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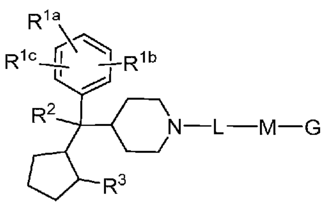
(54) Title: PIPERIDINE COMPOUNDS AS MENIN INHIBITORS



(Ia)

(57) Abstract: The present disclosure provides compounds represented by Formula (Ia): and the pharmaceutically acceptable salts thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, L, M and G are as defined as set forth in the specification. The present disclosure also provides compounds of Formula Ia for use to treat a condition or disorder responsive to menin inhibition such as cancer.

PIPERIDINE COMPOUNDS AS MENIN INHIBITORS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/908,462, filed September 30, 2019, and U.S. Provisional Application No. 63/007,037, filed April 8, 2020, the disclosures of each of which are incorporated by reference in their entireties.

U.S. GOVERNMENT LICENSE RIGHTS

[0002] This invention was made with U.S. government support under Grant No. CA208267 awarded by the National Institutes of Health. The U.S. government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] The present disclosure provides compounds as menin inhibitors and therapeutic methods of treating conditions and diseases wherein inhibition of menin provides a benefit.

Background

[0004] Mixed-lineage leukemia (MLL) is a proto-oncogene that was originally discovered at the site of chromosomal translocations in human leukemias. Due to chromosomal translocations, MLL is fused with more than 40 different partner proteins to yield a diverse collection of chimeric fusion proteins. The MLL protein is a histone methyltransferase that covalently modifies chromatin and is mutated in certain subsets of acute leukemia. Many of the fusion partners constitutively activate novel transcriptional effector properties of MLL that often correlate with its oncogenic potential in animal models of acute leukemia. MLL normally associates with a group of highly conserved cofactors to form a macromolecular complex that includes menin, a product of the MEN1 tumor suppressor gene. The MEN1 gene is mutated in heritable and sporadic endocrine tumors.

[0005] Menin is in involved in a diverse network of protein-protein interactions. Cierpicki and Grembecka, *Future Med. Chem.* *6*:447-462 (2014). Overexpression of menin leads to inhibition of Ras-transformed cells. Menin interacts with the transcription factors JunD and NF-κB and represses their activation of gene transcription. Studies on these interacting proteins suggest that menin exerts its effects predominantly through inhibitory effects on transcription. But an alternative possibility is that menin mediates its effects through transcriptional activation of target genes. Additionally, menin interacts with RPA2, a component of a single-stranded DNA-binding protein involved in DNA repair and replication. Menin also interacts with FANCD2, a nuclear protein that plays a critical role in maintaining genome stability with breast cancer 1 gene (Brea1) product.

[0006] The mechanisms by which menin, which does not have significant homology with other proteins, functions as a tumor suppressor are not completely known. Menin plays a role in regulating cellular proliferation because Men1 knockout mice show increased proliferation in neuroendocrine tissues, down-modulation of menin in epithelial cells increases proliferation, and Men1 knockout fibroblasts proliferate more rapidly than wild-type cells as assayed by tritiated thymidine incorporation. MEN1 cells also have increased sensitivity to DNA-damaging agents. Menin interacts with promoters of HOX genes.

[0007] Certain oncogenic MLL fusion proteins stably associate with menin through a high-affinity interaction that is required for the initiation of MLL-mediated leukemogenesis. Menin is essential for maintenance of MLL-associated but no other oncogene induced myeloid transformation. Acute genetic ablation of menin reverses HOX gene expression mediated by MLL-menin promoter-associated complexes, and specifically eliminates the differentiation arrest and oncogenic properties of MLL-transformed leukemic blasts.

[0008] MLL fusion proteins, a consequence of acquired genetic aberrations, transform hematopoietic cells through two alternate mechanisms, by either constitutive transcriptional effector activity or inducing forced MLL dimerization and oligomerization. Both mechanisms result in the inappropriate expression of a subset of HOX genes, particularly HOXA9, whose consistent expression is a characteristic feature of human MLL leukemias.

[0009] Aberrant expression of *HOX* genes is also found in AML patients with mutations in *NPM1*. NPM1 localizes predominantly in the nucleus and functions in diverse cellular processes, including ribosome assembly, nucleosome assembly and cell proliferation. Mutations in NPM1 lead to abnormal cytoplasmic localization and constitute one of the second most frequent mutations in AML accounting for nearly 30% of all AML patients. It has been recently demonstrated that menin contributes to modulation of HOX genes and cell proliferation in NPM1 mutant AML cells *in vitro* and *in vivo*, although the mechanism remains mostly unknown.

[00010] Menin interacts with transcription activators, e.g., sc-Myb, MLL1, SMAD 1,3,5, Pem, Runx2, Hlbx9, ER, PPARγ, vitamin D receptor, transcription repressors, e.g., JunD, Sin3A, HDAC, EZH2, PRMT5, NFκB, Sirt1, CHES1, cell signaling proteins, e.g., AKT, SOS1/GEF, β-catenin, SMAD 1,3,5, NFκB, and other proteins, e.g., cell cycle: RPA2, ASK; DNA repair: FANCD2; cell structure: GFAP, vimenten, NMMHCIIA, IQGAP1; Others: HSP70, CHIP, ("menin-interacting proteins") involved in regulating gene transcription and cell signaling. Matkar, *Trends in Biochemical Sciences 38*: 394-402 (2013). Targeting menin interactions, e.g., menin–MLL interaction, with small molecules represents an attractive strategy to develop new anticancer agents. *See, e.g.*, Cierpicki and Grembecka, *Future Med. Chem. 6*:447-462 (2014); He *et al.*, *J. Med. Chem. 57*:1543−1556 (2014); and Borkin *et al.*, *Cancer Cell 27*:589–602 (2015); Krivtsov *et al. Cancer Cell 36*: 660-673 (2019); Klossowski *et al. J. Clin. Invest. 130*:981-997 (2020); Uckelmann *et al. Science 367*:586-590 (2020).

[00011] 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; 2016/0046647, and 2019/0152947, and WO2018/183857, WO2019/191526, and WO 2020/072391. Peptides that disrupt the interaction of MLL and menin are disclosed in U.S. Patent Application Publication No. 2009/0298772.

[00012] 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

[00013] In one aspect, the present disclosure provides piperidines, and related analogs, represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, below, and the pharmaceutically acceptable salts 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.

[00014] In another aspect, 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.

[00015] In another aspect, 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 of 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.

[00016] In another aspect, 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.

[00017] In another aspect, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier.

[00018] In another aspect, 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.

[00019] In another aspect, 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.

[00020] In another aspect, the present disclosure provides a Compound of the Disclosure for use in treatment of a disease or condition of interest, e.g., cancer.

[00021] In another aspect, 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.

[00022] In another aspect, 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.

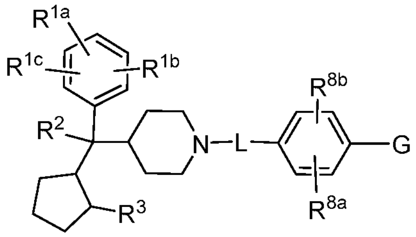
[00023] In another aspect, the present disclosure provides methods of preparing Compounds of the Disclosure.

[00024] 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 THE INVENTION

[00025] Compounds of the Disclosure are menin inhibitors. In some embodiments, Compounds of the Disclosure covalently bind to and inhibit the function of menin.

[00026] In one embodiment, Compounds of the Disclosure are compounds represented by Formula **I**:



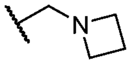
I,

[00027] and the pharmaceutically acceptable salts thereof, wherein:

[00028] R^{1a}, R^{1b}, and R^{1c} are each independently selected from the group consisting of hydrogen and halo;

[00029] G is $-SO_2-X-Z^2$;

[00030] R^2 is selected from the group consisting of: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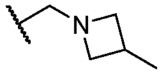
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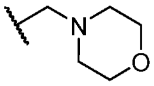
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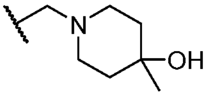
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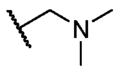
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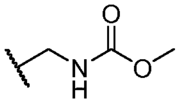
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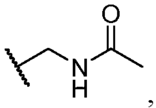
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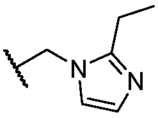
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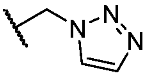
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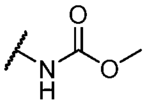
[00031] R^3 is selected from the group consisting of: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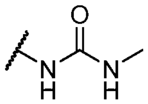
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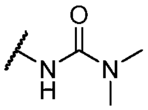
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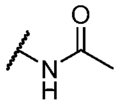
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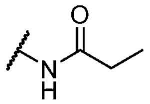
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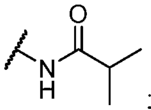
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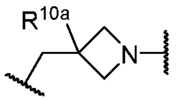
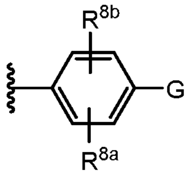
[00032] L is

, wherein the nitrogen atom of L is attached to

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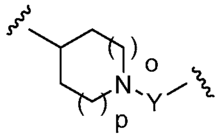
[00033] R^{10a} is selected from the group consisting of hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and hydroxy;

[00034] X is selected from the group consisting of: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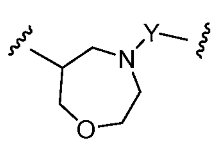
X-1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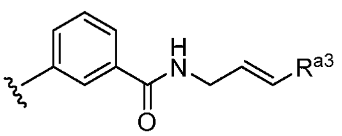
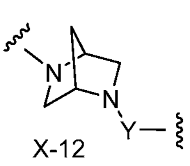
X-9


, and
X-10


X-12
;

[00035] wherein Y is attached to Z^2;

[00036] Y is -C(=O)-;

[00037] o and p are each independently 0, 1, 2, or 3;

[00038] Z^2 is selected from the group consisting of $-C(R^{13a})=C(R^{13b})(R^{13c})$, $-C{\equiv}CR^{13d}$, and R^{a4}, wherein Z^2 is absent when X is X-10;

[00039] R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and halo;

[00040] R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen, methyl, and dimethylaminomethyl;

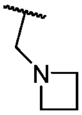
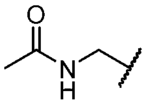
[00041] R^{a3} is selected from the group consisting of alkoxycarbonyl and alkylsulfonyl;

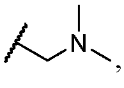
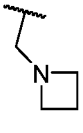
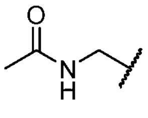
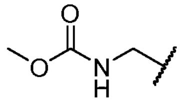
[00042] R^{a4} is $-N(H)CH_2CH=CH-R^{a5}$; and

