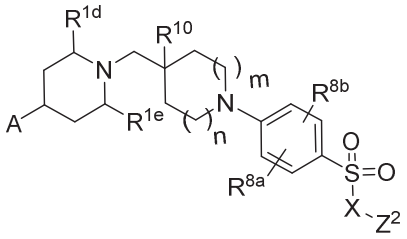
[0008] Small molecules that disrupt the interaction of MLL and menin are disclosed in U.S. Patent Nos. 9,212,180 and 9,216,993; and U.S. Patent Application Publication Nos. 2011/0065690; 2014/0275070; 2016/0045504; and 2016/0046647. Peptides that disrupt the interaction of MLL and menin are disclosed in U.S. Patent Application Publication No. 2009/0298772.

[0009] There is an ongoing need for new agents, e.g., small molecules, for treating cancer and other diseases responsive to menin inhibition.

BRIEF SUMMARY OF THE INVENTION

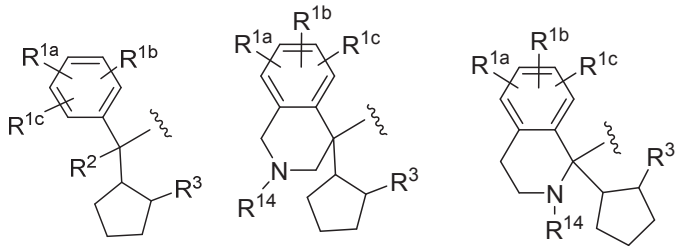
In one aspect, the present disclosure refers to a compound having Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is selected from the group consisting of:



A-1 , A-2 and A-3 ;

R^{1a}, R^{1b}, and R^{1c} are each independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

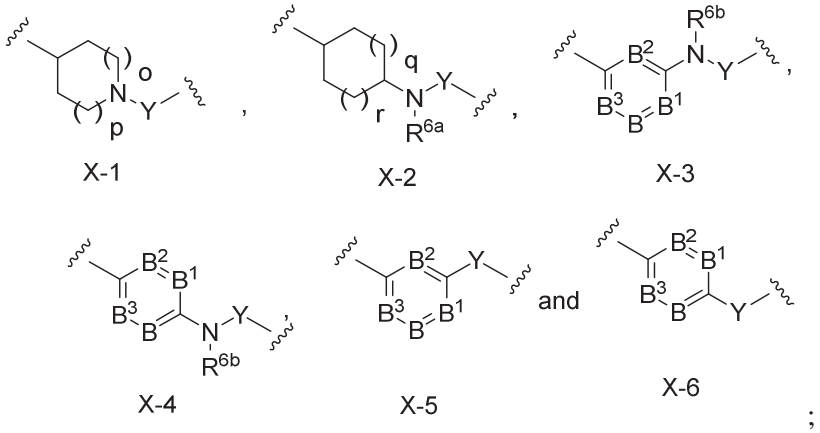
R^{1d} and R^{1e} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

R^2 is selected from the group consisting of hydroxy, amino, cyano, and -CH_2R^4;R^3 is selected from the group consisting of hydrogen, -$OC(=O)NR^{11a}R^{11b}$, -$NHC(=O)R^5$, and -NHZ^1;

R^4 is selected from the group consisting of amino, optionally substituted aryl, and optionally substituted heteroaryl;

R^5 is selected from the group consisting of -$NR^{12a}R^{12b}$, C_{1-4} alkoxy, and C_{1-4} alkyl;

X is selected from the group consisting of:



;

wherein Y is attached to Z^2; or

X is absent;

Y is selected from the group consisting of -C(=O)- and -$S(=O)_2$-;

R^{6a} and R^{6b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

m, n, o, p, q, and r are each independently 0, 1, 2, or 3;

Z^1 is selected from the group consisting of -$C(=O)R^7$ and -$S(=O)_2R^7$;

Z^2 is selected from the group consisting of -$CH=CHR^{13}$, -$C\equiv CR^{13}$, -CH_2Cl, -CH_2Br, -CH_2I, alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl,

with proviso that Z^2 is -$CH=CHR^{13}$, -$C\equiv CR^{13}$, -CH_2Cl, -CH_2Br, or -CH_2I, when R^3 is hydrogen, -$OC(=O)NR^{11a}R^{11b}$, or -$NHC(=O)R^5$,

R^7 is selected from the group consisting of -$CH=CHR^{13}$, -$C\equiv CR^{13}$, -CH_2Cl, -CH_2Br, and -CH_2I;

R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen, hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^{9a} is selected from the group consisting of hydrogen, hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^{10} is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and hydroxy;

R^{11a} and R^{11b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl; or

R^{11a} and R^{11b} taken together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclo; and

R^{12a} and R^{12b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl; or

R^{12a} and R^{12b} taken together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclo;

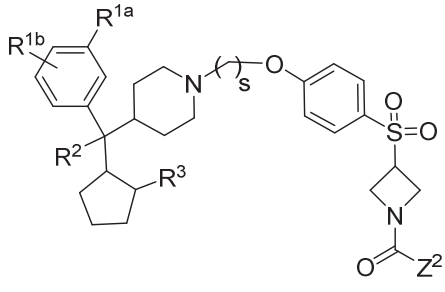
R^{13} is selected from the group consisting of hydrogen, C_{1-4} alkyl, and (amino)alkyl;

R^{14} is selected from the group consisting of hydrogen and C_{1-4} alkyl; and

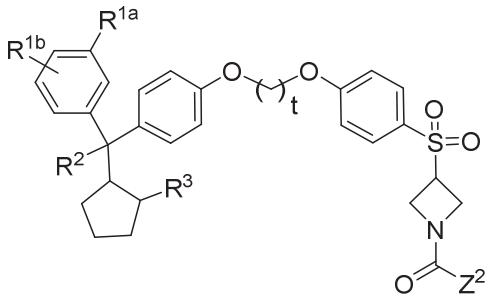
B, B^1, B^2, and B^3 are each independently selected from the group consisting of $=CR^{9a}$- and =N-,

with proviso that at least one of B, B^1, B^2, and B^3 is $=CR^{9a}$-.

In another aspect, the present disclosure refers to a compound having Formula **XV** or Formula **XVI**:



XV,



XVI,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{1a} and R^{1b} are each independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^2 is selected from the group consisting of hydroxy, amino, cyano, and $-CH_2R^4$;

R^3 is selected from the group consisting of hydrogen, $-OC(=O)NR^{11a}R^{11b}$, $-NHC(=O)R^5$, and $-NHZ^1$;

R^4 is selected from the group consisting of amino, optionally substituted aryl, and optionally substituted heteroaryl;

R^5 is selected from the group consisting of $-NR^{12a}R^{12b}$, C_{1-4} alkoxy, and C_{1-4} alkyl;

Z^1 is selected from the group consisting of $-C(=O)R^7$ and $-S(=O)_2R^7$;

Z^2 is selected from the group consisting of $-CH=CHR^{13}$, $-C\equiv CR^{13}$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl,

with proviso that Z^2 is $-CH=CHR^{13}$, $-C\equiv CR^{13}$, $-CH_2Cl$, $-CH_2Br$, or $-CH_2I$, when R^3 is hydrogen, $-OC(=O)NR^{11a}R^{11b}$, or $-NHC(=O)R^5$,

R^7 is selected from the group consisting of $-CH=CHR^{13}$, $-C\equiv CR^{13}$, $-CH_2Cl$, $-CH_2Br$, and $-CH_2I$;

R^{11a} and R^{11b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl; or

R^{11a} and R^{11b} taken together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclo; and

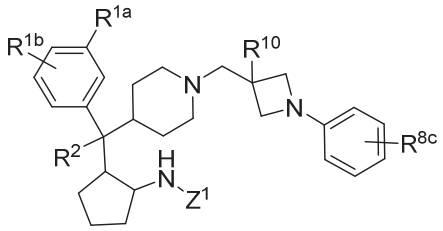
R^{12a} and R^{12b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl; or

R^{12a} and R^{12b} taken together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclo;

R^{13} is selected from the group consisting of hydrogen, C_{1-4} alkyl, and (amino)alkyl; and

s is 2, 3, 4, or 5.

