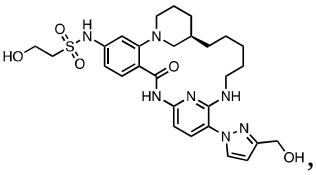
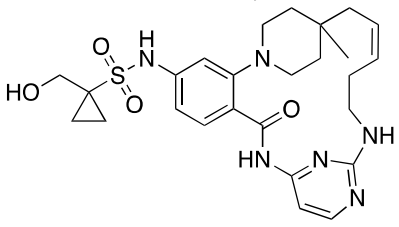
(V).

16. The compound of any one of claims 11 to 15, or a pharmaceutical salt or solvate thereof, wherein R^2 is a 5- to 8- membered heteroaryl.

17. The compound of any one of claims 11 to 16, or a pharmaceutical salt or solvate thereof, wherein R^2 is a pyrazolyl.

18. The compound of any one of claims 11 to 17, or a pharmaceutical salt or solvate thereof, wherein L^{1b} is optionally substituted C_1-C_6 alkylene, optionally substituted C_2-C_6 alkenylene, or optionally substituted C_2-C_6 alkynylene.

19. A compound selected from:


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, or a pharmaceutically acceptable salt or solvate thereof.

20. A pharmaceutical composition comprising a compound, or pharmaceutically acceptable salt or solvate thereof, as described in any one of claims 1 to 19, and a pharmaceutically acceptable excipient.

21. Use of a compound as described in any one of claims 1 to 19 in the manufacture of a medicament for treating cancer in a patient in need thereof.

22. The use of claim 21 wherein the cancer is bladder cancer, endometrial cancer, lung squamous cell cancer, breast cancer, colon cancer, kidney cancer, liver cancer, lung cancer, small cell lung cancer, esophagus cancer, gall-bladder cancer, brain cancer,

head and neck cancer, ovarian cancer, pancreas cancer, stomach cancer, cervix cancer, thyroid cancer, prostate cancer or skin cancer.