[00043] R^{a5} is selected from the group consisting of alkoxycarbonyl and alkylsulfonyl;

[00044] provided:

[00045] when X is X-1, o and p are each 0, and Z^2 is $C(R^{13a})=C(R^{13b})(R^{13c})$, then none of R^{13a}, R^{13b} and R^{13c} is dimethylaminomethyl;

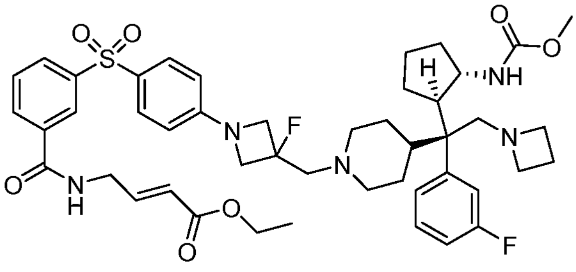
[00046] when X is X-1, R^{10a} is hydrogen, F, OH, methyl or methoxy, Z^2 is $-C{\equiv}CR^{13d}$, and R^2 is  or , then R^{13d} is not hydrogen or methyl;

[00047] when X is X-1, Z^2 is $CH=CH_2$, and R^2 is , , , or , then R^{10a} is not hydrogen, F, OH, fluoromethyl, methyl or methoxy;

[00048]

[00049] when X is X-9 and Z^2 is $CH=CH_2$, then R^{10a} is not hydrogen, F, or methyl; and

[00050] the compound of formula (I) is not



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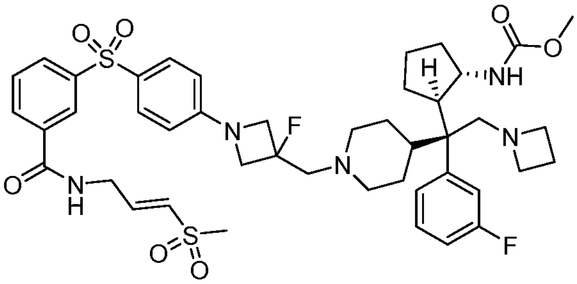

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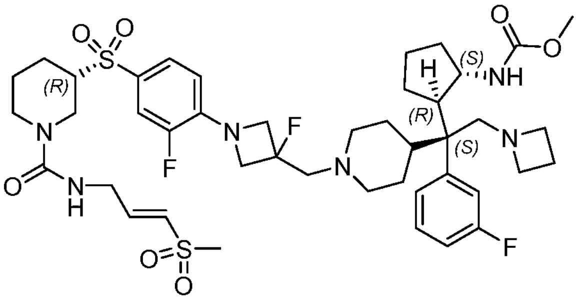

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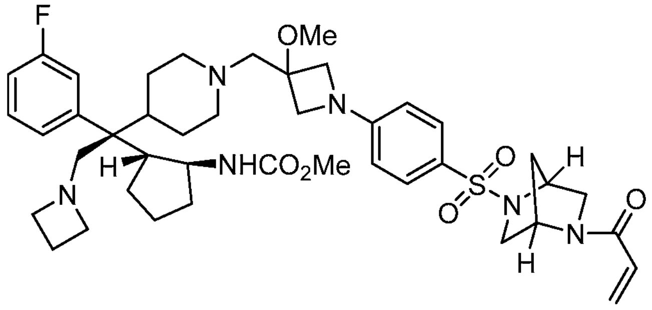
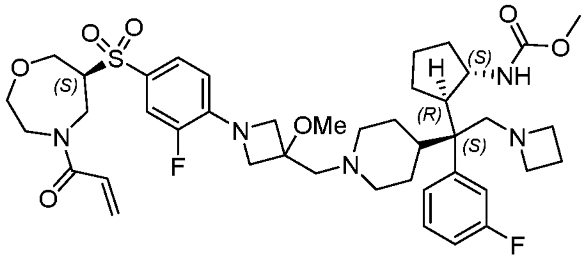
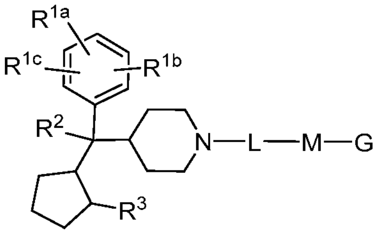


; or



.

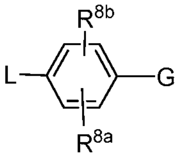
[00051] In one embodiment, Compounds of the Disclosure are compounds represented by Formula **Ia**,



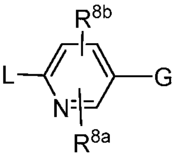
Ia

or a pharmaceutically acceptable salt thereof, wherein

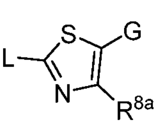
[00052] L-M-G is



M-1

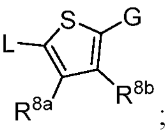


M-2



M-3

, or

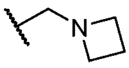


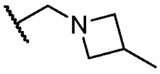
M-4

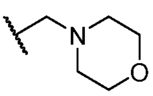
[00053] R^{1a}, R^{1b}, and R^{1c} are each independently selected from the group consisting of hydrogen and halo;

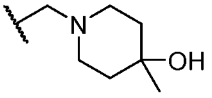
[00054] G is $-SO_2-X-Z^2$ or $-CH_2-X-Z^2$;

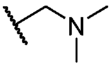
[00055] R^2 is selected from the group consisting of:

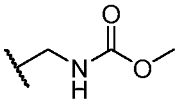


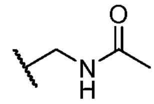


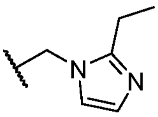




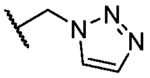






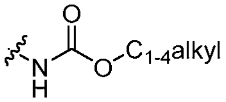


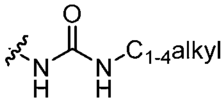
, and

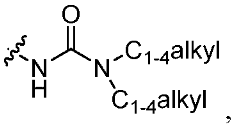


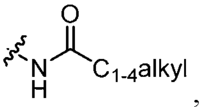
;

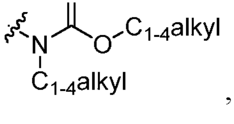
[00056] R^3 is selected from the group consisting of:



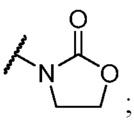




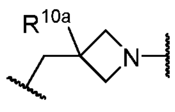




, and

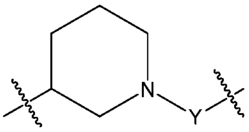


;

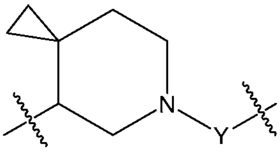
[00057] L is 

, wherein the nitrogen atom of L is attached to the M; each R^{10a} is independently selected from the group consisting of hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and hydroxy;

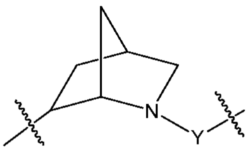
[00058] X is selected from the group consisting of:



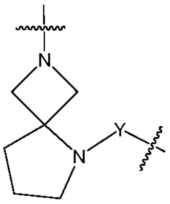
X-20 ,



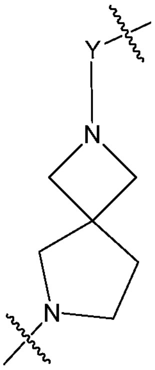
X-21 ,



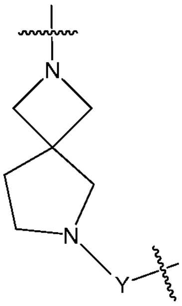
X-22 ,



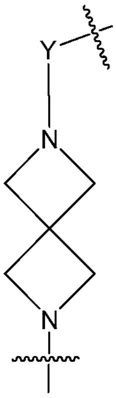
X-23 ,



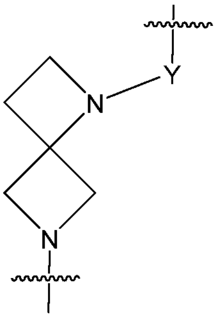
X-24 ,



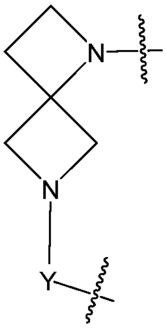
X-25 ,



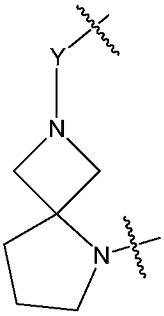
X-26 ,



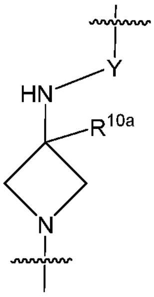
X-27 ,



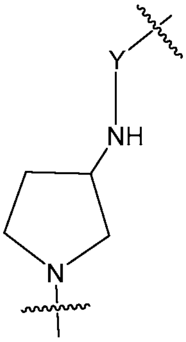
X-28 ,



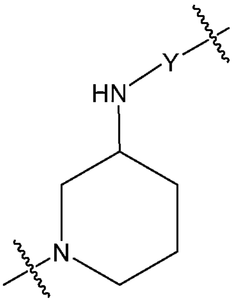
X-29 ,



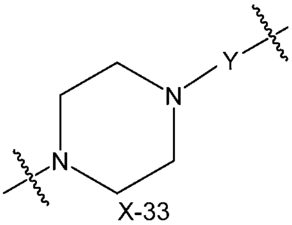
X-30 ,



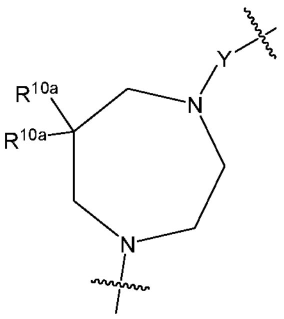
X-31 ,



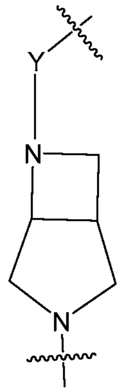
X-32 ,



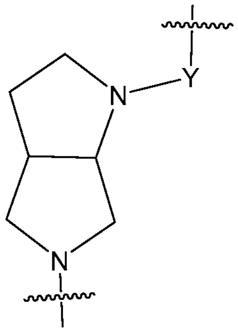
X-33 ,



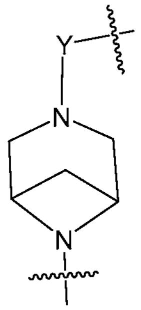
X-34 ,



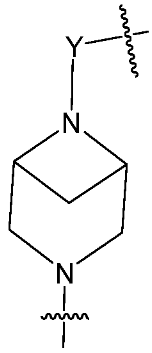
X-35 ,



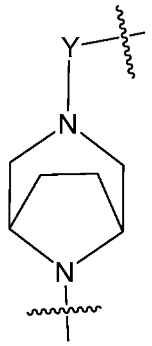
X-36 ,



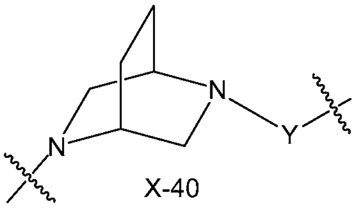
X-37 ,



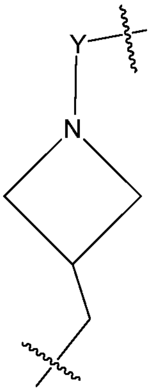
X-38 ,



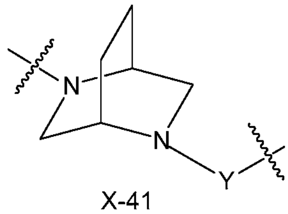
X-39 ,



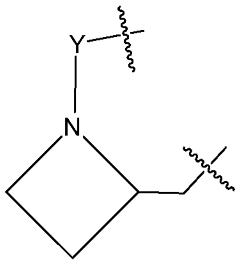
X-40 ,



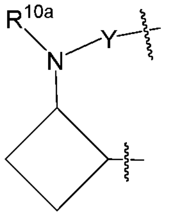
X-42 ,



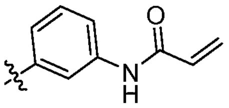
X-41 ,



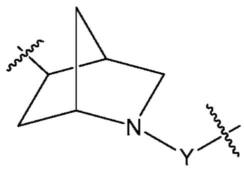
X-43 ,



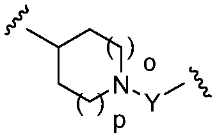
X-44 ,



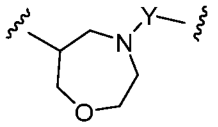
X-45 ,



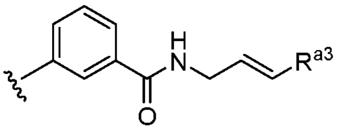
X-46



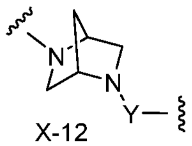
X-1,



X-9,



X-10, and



X-12;

[00059] wherein Y is attached to Z^2;

[00060] Y is -C(=O)- ;

[00061] o and p are each independently 0, 1, 2, or 3;

[00062] Z^2 is selected from the group consisting of $-C(R^{13a})=C(R^{13b})(R^{13c})$, $-C{\equiv}CR^{13d}$, and R^{a4},

[00063] Z^2 is absent when X is X-10 or when X is X-45;

[00064] R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen, $-SO_2$-C_1-C_6 alkyl and halo;

[00065] R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and di-C_1-C_6 alkylaminoC_1-C_4 alkyl;

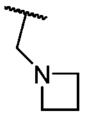
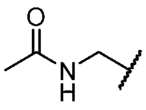
[00066] R^{a3} is selected from the group consisting of C_1-C_6 alkoxycarbonyl-, heterocyclyl-carbonyl-, halo-substituted heterocyclyl-carbonyl-, C_1-C_6 alkylamide and C_1-C_6 alkylsulfonyl;

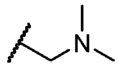
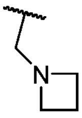
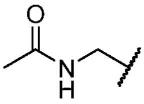
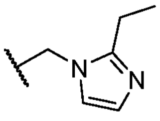
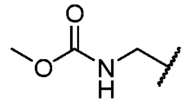
[00067] R^{a4} is $-N(H)CH_2CH=CH-R^{a5}$; and

[00068] R^{a5} is selected from the group consisting of C_1-C_6 alkoxycarbonyl-, heterocyclyl-carbonyl-, halo-substituted heterocyclyl-carbonyl-, C_1-C_6 alkylamide and C_1-C_6 alkylsulfonyl;

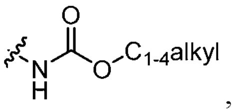
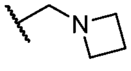
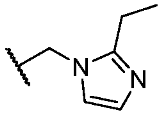
[00069] provided:

[00070] when X is X-1, o and p are each 0, and Z^2 is $C(R^{13a})=C(R^{13b})(R^{13c})$, then none of R^{13a}, R^{13b} and R^{13c} is dimethylaminomethyl;

[00071] when X is X-1 or X-20, R^{10a} is hydrogen, F, OH, methyl or methoxy, Z^2 is $-C{\equiv}CR^{13d}$, and R^2 is  or  , then R^{13d} is not hydrogen or methyl;

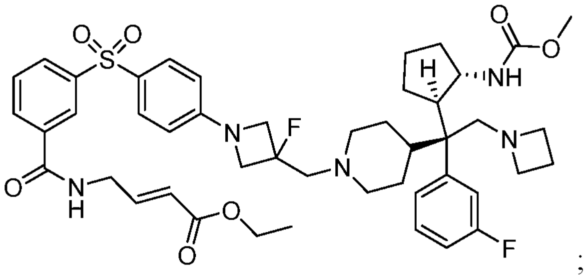
[00072] when X is X-1 or X-20, Z^2 is $CH{=}CH_2$, and R^2 is , , , , or , then R^{10a} is not hydrogen, F, OH, fluoromethyl, methyl or methoxy;

when X is X-9 and Z^2 is $CH{=}CH_2$, then R^{10a} is not hydrogen, F, or methyl;

when X is X-45 and R^3 is , then R^2 is not  or 

[00073] and

[00074] the compound of formula (I) is not



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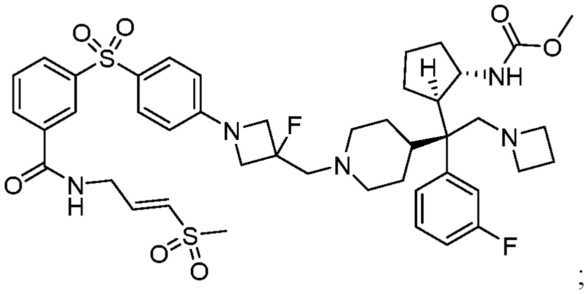

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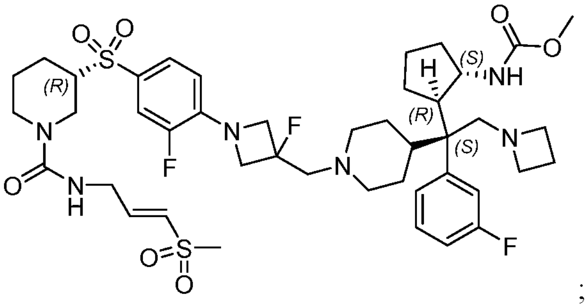

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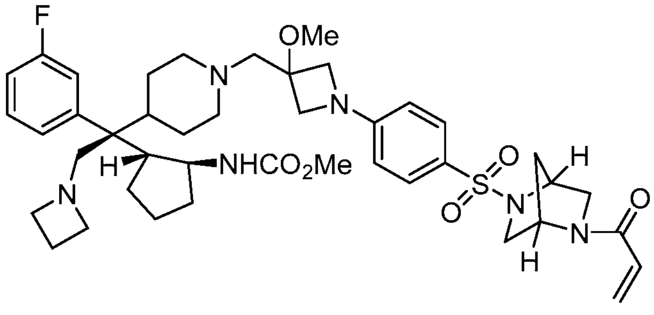

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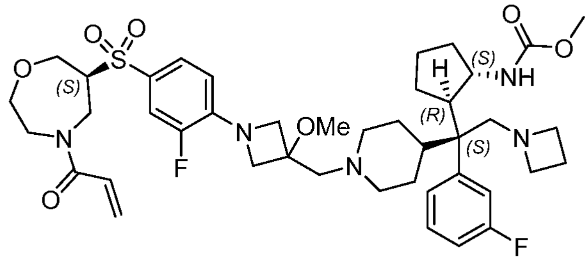

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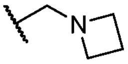
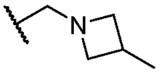
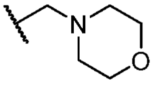
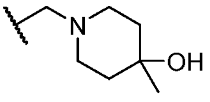
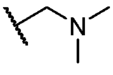
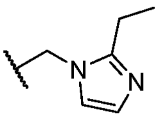
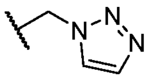
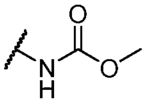
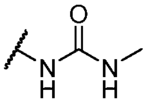
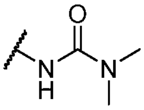
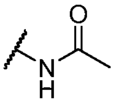
[00075] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **I** or Formula **Ia**, and the pharmaceutically acceptable salts thereof, wherein: R^{10a} is hydrogen, fluoro, cyano, methyl, methoxy, ethoxy, or hydroxy.

[00076] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **I** or Formula **Ia**, and the pharmaceutically acceptable salts thereof, wherein:

[00077] R^2 is , , , , , , or ;

[00078] R^3 is , , , or ;

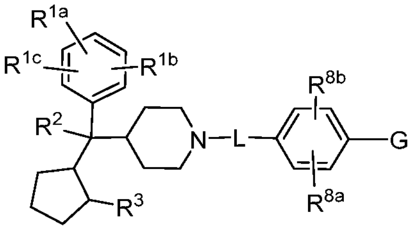
[00079] X is X-1;

[00080] Z^2 is selected from the group consisting of $-C(R^{13a})=C(R^{13b})(R^{13c})$ and $-C{\equiv}CR^{13d}$;

[00081] R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and fluoro; and

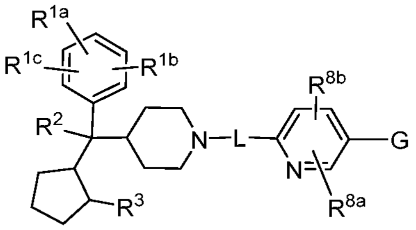
[00082] R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen and dimethylaminomethyl.