In yet another aspect, the present disclosure refers to a compound having Formula **XVII**:



XVII,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{1a} and R^{1b} are each independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^2 is selected from the group consisting of hydroxy, amino, cyano, and $-CH_2R^4$;

R^4 is selected from the group consisting of amino, optionally substituted aryl, and optionally substituted heteroaryl;

Z^1 is selected from the group consisting of $-C(=O)R^7$ and $-S(=O)_2R^7$;

R^7 is selected from the group consisting of $-CH=CHR^{13}$, $-C\equiv CR^{13}$, $-CH_2Cl$, $-CH_2Br$, and $-CH_2I$;

R^{10} is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and hydroxy; and

R^{8c} is selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

In still another aspect, there is provided a pharmaceutical composition comprising the compound as disclosed herein, or the pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. In another aspect, there is also provided the pharmaceutical composition as disclosed herein for use in therapy. In another aspect of the present disclosure, there is also provided the use of the compound of the present disclosure, or a pharmaceutically acceptable salt or solvate thereof, for

the manufacture of a medicament for treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

[0010] In one example, the present disclosure provides piperidines, and related analogs, represented by any one or more of Formulae **I**-**XXI**, below, and the pharmaceutically acceptable salts and solvates, e.g., hydrates, thereof, collectively referred to herein as "Compounds of the Disclosure." Compounds of the Disclosure are inhibitors of menin and are thus useful in treating diseases or conditions wherein inhibition of menin provides a therapeutic benefit to a patient.

[0011] In another example, the present disclosure provides a method of irreversibly inhibiting menin in a patient, comprising administering to the patient an effective amount of a Compound of the Disclosure.

[0012] In another example, the present disclosure provides methods of treating a condition or disease by administering a therapeutically effective amount of a Compound of the Disclosure to a patient, e.g., a human, in need thereof. The disease or condition is treatable by inhibition menin, for example, a cancer, e.g., leukemia, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection. Also provided are methods of preventing the proliferation of unwanted proliferating cells, such as cancer, in a subject comprising administering a therapeutically effective amount of a Compound of the Disclosure to a subject at risk of developing a condition characterized by unwanted proliferating cells. In some embodiments, the Compounds of the Disclosure reduce the proliferation of unwanted cells by inducing apoptosis and/or differentiation in those cells.

[0013] In another example, the present disclosure provides a method of inhibiting menin in an individual, comprising administering to the individual an effective amount of at least one Compound of the Disclosure.

[0014] In another example, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier.

[0015] In another example, the present disclosure provides a composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier for use treating diseases or conditions wherein inhibition of menin provides a benefit, *e.g.*, cancer.

[0016] In another example, the present disclosure provides a composition comprising: (a) a Compound of the Disclosure; (b) a second therapeutically active agent; and (c) optionally an excipient and/or pharmaceutically acceptable carrier.

[0017] In another example, the present disclosure provides a Compound of the Disclosure for use in treatment of a disease or condition of interest, e.g., cancer.

[0018] In another example, the present disclosure provides a use of a Compound of the Disclosure for the manufacture of a medicament for treating a disease or condition of interest, e.g., cancer.

[0019] In another example, the present disclosure provides a kit comprising a Compound of the Disclosure, and, optionally, a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and a package insert containing directions for use in the treatment of a disease or condition, e.g., cancer.

[0020] In another example, the present disclosure provides methods of preparing Compounds of the Disclosure.

[0021] It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

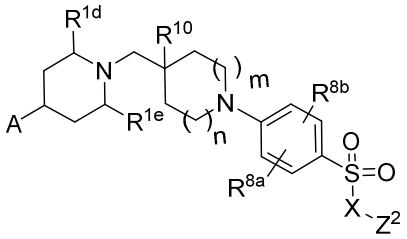
DETAILED DESCRIPTION OF DRAWINGS

[0022] Fig. 1 is a mass spectrograph of menin Apo protein.

[0023] Fig. 2 is a mass spectrograph of menin protein + Cpd. No. 1.

What is Claimed Is:

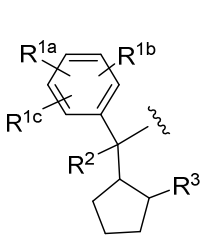
1. A compound having Formula **I**:



I,

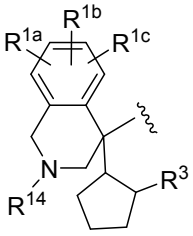
or a pharmaceutically acceptable salt or solvate thereof, wherein:

A is selected from the group consisting of:



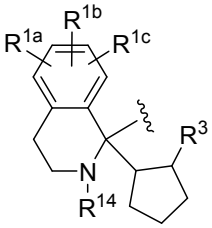
A-1

,



A-2

and



A-3

;

R^{1a}, R^{1b}, and R^{1c} are each independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^{1d} and R^{1e} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

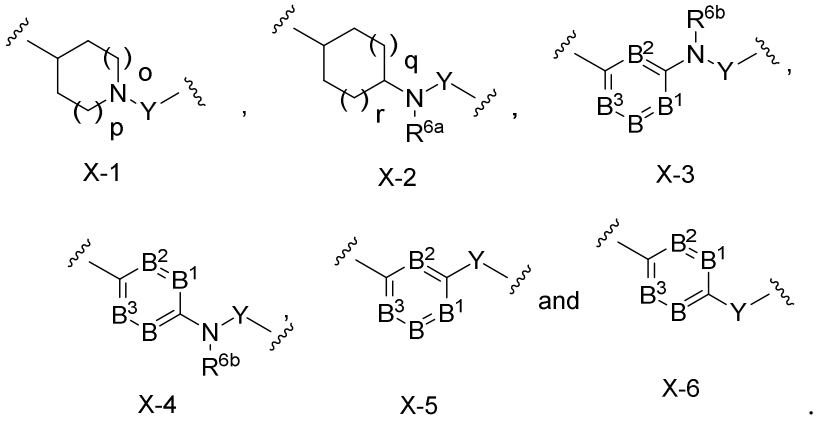
R^2 is selected from the group consisting of hydroxy, amino, cyano, and $-CH_2R^4$;

R^3 is selected from the group consisting of hydrogen, $-OC(=O)NR^{11a}R^{11b}$, $-NHC(=O)R^5$, and $-NHZ^1$;

R^4 is selected from the group consisting of amino, optionally substituted aryl, and optionally substituted heteroaryl;

R^5 is selected from the group consisting of $-NR^{12a}R^{12b}$, C_{1-4} alkoxy, and C_{1-4} alkyl;

X is selected from the group consisting of:



;

wherein Y is attached to Z^2; or

X is absent;

Y is selected from the group consisting of -C(=O)- and -$S(=O)_2$-;

R^{6a} and R^{6b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl;

m, n, o, p, q, and r are each independently 0, 1, 2, or 3;

Z^1 is selected from the group consisting of -C(=O)R^7 and -$S(=O)_2R^7$;

Z^2 is selected from the group consisting of -CH=CHR^{13}, -C≡CR^{13}, -CH_2Cl, -CH_2Br, -CH_2I, alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl,

with proviso that Z^2 is -CH=CHR^{13}, -C≡CR^{13}, -CH_2Cl, -CH_2Br, or -CH_2I, when R^3 is hydrogen, -OC(=O)N$R^{11a}R^{11b}$, or -NHC(=O)R^5,

R^7 is selected from the group consisting of -CH=CHR^{13}, -C≡CR^{13}, -CH_2Cl, -CH_2Br, and -CH_2I;

R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen, hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^{9a} is selected from the group consisting of hydrogen, hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^{10} is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and hydroxy;

R^{11a} and R^{11b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl; or

R^{11a} and R^{11b} taken together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclo; and

R^{12a} and R^{12b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl; or

R^{12a} and R^{12b} taken together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclo;

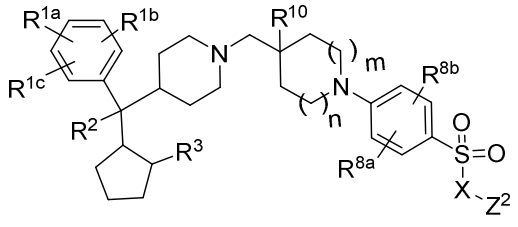
R^{13} is selected from the group consisting of hydrogen, C_{1-4} alkyl, and (amino)alkyl;

R^{14} is selected from the group consisting of hydrogen and C_{1-4} alkyl; and

B, B^1, B^2, and B^3 are each independently selected from the group consisting of $=CR^{9a}$- and =N-,

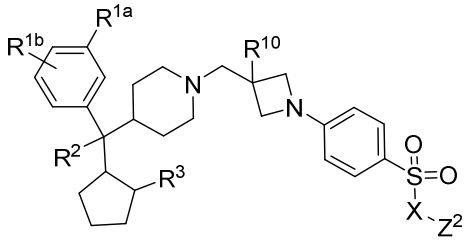
with proviso that at least one of B, B^1, B^2, and B^3 is $=CR^{9a}$-.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having Formula **I-A-I**:



I-A-I.

3. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having Formula **X**:



X,

wherein:

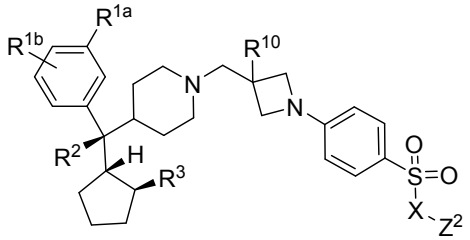
X is selected from the group consisting of X-1, X-2, X-3, X-4, X-5, and X-6; or

X is absent;

Z^2 is selected from the group consisting of -CH=CHR^{13} and -C≡CR^{13}; and

R^3 is selected from the group consisting of -OC(=O)N$R^{11a}R^{11b}$ and -NHC(=O)R^5.

4. The compound of claim 1 or 3, or a pharmaceutically acceptable salt or solvate thereof, having Formula **XI**:



XI.

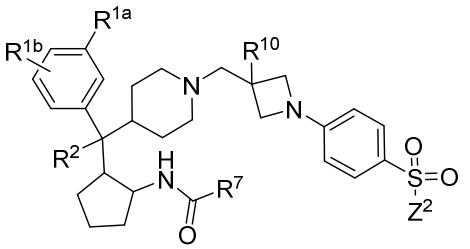
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein X is X-1.

6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein X is X-2.

7. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein X is X-3 and B, B^1, B^2, and B^3 are =CR^{9a}-.

8. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein X is X-4 and B, B^1, B^2, and B^3 are =CR^{9a}-.

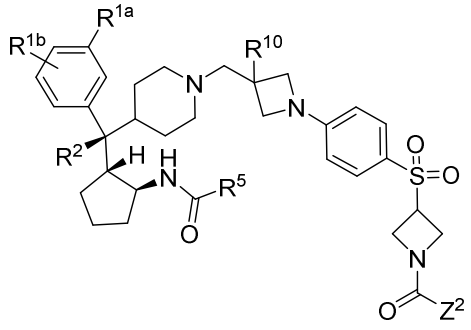
9. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, having Formula **XII**:



XII

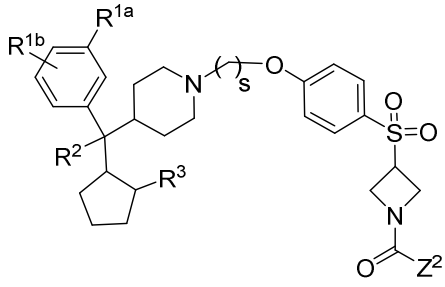
wherein Z^2 is selected from the group consisting of alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl.

10. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, having Formula **XIV**:

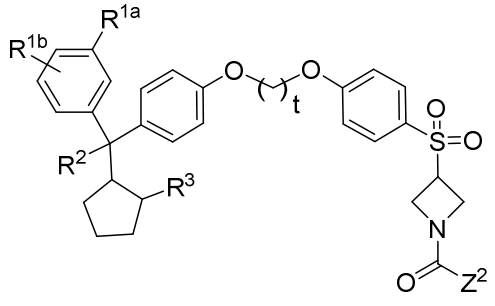


XIV.

11. A compound having Formula **XV** or Formula **XVI**:



XV,



XVI,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{1a} and R^{1b} are each independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^2 is selected from the group consisting of hydroxy, amino, cyano, and $-CH_2R^4$;

R^3 is selected from the group consisting of hydrogen, -OC(=O)$NR^{11a}R^{11b}$, -NHC(=O)R^5, and -NHZ^1;

R^4 is selected from the group consisting of amino, optionally substituted aryl, and optionally substituted heteroaryl;

R^5 is selected from the group consisting of -$NR^{12a}R^{12b}$, C_{1-4} alkoxy, and C_{1-4} alkyl;

Z^1 is selected from the group consisting of -C(=O)R^7 and -$S(=O)_2R^7$;

Z^2 is selected from the group consisting of -CH=CHR^{13}, -C≡CR^{13}, -CH_2Cl, -CH_2Br, -CH_2I, alkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted cycloalkyl,

with proviso that Z^2 is -CH=CHR^{13}, -C≡CR^{13}, -CH_2Cl, -CH_2Br, or -CH_2I, when R^3 is hydrogen, -OC(=O)$NR^{11a}R^{11b}$, or -NHC(=O)R^5,

R^7 is selected from the group consisting of -CH=CHR^{13}, -C≡CR^{13}, -CH_2Cl, -CH_2Br, and -CH_2I;

R^{11a} and R^{11b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl; or

R^{11a} and R^{11b} taken together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclo; and

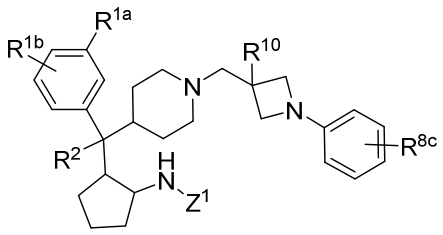
R^{12a} and R^{12b} are independently selected from the group consisting of hydrogen and C_{1-4} alkyl; or

R^{12a} and R^{12b} taken together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocyclo;

R^{13} is selected from the group consisting of hydrogen, C_{1-4} alkyl, and (amino)alkyl; and

s is 2, 3, 4, or 5.

12. A compound having Formula **XVII**:



XVII,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{1a} and R^{1b} are each independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^2 is selected from the group consisting of hydroxy, amino, cyano, and $-CH_2R^4$;

R^4 is selected from the group consisting of amino, optionally substituted aryl, and optionally substituted heteroaryl;

Z^1 is selected from the group consisting of $-C(=O)R^7$ and $-S(=O)_2R^7$;

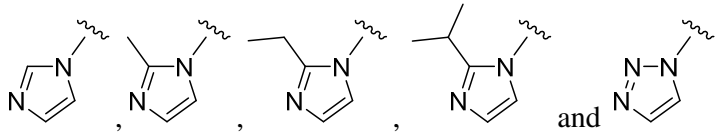
R^7 is selected from the group consisting of $-CH=CHR^{13}$, $-C\equiv CR^{13}$, $-CH_2Cl$, $-CH_2Br$, and $-CH_2I$;

R^{10} is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and hydroxy; and

R^{8c} is selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is cyano.

14. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is CH_2R^4 and R^4 is:



15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is hydrogen.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen and halogen.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt or solvate thereof, wherein:

Z^2 is -CH=CHR^{13};

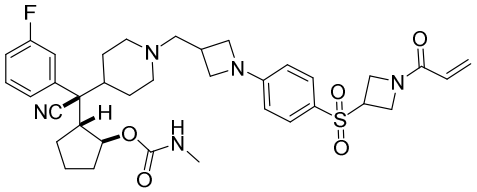
R^{13} is -CH_2-N$R^{22c}R^{22d}$; and

R^{22c} and R^{22d} are each independently selected from the group consisting of hydrogen and C_{1-4} alkyl, or

R^{22c} and R^{22d} are taken together to form a 4- to 8-membered optionally substituted heterocyclo.

18. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is any one or more of :

1



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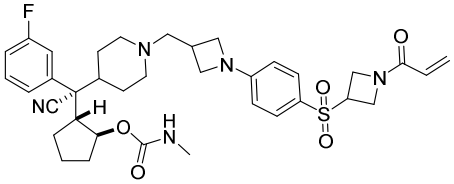

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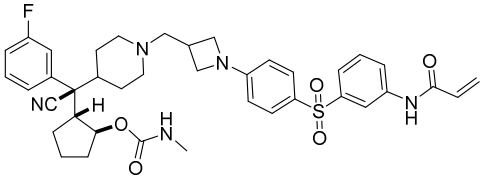

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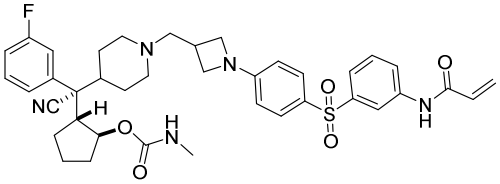

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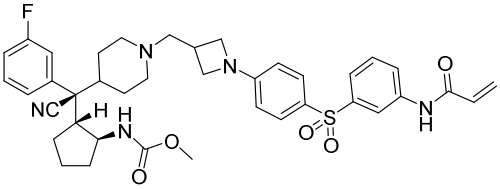

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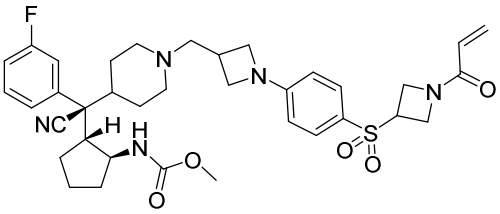

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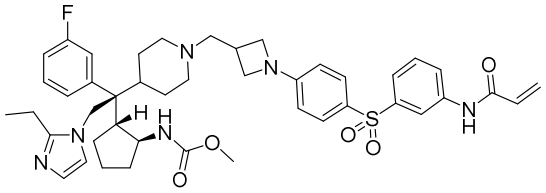

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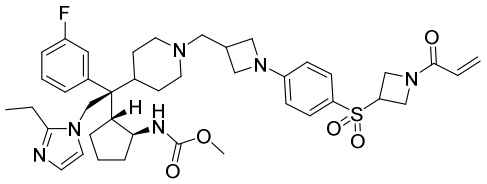

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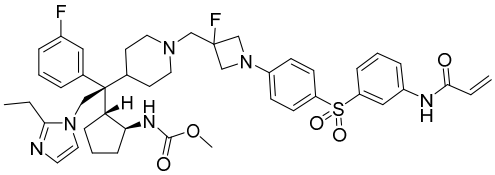

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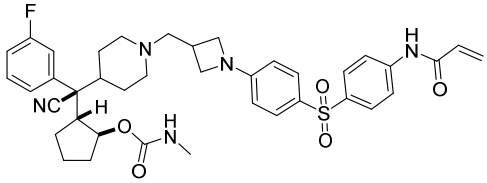

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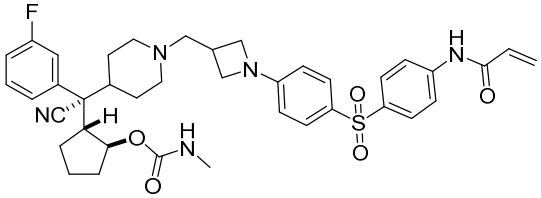

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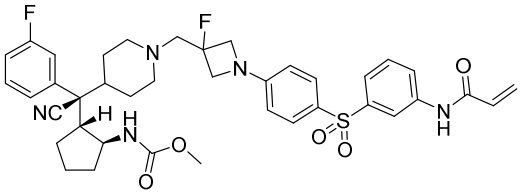

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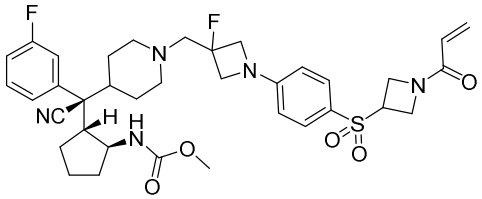

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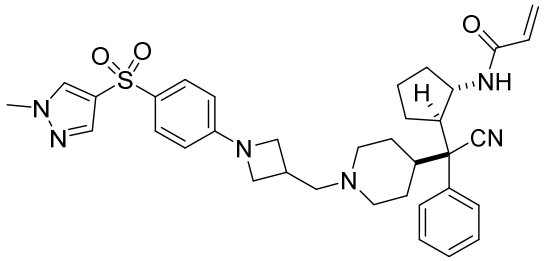

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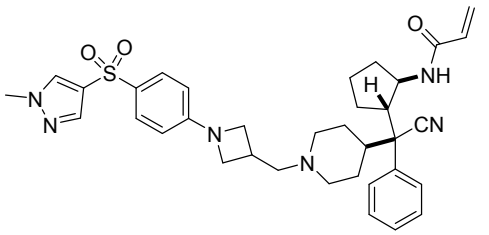

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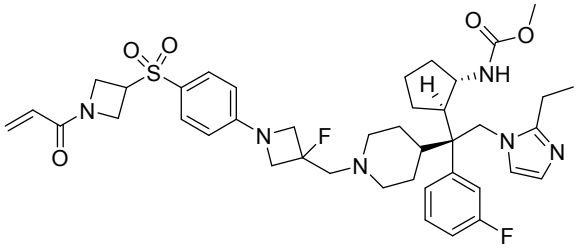

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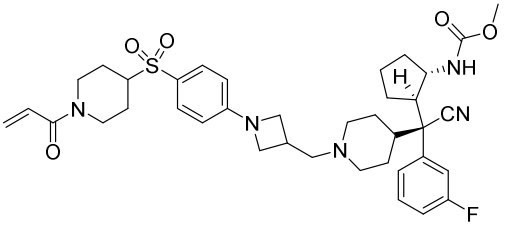

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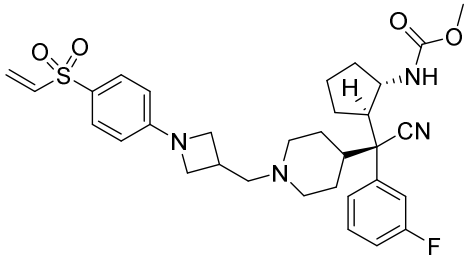

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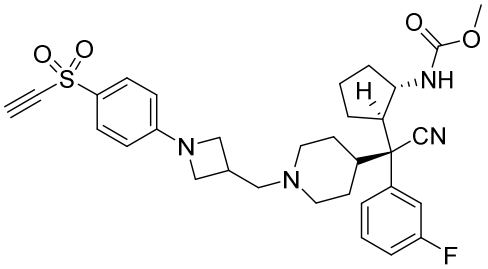