[00083] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of formulae **Ib**-**Ie**:



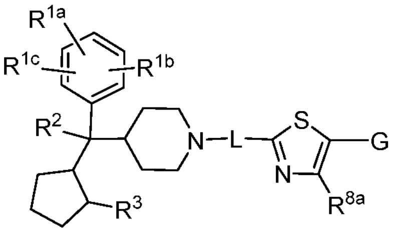
Ib,

[00084] or Formula **Ic**:



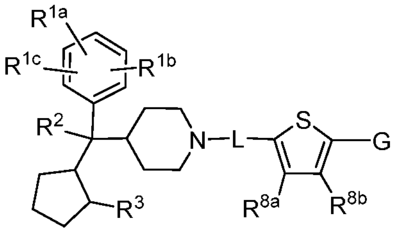
Ic;

[00085] or Formula **Id**:



Id;

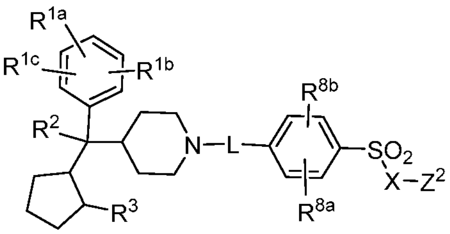
[00086] or Formula **Ie**:



Ie;

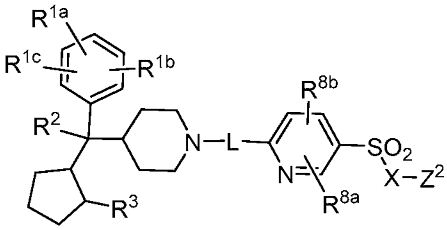
[00087] or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^{8a}, R^{8b}, R^{10a}, L, G and remaining variables are defined above in accordance with Formula **I** or Formula **Ia**.

[00088] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of formulae **Ig**-**Ij**:



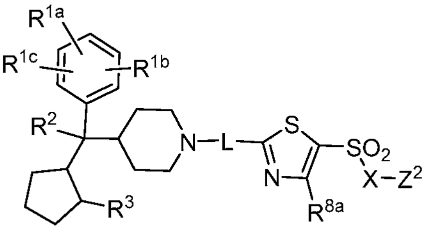
Ig,

[00089] or Formula **Ih**:



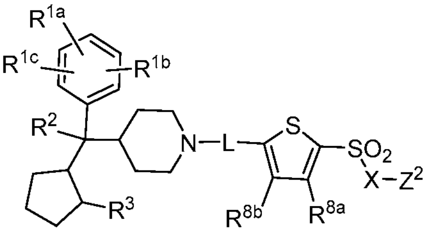
Ih,

[00090] or Formula **Ii**:



Ii,

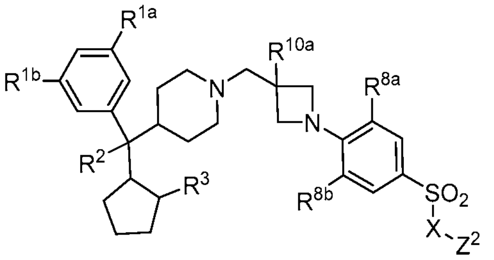
[00091] or Formula **Ij**:



Ij,

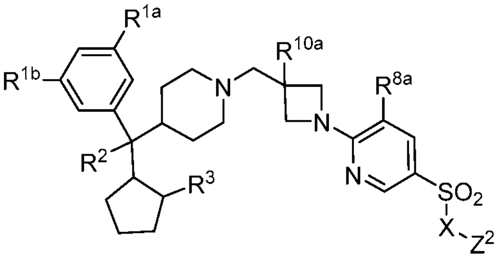
[00092] or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^{8a}, R^{8b}, L, X, Z^2 and remaining variables are defined above in accordance with Formula **I** or Formula **Ia**.

[00093] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of formulae **XI-XIc**:



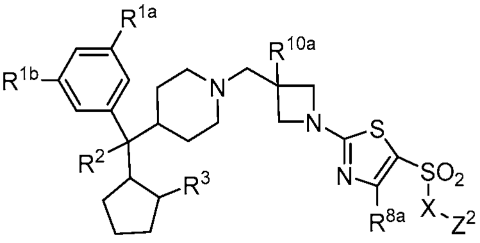
XI,

[00094] or Formula **XIa**:



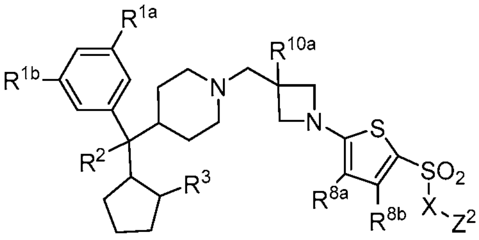
XIa,

[00095] or Formula **XIb**:



XIb,

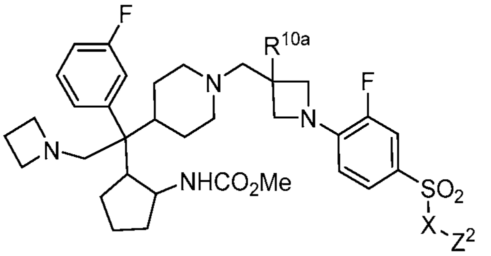
[00096] or Formula **XIc**:



XIc,

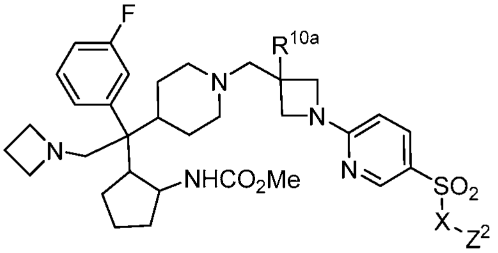
[00097] or a pharmaceutically acceptable salt thereof, wherein R^{1a}, R^{1b}, R^2, R^3, R^{8a}, R^{8b}, R^{10a}, X, Z^2 and remaining variables are defined above in accordance with Formula **I** or Formula **Ia**.

[00098] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of formulae **XII-XIIc**:



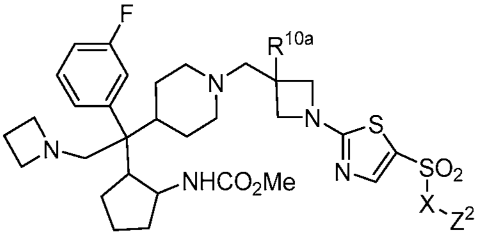
XII,

[00099] or Formula **XIIa**:



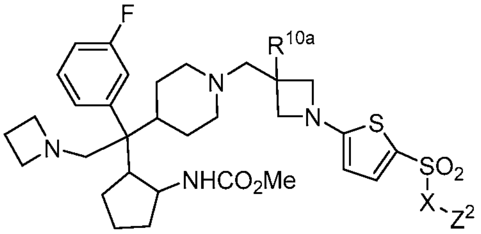
XIIa,

[000100] or Formula **XIIb**:



XIIb,

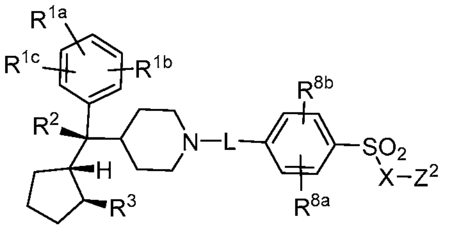
[000101] or Formula **XIIc**:



XIIc,

[000102] or a pharmaceutically acceptable salt thereof, wherein R^{10a}, X, Z^2 and remaining variables are defined above in accordance with Formula **I** or Formula **Ia**.

[000103] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **II-IX**:



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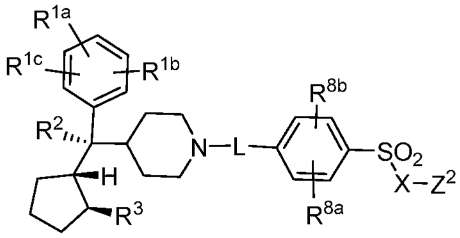

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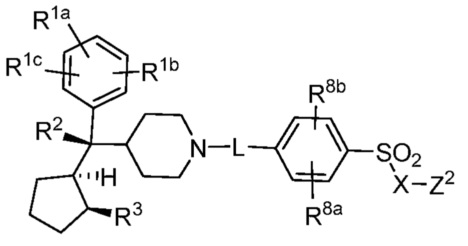
Formula **II**

Formula **III**



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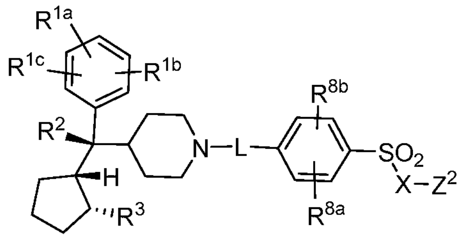

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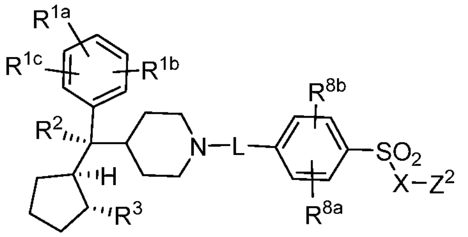
Formula **IV**

Formula **V**



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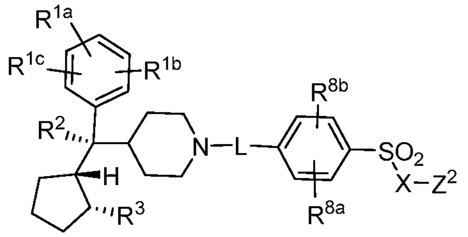

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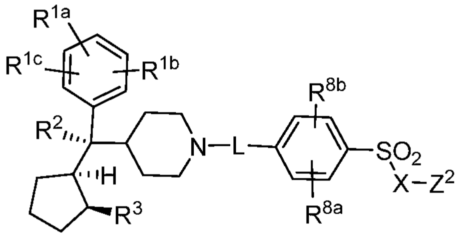
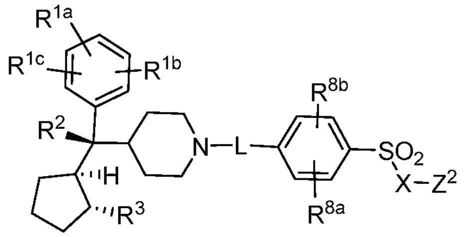
Formula **VI**

Formula **VII**



and



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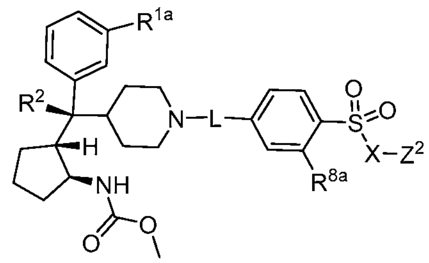
Formula **VIII**

Formula **IX**

[000104] and the pharmaceutically acceptable salts thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^{8a}, R^{8b}, L, X, and Z^2 are as defined in connection with Formula **I** or Formula **Ia**.