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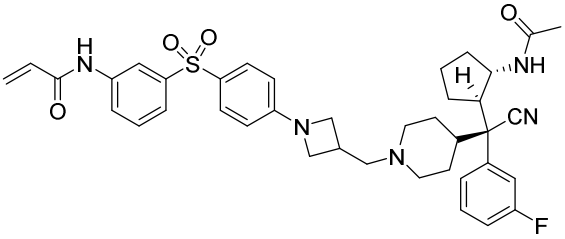

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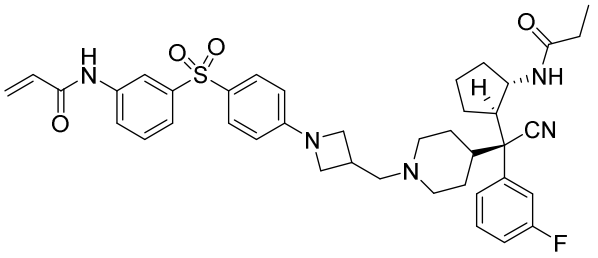

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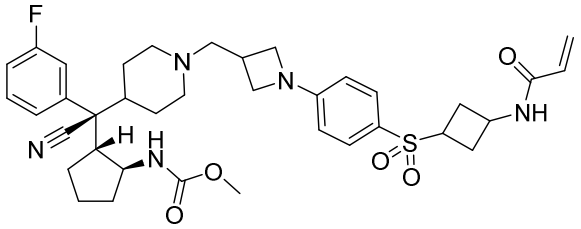

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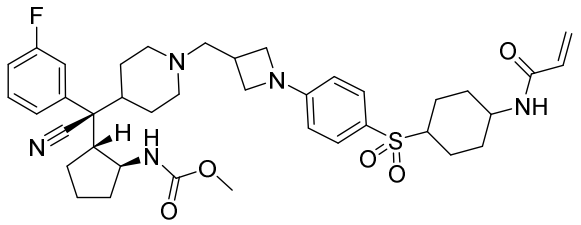

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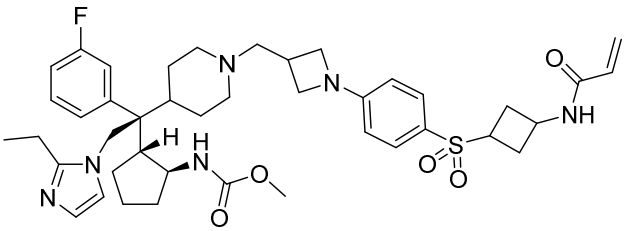

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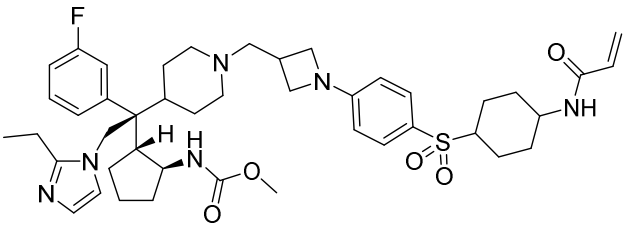

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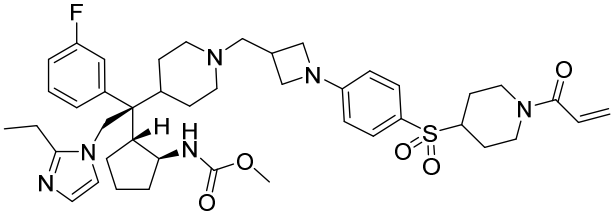

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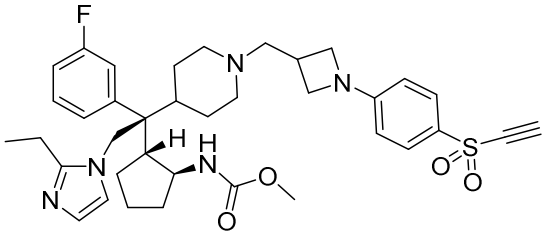

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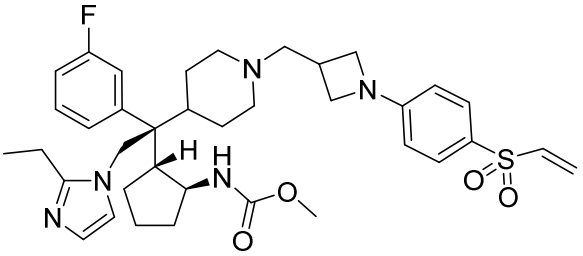

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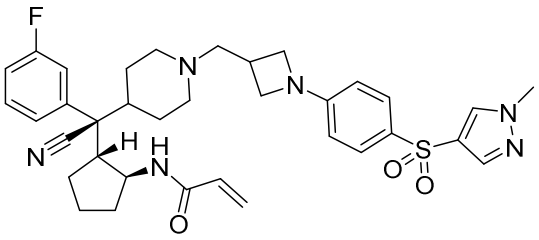

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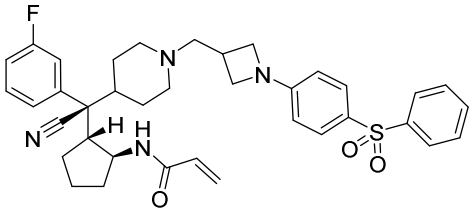

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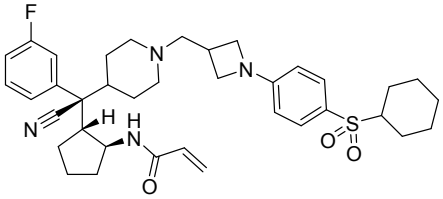

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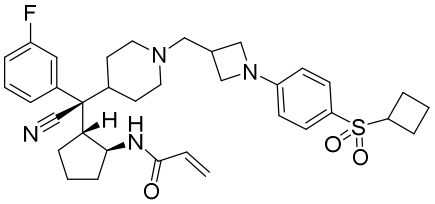

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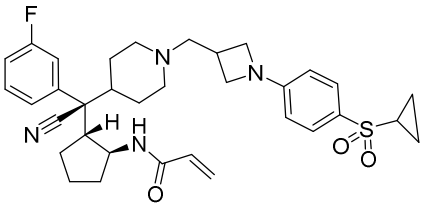

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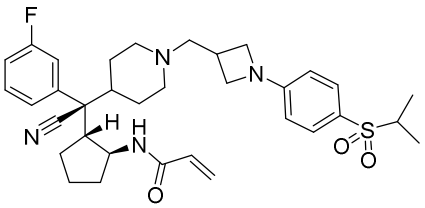

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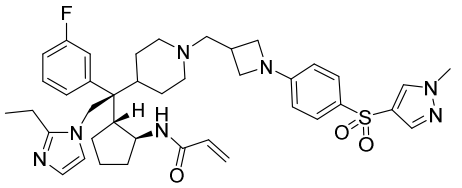

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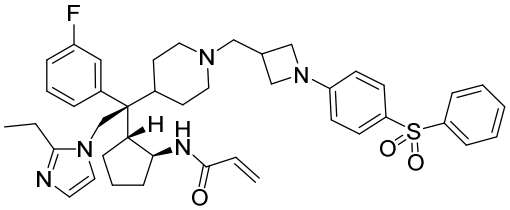

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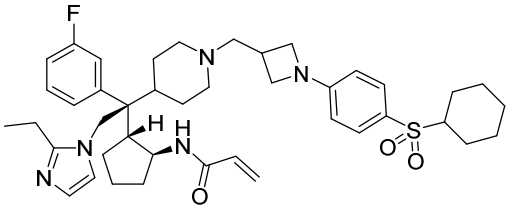