[000105] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **X**:

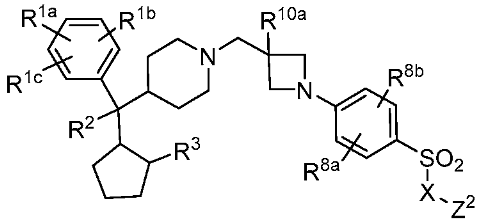


X,

[000106] and the pharmaceutically acceptable salts thereof, wherein R^{1a}, R^2, R^{8a}, L, X, and Z^2 are as defined in connection with Formula **I** or Formula **Ia**. In another embodiment, compounds of the Disclosure are compounds represented by a compound

having Formula X and the pharmaceutically acceptable salts thereof, wherein R^{1a} and R^{8a} are independently fluoro, and R^2, L, X, and Z^2 are as defined in connection with Formula **I** or Formula **Ia.**

[000107] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-X**, and the pharmaceutically acceptable salts thereof. In another embodiment, compounds of the Disclosure are compounds represented by a compound having Formula **XI'**:



XI',

and the pharmaceutically acceptable salts thereof, wherein R^{1a}, R^{1b}, R^{1c}, R^2, R^3, R^{10a}, R^{8a}, R^{8b}, X, and Z^2 are as defined in connection with Formula **I** or Formula **XI**.

[000108] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1a} is hydrogen.

[000109] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1b} is hydrogen.

[000110] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1c} is hydrogen.

[000111] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1a} is halogen.

[000112] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1a} is fluoro.

[000113] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1b} is halogen.

[000114] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1b} is fluoro.

[000115] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1c} is halogen.

[000116] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{1c} is fluoro.

[000117] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein at least one of R^{1a}, R^{1b} and R^{1c} is a halogen.

[000118] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein at least one of R^{1a}, R^{1b} and R^{1c} is fluoro.

[000119] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a3} is alkoxycarbonyl.

[000120] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a3} is alkylsulfonyl.

[000121] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a3} is methoxycarbonyl.

[000122] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a3} is ethoxycarbonyl.

[000123] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a3} is methylsulfonyl.

[000124] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a3} is halo-substituted heterocyclyl-carbonyl.

[000125] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein Z^2 is R^{a4}.

[000126] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a5} is alkoxycarbonyl.

[000127] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a5} is methoxycarbonyl.

[000128] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a5} is ethoxycarbonyl.

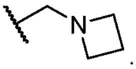
[000129] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a5} is alkylsulfonyl.

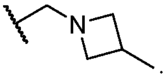
[000130] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a5} is methylsulfonyl.

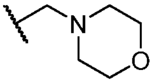
[000131] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a5} is heterocyclyl-carbonyl.

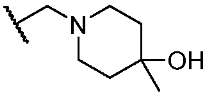
[000132] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a5} is halo-substituted heterocyclyl-carbonyl.

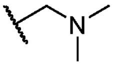
[000133] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{a5} is fluoro-substituted heterocyclyl-carbonyl.

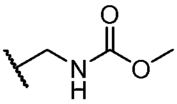
[000134] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

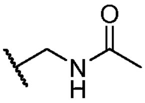
[000135] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

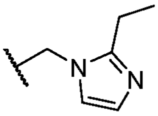
[000136] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

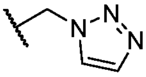
[000137] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

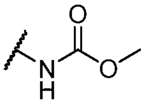
[000138] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

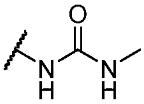
[000139] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

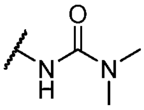
[000140] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

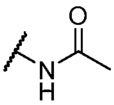
[000141] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

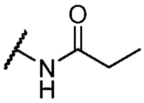
[000142] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^2 is .

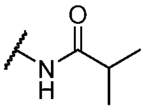
[000143] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^3 is .

[000144] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^3 is .

[000145] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^3 is .

[000146] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^3 is .

[000147] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^3 is .

[000148] Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^3 is .

[000149] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{8a} and R^{8b} are hydrogen.

[000150] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein at least one of R^{8a} and R^{8b} is fluoro.

[000151] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein both R^{8a} and R^{8b} are fluoro.

[000152] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein: R^{10a} is hydrogen, fluoro, cyano, methyl, methoxy, ethoxy, or hydroxy.

[000153] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{10a} is hydrogen.

[000154] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{10a} is fluoro.

[000155] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{10a} is cyano.

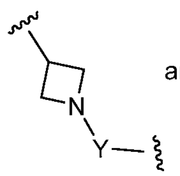
[000156] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{10a} is methyl.

[000157] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{10a} is methoxy.

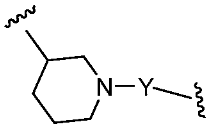
[000158] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{10a} is ethoxy.

[000159] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{10a} is hydroxy.

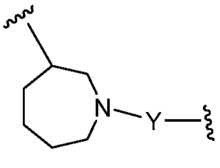
[000160] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein X is X-1. In another embodiment, o and p are 0. In another embodiment, X-1 is selected from the group consisting of:



and



and



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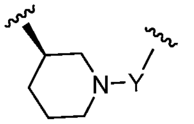
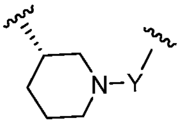
[000161] In another embodiment, X-1 is selected from the group consisting of:



and



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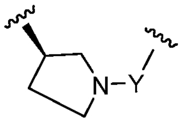
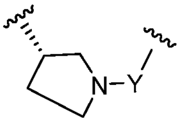
[000162] In another embodiment, X-1 is selected from the group consisting of:



and



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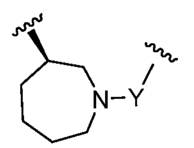
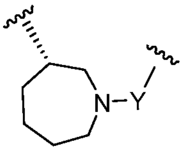
[000163] In another embodiment, X-1 is selected from the group consisting of:

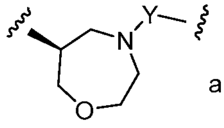


and

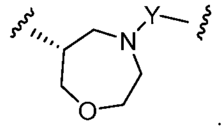


[000164] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein X is X-9.

[000165] In another embodiment, X-9 is selected from the group consisting of



and



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[000166] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein X is X-10.

[000167] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein X is X-12.

[000168] In another embodiment, Compounds of the Disclosure are compounds those wherein X is X-21, X-22, X-23, X-24, X-25, X-26, X-27, X-28, X-29, X-30, X-31, X-32, X-33, X-34, X-35, X-36, X-37, X-38, X-39, X-40, X-41, X-42, X-43, X-44, or X-46.

[000169] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein X is X-45.

[000170] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein X is selected from the group consisting of X-21, X-22, X-23, X-24, X-25, X-26, X-27, X-28, X-29, X-30, X-31, X-32, X-33, X-34, X-35, X-36, X-37, X-38, X-39, X-40, X-41, X-42, X-43, X-44, and X-46.

[000171] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein Z^2 is $-C(R^{13a})=C(R^{13b})(R^{13c})$. In another embodiment, R^{13a}, R^{13b}, and R^{13c} are each hydrogen. In another embodiment, R^{13a} is dimethylaminomethyl, and R^{13b} and R^{13c} are independently selected from the group consisting of hydrogen and methyl. In another embodiment, R^{13a} is hydrogen, and R^{13b} and R^{13c} are independently selected from the group consisting of hydrogen, methyl and dimethylaminomethyl. In another embodiment, R^{13a} and R^{13b} are hydrogen, and R^{13c} is dimethylaminomethyl or methyl. In another embodiment, R^{13a} and R^{13b} are hydrogen, and R^{13c} is dimethylaminomethyl.

[000172] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each hydrogen.

[000173] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen and dimethylaminomethyl.

[000174] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen and methyl.

[000175] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein two of R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of methyl and dimethylaminomethyl.

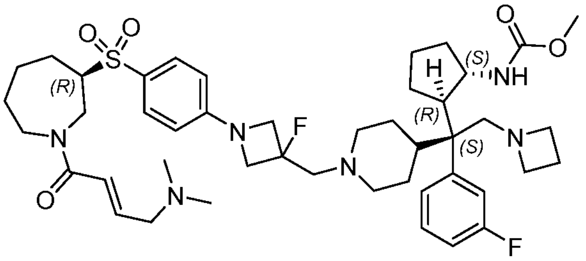
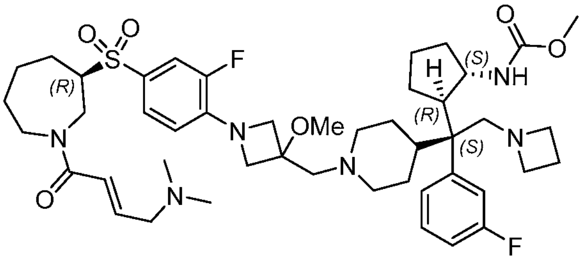
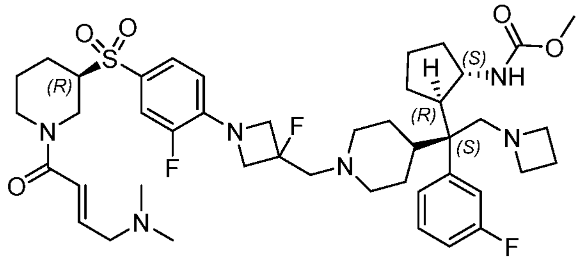
[000176] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein no more that one of R^{13a}, R^{13b}, R^{13c}, and R^{13d} is different from hydrogen.

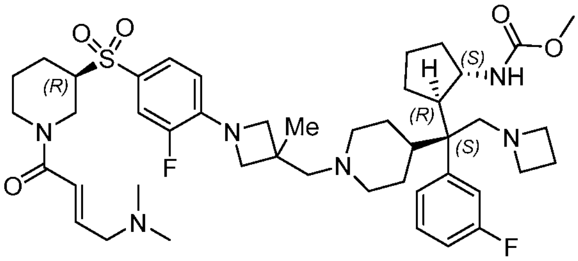
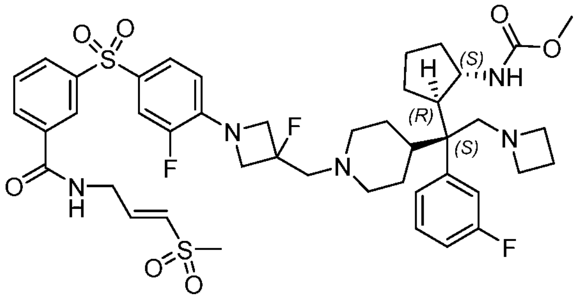
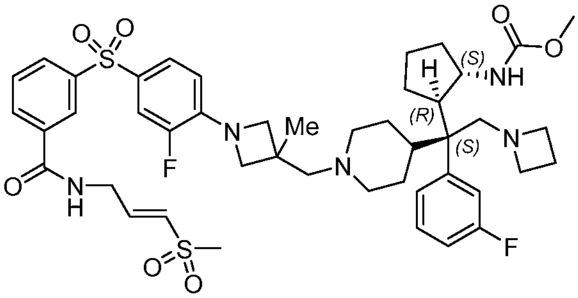
[000177] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein one or two of R^{13a}, R^{13b}, R^{13c}, and R^{13d} are not hydrogen.