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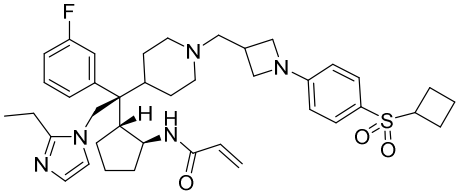

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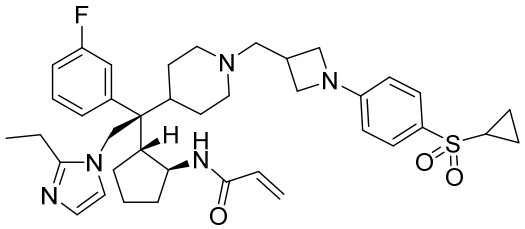

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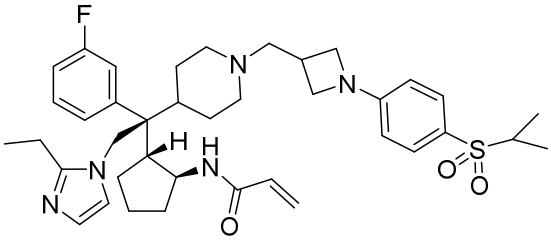

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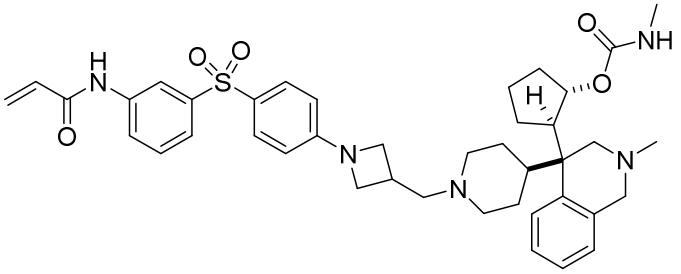

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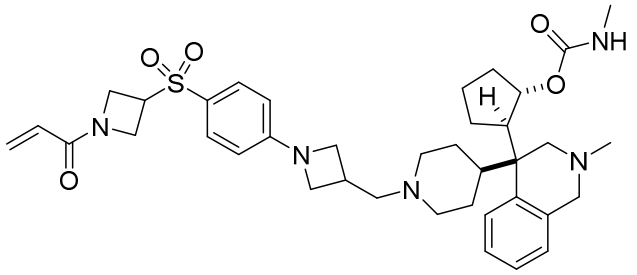

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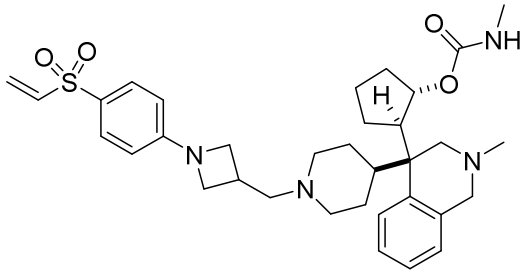

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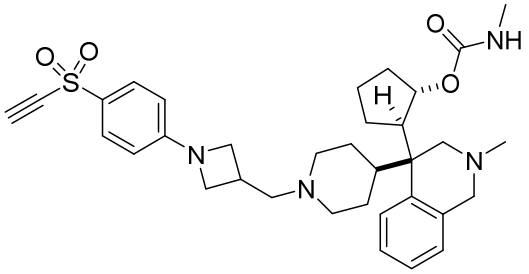

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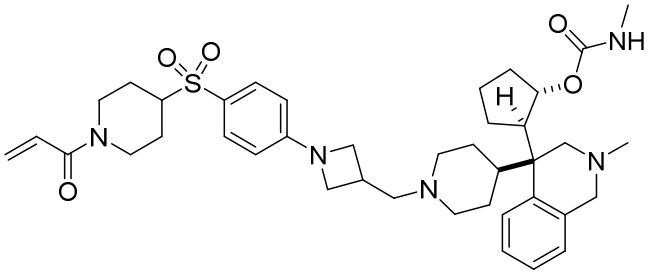

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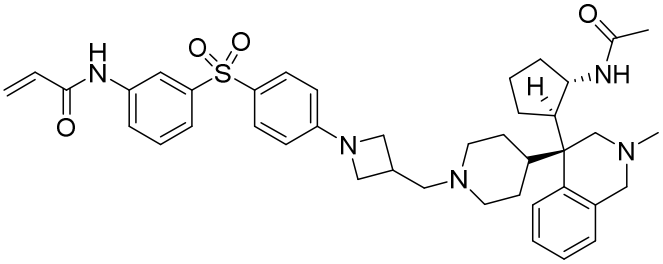

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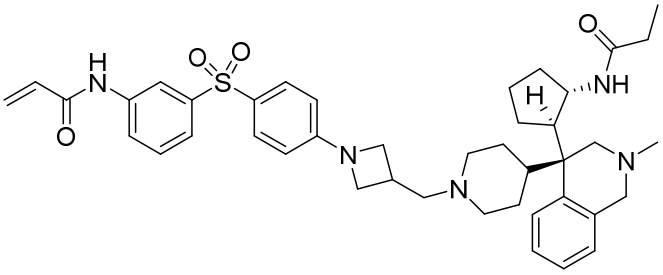

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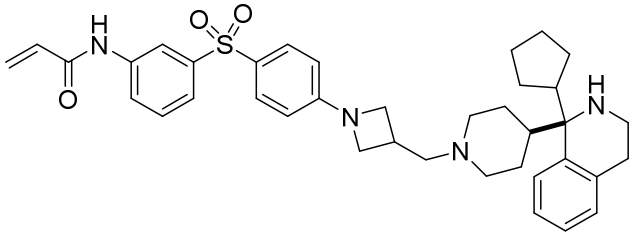

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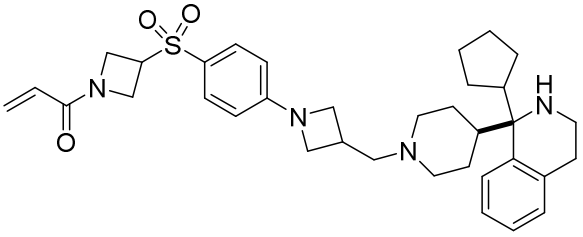

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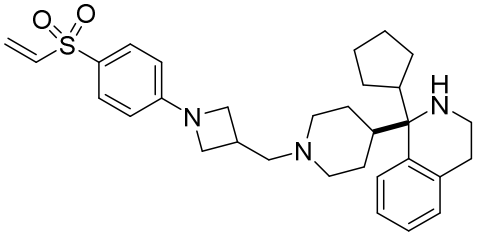

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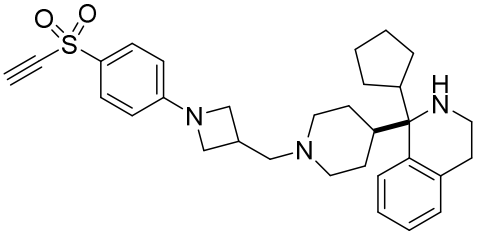

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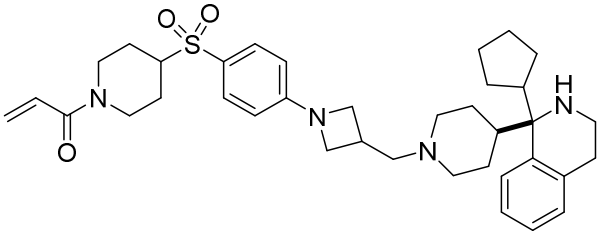

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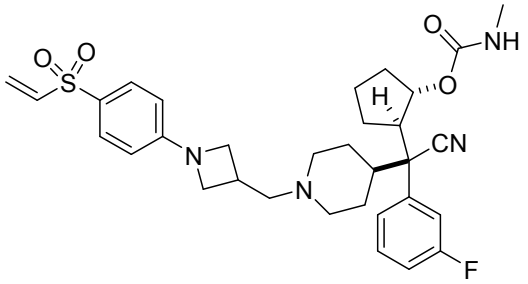

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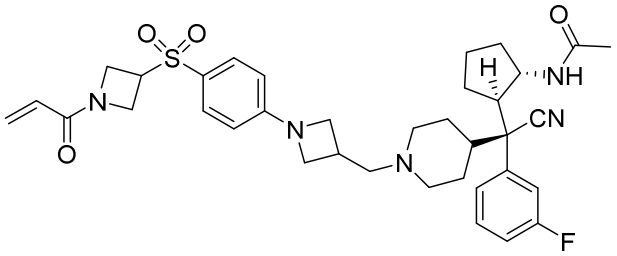

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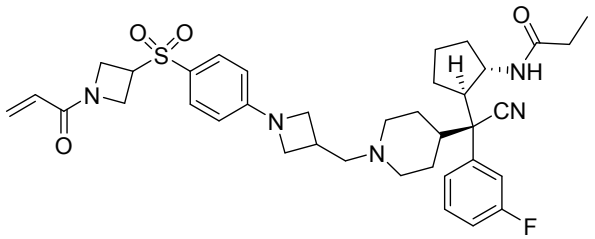

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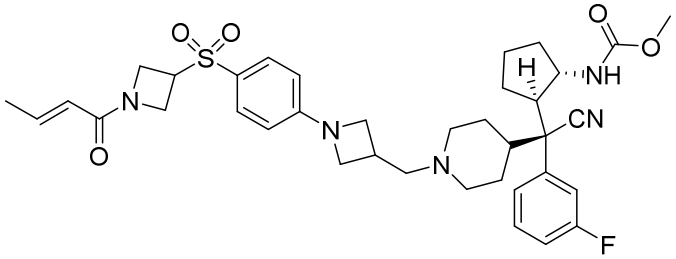

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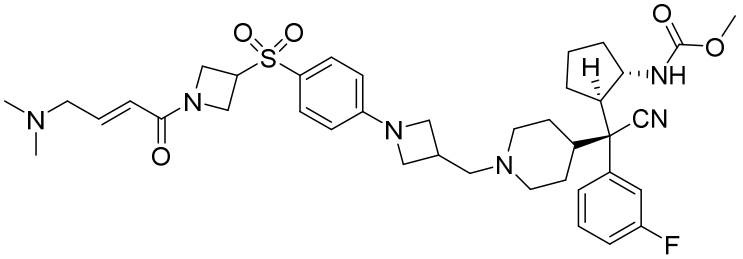

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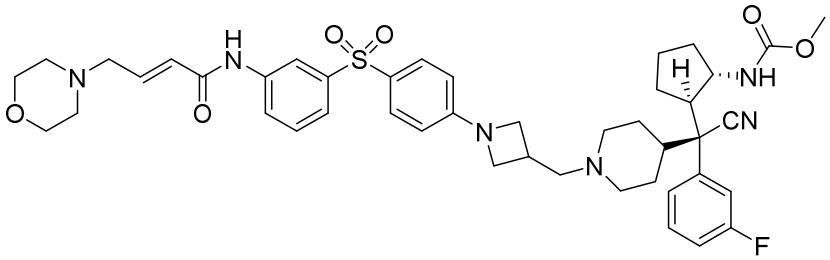

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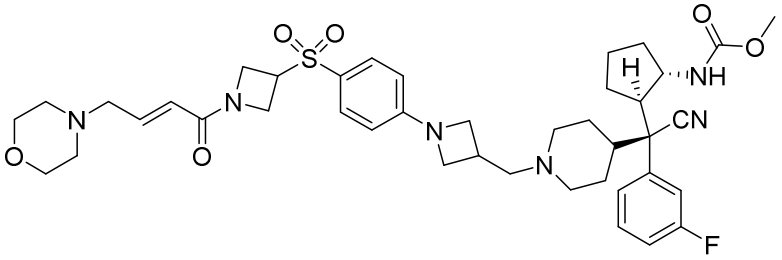

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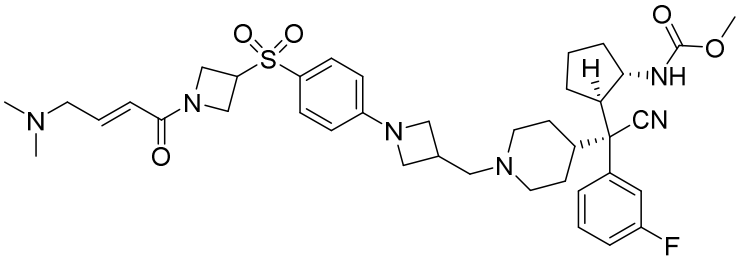

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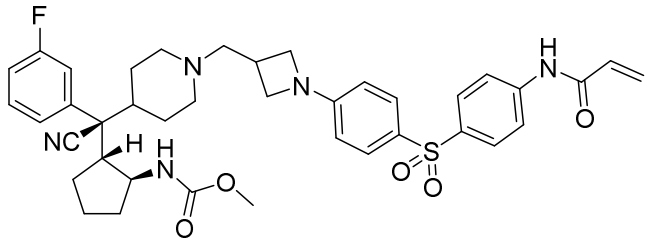

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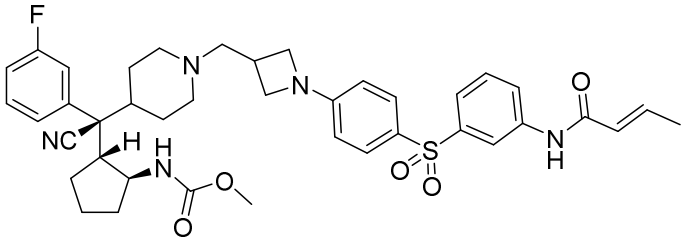

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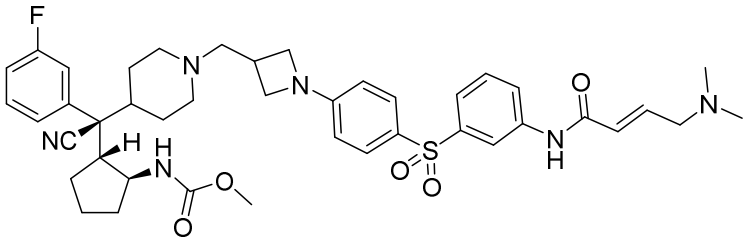

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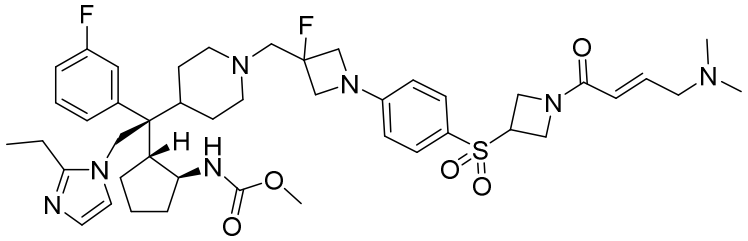

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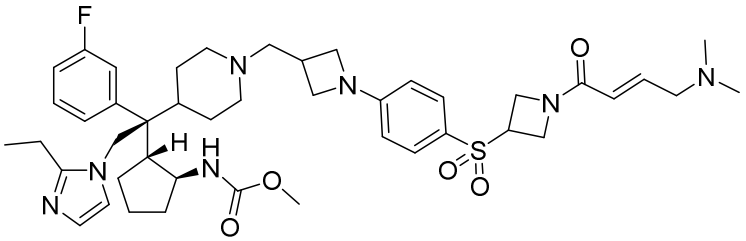