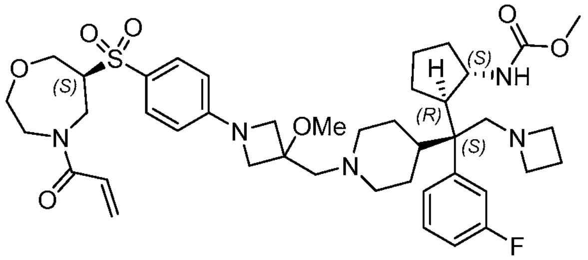
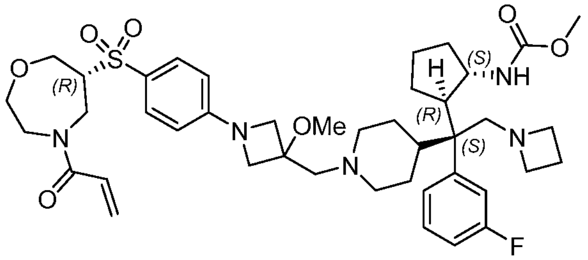
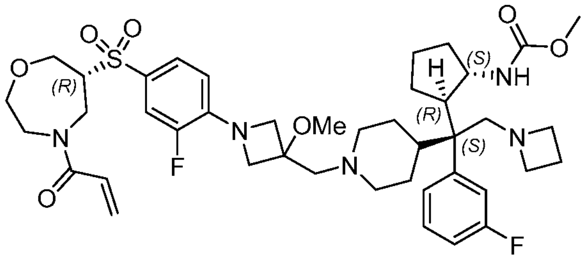
[000178] In another embodiment, Compounds of the Disclosure are compounds represented by any one or more of Formulae **I-XII, Ia-Ij, XIa-XIc, XIIa-XIIc**, and the pharmaceutically acceptable salts thereof, wherein Z^2 is $-C{\equiv}CR^{13d}$. In another embodiment, R^{13d} is hydrogen. In another embodiment, R^{13d} is methyl.

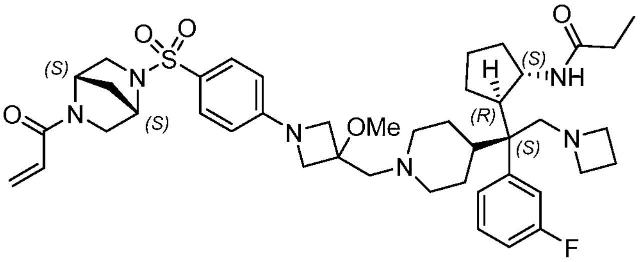
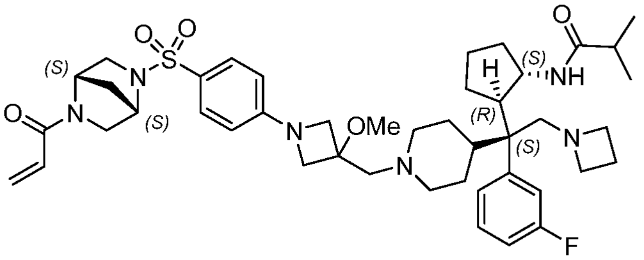
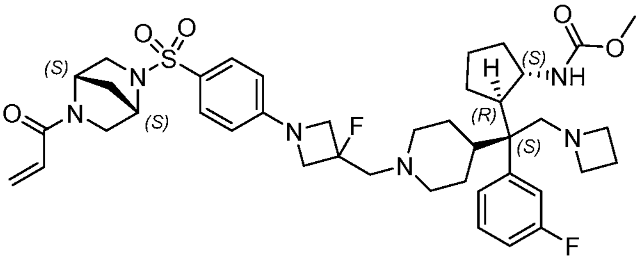
[000179] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **I** or **Ia** selected from any one or more of the compounds of Table 1 and Table 1A. Tables 1 and 1A further provides the chemical names of the compounds of Tables 1 and 1A generated by Chemdraw® Professional version 16.0. In the event of any ambiguity between their chemical structure and chemical name, Compounds of the Disclosure are defined by their chemical structure.

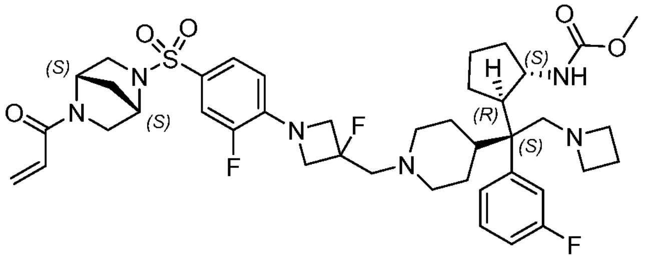
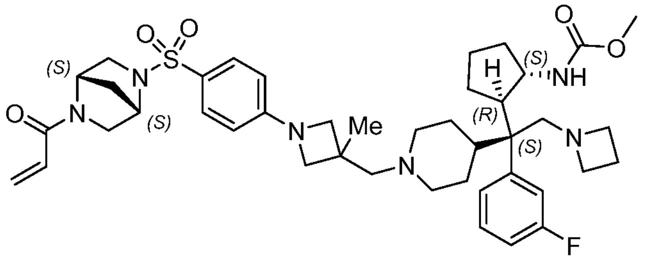
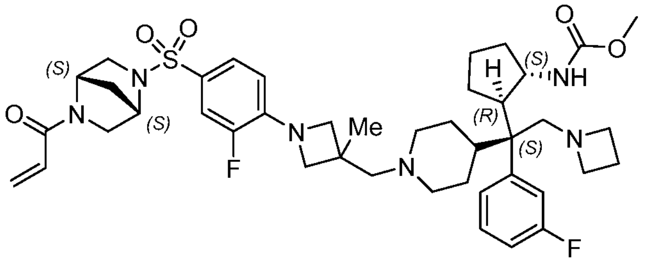
[000180] Table 1

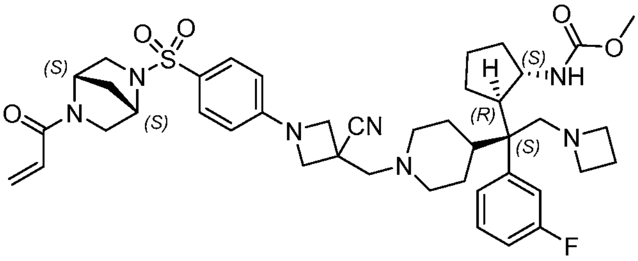
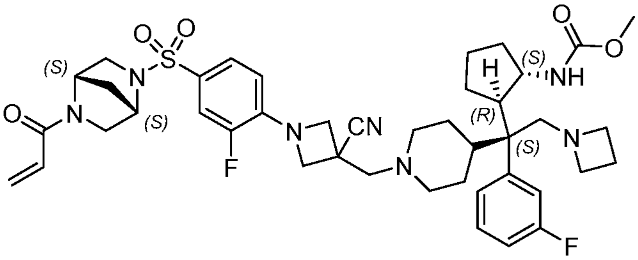
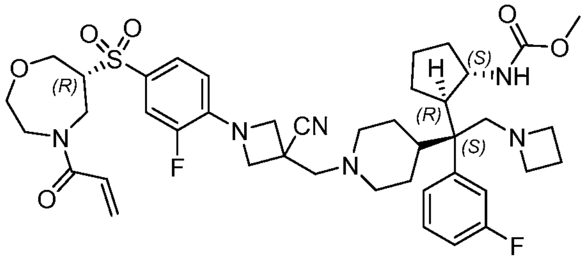
Cpd. No	**Structure**	**MS (ESI) m/z $[M+H]^+$**
1	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((R)-1-((E)-4-(dimethylamino)but-2-enoyl)azepan-3-yl)sulfonyl)phenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	839.59
2	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((R)-1-((E)-4-(dimethylamino)but-2-enoyl)azepan-3-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	869.75
3	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((R)-1-((E)-4-(dimethylamino)but-2-enoyl)piperidin-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	843.75

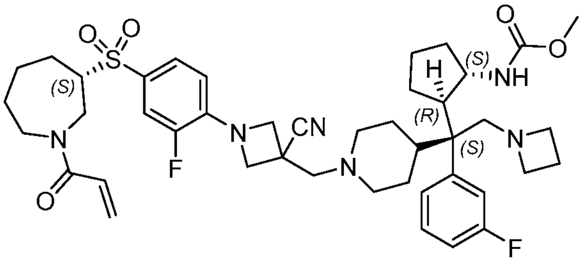
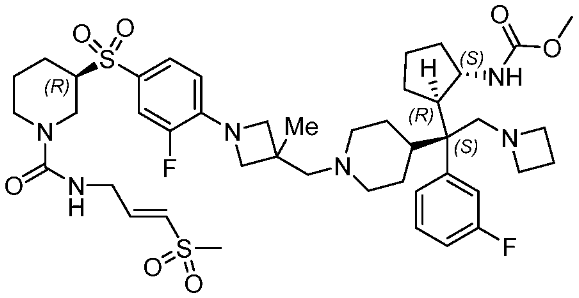
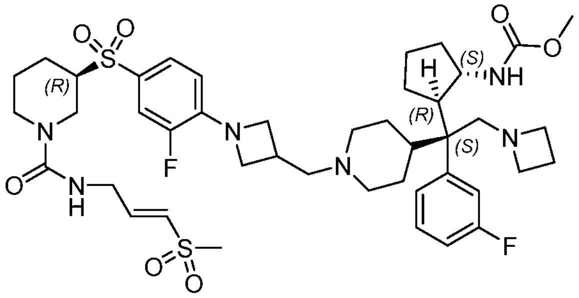
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
4	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((R)-1-((E)-4-(dimethylamino)but-2-enoyl)piperidin-3-yl)sulfonyl)-2-fluorophenyl)-3-methylazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	839.75
5	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-((3-(((E)-3-(methylsulfonyl)allyl)carbamoyl)phenyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	886.60
6	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(2-fluoro-4-((3-(((E)-3-(methylsulfonyl)allyl)carbamoyl)phenyl)sulfonyl)phenyl)-3-methylazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	882.60