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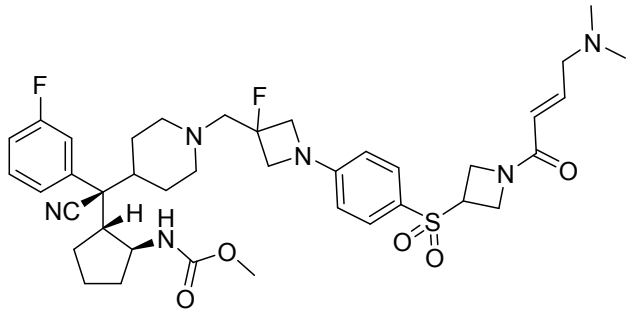

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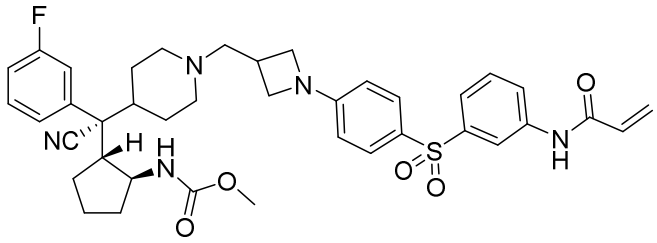

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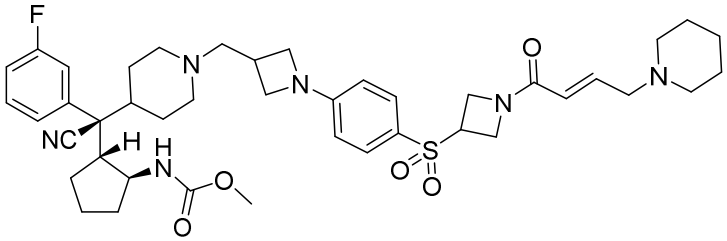

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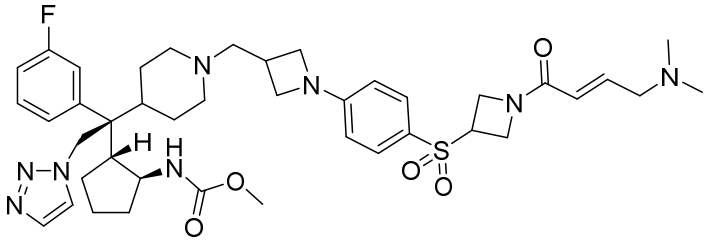

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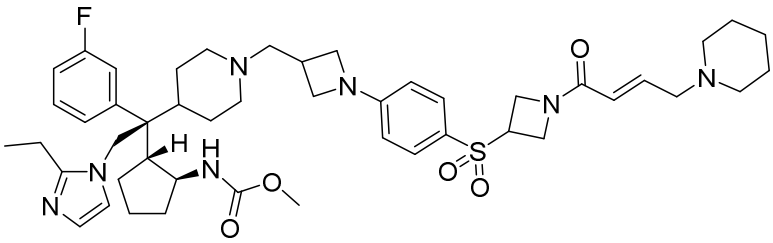
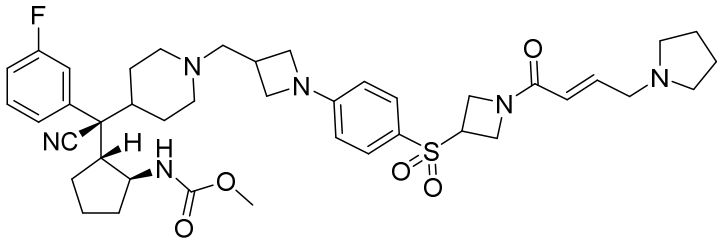
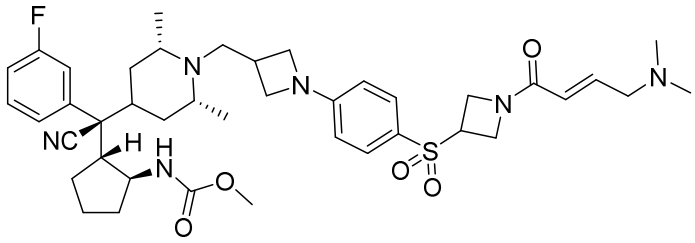
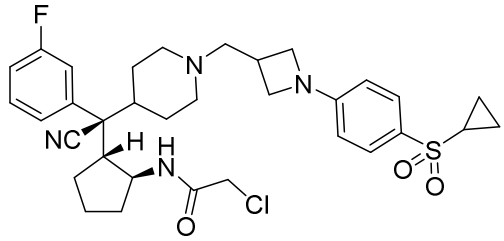
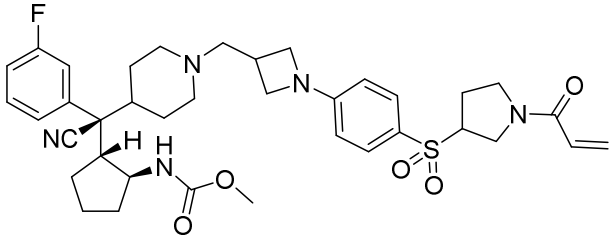
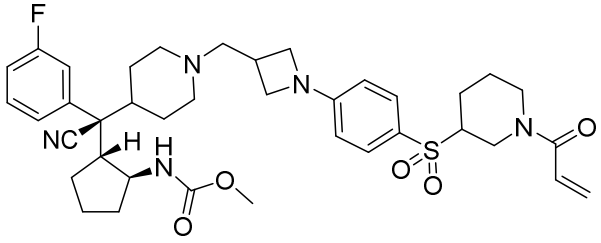


74 

75 

76 

77 

78 

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19. The compound of claim 11, wherein the compound is selected from the group consisting of:

methyl ((1S,2R)-2-((S)-cyano(1-(3-(4-((1-((E)-4-(dimethylamino)but-2-enoyl)azetidin-3-yl)sulfonyl) phenoxy)propyl)piperidin-4-yl)(3-fluorophenyl)methyl)cyclopentyl) carbamate;

methyl ((1S,2R)-2-((R)-(4-(2-(4-((1-acryloylazetidin-3-yl)sulfonyl)phenoxy)ethoxy)phenyl)(cyano)(3-fluorophenyl)methyl)cyclopentyl) carbamate; and

methyl ((1S,2R)-2-((S)-(4-(2-(4-((1-acryloylazetidin-3-yl)sulfonyl)phenoxy)ethoxy)phenyl)(cyano)(3-fluorophenyl)methyl)cyclopentyl) carbamate, or a pharmaceutically acceptable salt or solvate thereof.

20. The compound of claim 12, wherein the compound is selected from the group consisting of:

N-((1S,2R)-2-((S)-cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(3-fluorophenyl)methyl)cyclopentyl)ethenesulfonamide;

N-((1S,2R)-2-((S)-cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(3-fluorophenyl)methyl)cyclopentyl)acrylamide;

2-chloro-N-((1S,2R)-2-((S)-cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(3-fluorophenyl)methyl)cyclopentyl)acetamide; and

N-((1S,2R)-2-((S)-cyano(1-((1-(4-cyanophenyl)azetidin-3-yl)methyl)piperidin-4-yl)(3-fluorophenyl)methyl)cyclopentyl)propiolamide, or a pharmaceutically acceptable salt or solvate thereof.

21. A pharmaceutical composition comprising the compound of any one of claims 1-20, or the pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

22. The pharmaceutical composition of claim 21 for use in therapy.

23. Use of the compound of any one of claims 1-20, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

24. The use of claim 23 for treatment of cancer.

25. The use of claim 24, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.