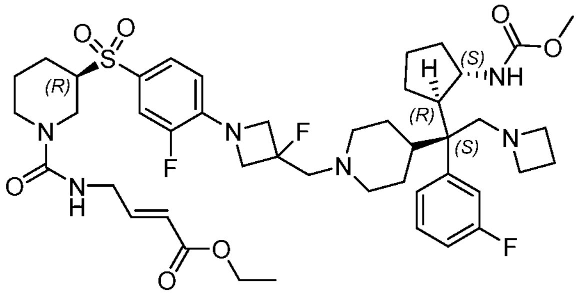
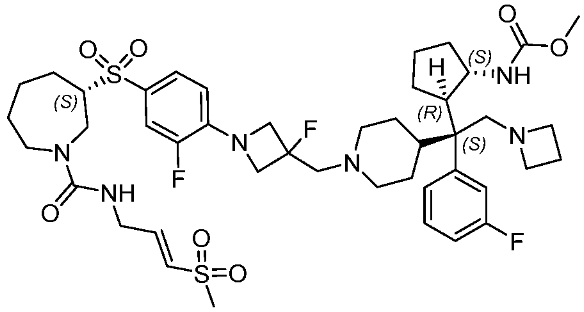
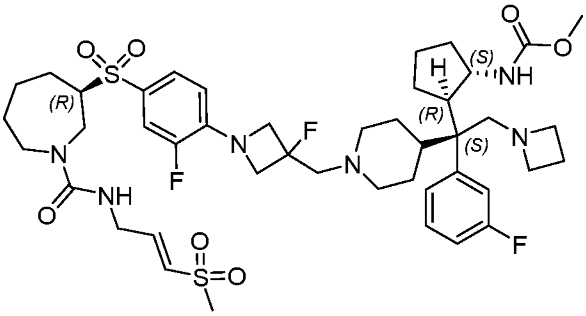
Cpd. No	**Structure**	**MS (ESI) m/z [M+H]$^+$**
7	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((S)-4-acryloyl-1,4-oxazepan-6-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	796.01
8	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((R)-4-acryloyl-1,4-oxazepan-6-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	796.48
9	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((R)-4-acryloyl-1,4-oxazepan-6-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	814.67

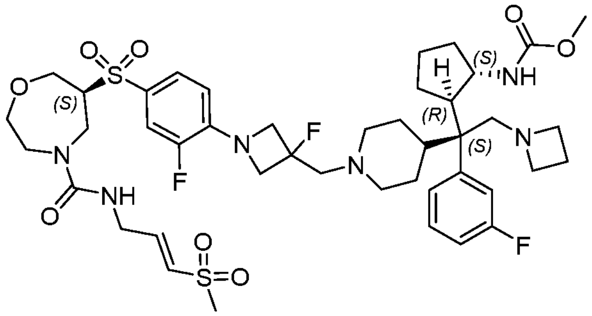
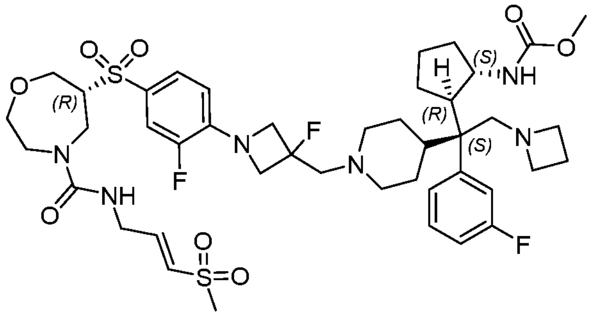
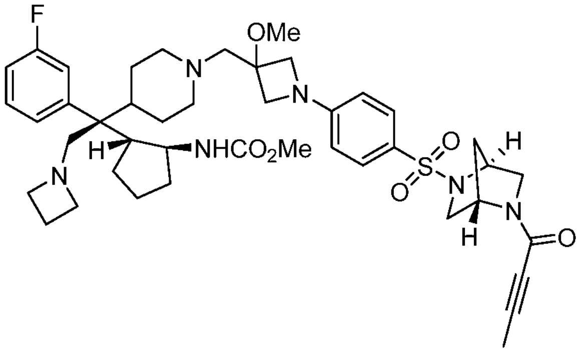
Cpd. No	Structure	MS (ESI) m/z [M+H]$^+$
10	 N-((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)propionamide	791.01
11	 N-((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)isobutyramide	805.72
12	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	781.00

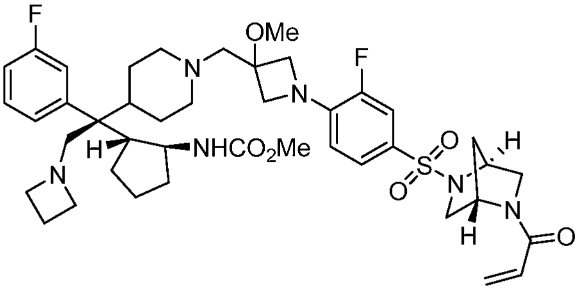
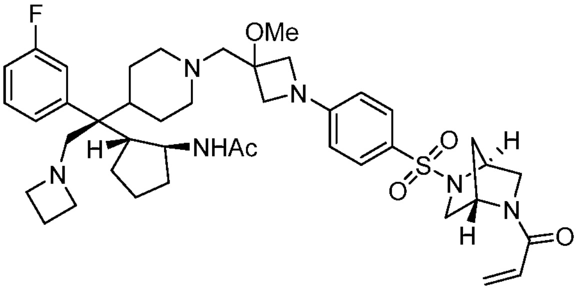
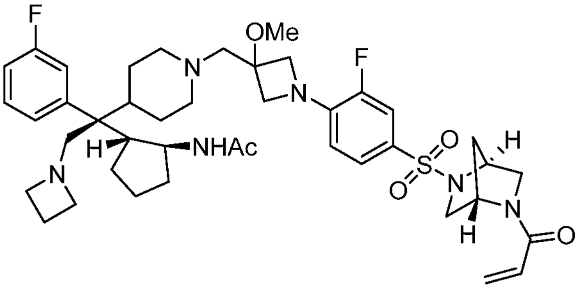
Cpd. No	**Structure**	**MS (ESI) m/z $[M+H]^+$**
13	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	799.61
14	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methylazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	777.63
15	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-methylazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	795.60

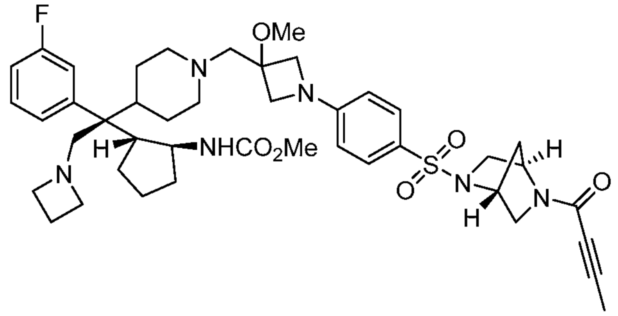
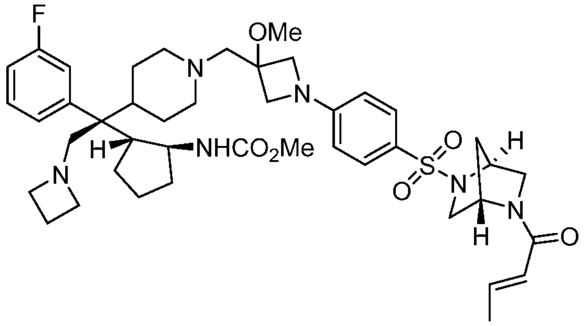
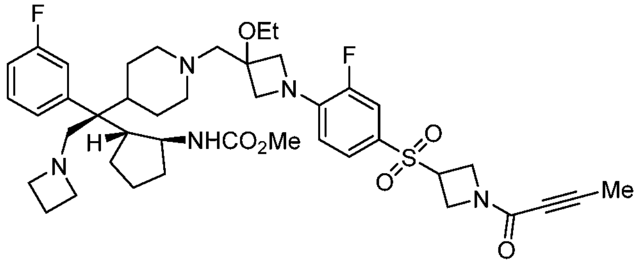
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
16	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-cyanoazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	788.60
17	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-cyanoazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	806.61
18	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((R)-4-acryloyl-1,4-oxazepan-6-yl)sulfonyl)-2-fluorophenyl)-3-cyanoazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	809.59

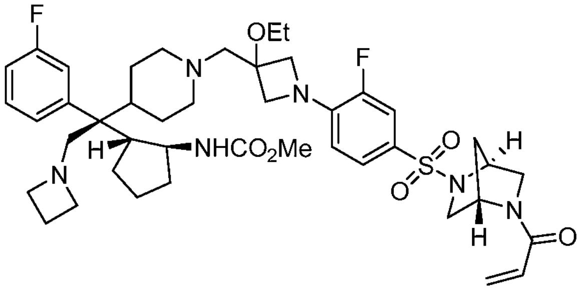
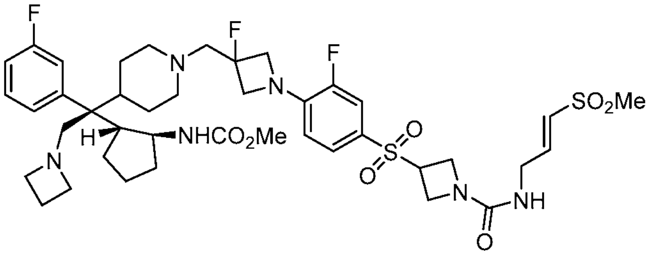
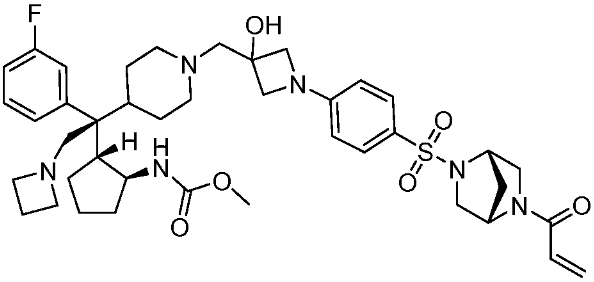
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
19	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((S)-1-acryloylazepan-3-yl)sulfonyl)-2-fluorophenyl)-3-cyanoazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.60
20	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(2-fluoro-4-(((R)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)piperidin-3-yl)sulfonyl)phenyl)-3-methylazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	889.64
21	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(2-fluoro-4-(((R)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)piperidin-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	875.60

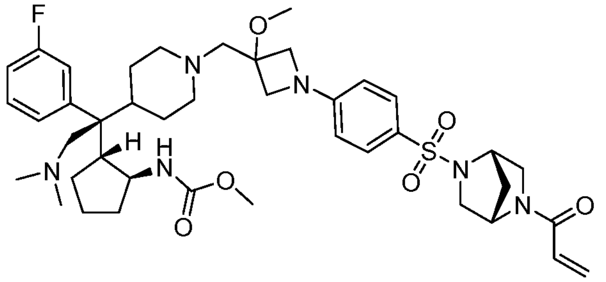
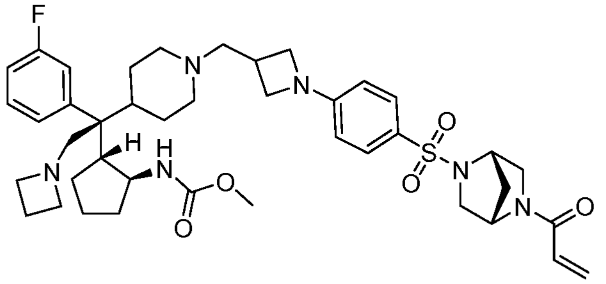
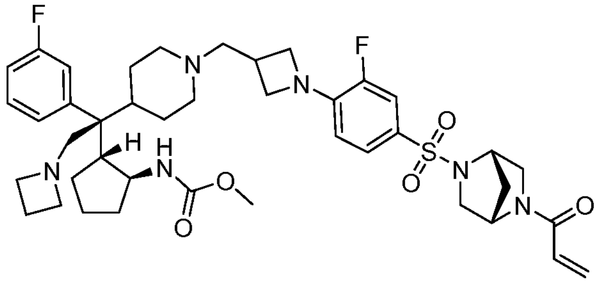
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
22	 ethyl (E)-4-((R)-3-((4-(3-((4-((S)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)ethyl)piperidin-1-yl)methyl)-3-fluoroazetidin-1-yl)-3-fluorophenyl)sulfonyl)piperidine-1-carboxamido)but-2-enoate	887.65
23	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-(((S)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)azepan-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	907.60
24	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-(((R)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)azepan-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	907.61

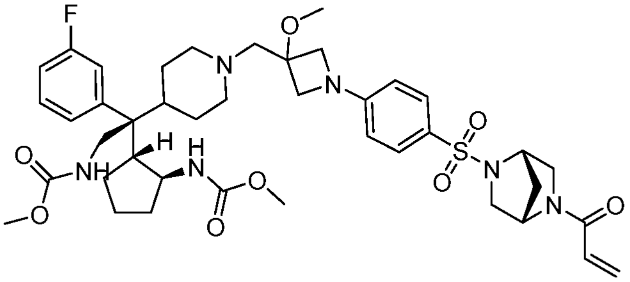
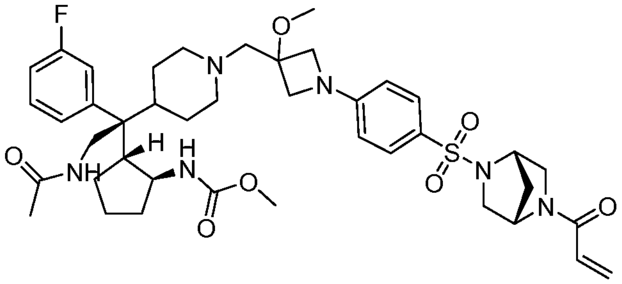
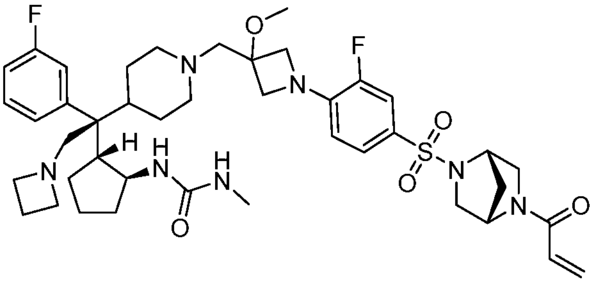
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
25	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-(((S)-4-(((E)-3-(methylsulfonyl)allyl)carbamoyl)-1,4-oxazepan-6-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	909.60
26	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-(((R)-4-(((E)-3-(methylsulfonyl)allyl)carbamoyl)-1,4-oxazepan-6-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	909.58
27	 methyl ((1S,2R)-2-(2-(azetidin-1-yl)-1-(1-((1-(4-(((1S,4S)-5-(but-2-ynoyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	805.73

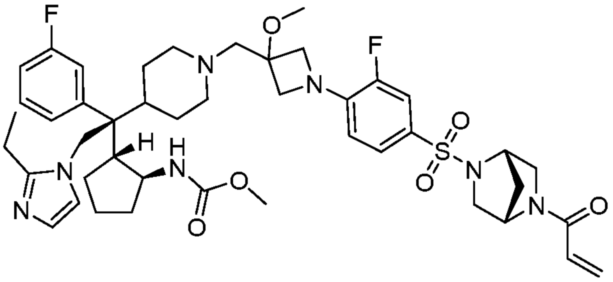
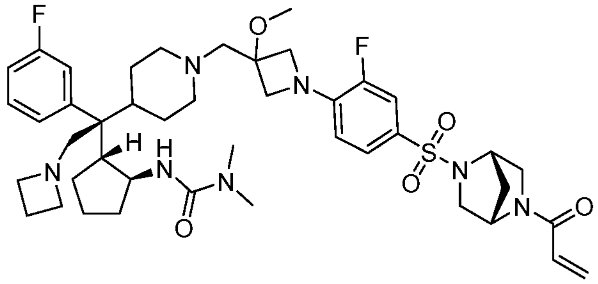
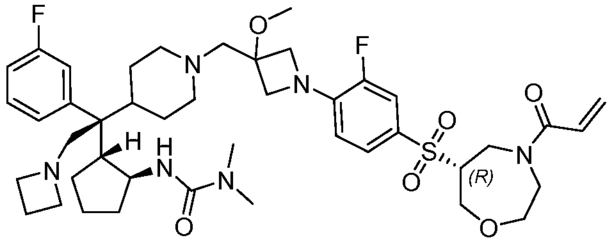
Cpd. No	**Structure**	**MS (ESI) m/z $[M+H]^+$**
28	 methyl ((1S,2R)-2-(1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	811.67
29	 N-((1S,2R)-2-(1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)acetamide	777.69
30	 N-((1S,2R)-2-(1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)acetamide	795.64

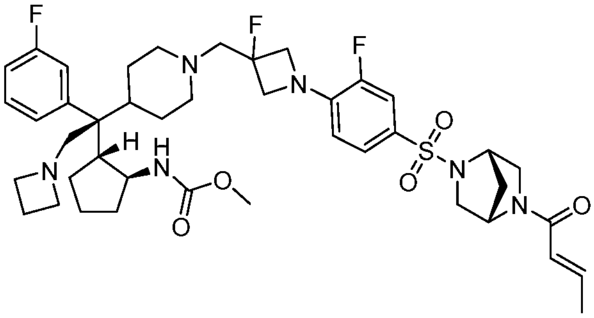
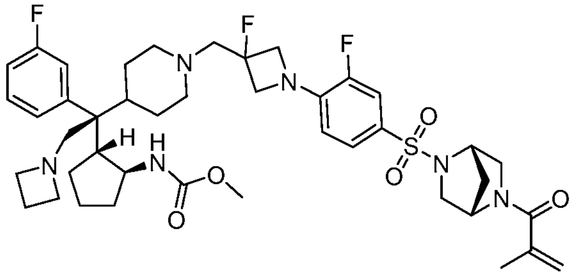
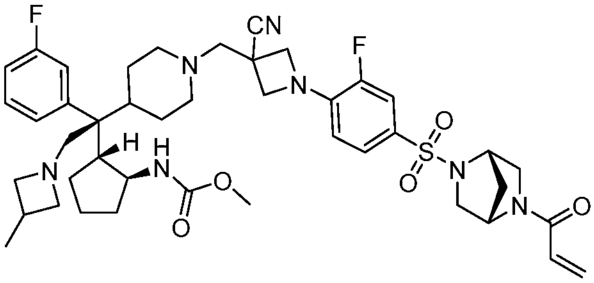
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
31	 methyl ((1S,2R)-2-(2-(azetidin-1-yl)-1-(1-((1-(4-(((1R,4R)-5-(but-2-ynoyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	805.66
32	 methyl ((1S,2R)-2-(2-(azetidin-1-yl)-1-(1-((1-(4-(((1S,4S)-5-((E)-but-2-enoyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.63
33	 methyl ((1S,2R)-2-(2-(azetidin-1-yl)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-2-fluorophenyl)-3-ethoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	795.53

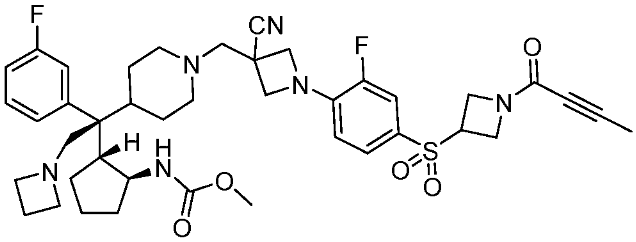
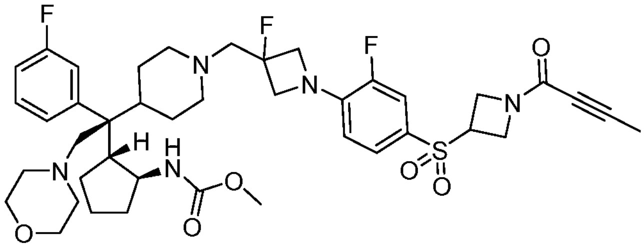
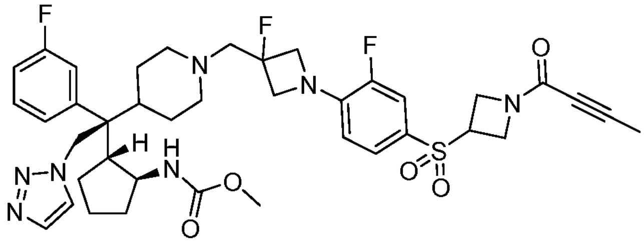
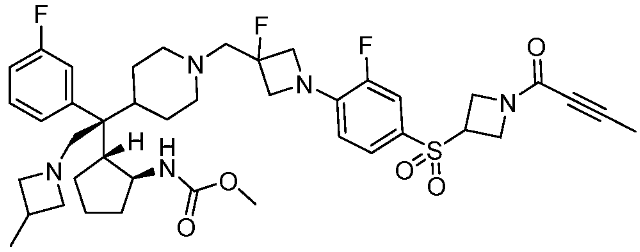
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
34	 methyl ((1S,2R)-2-(1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-ethoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	825.61
35	 methyl ((1S,2R)-2-(2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-((1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)azetidin-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	865.51
36	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-hydroxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	779.04

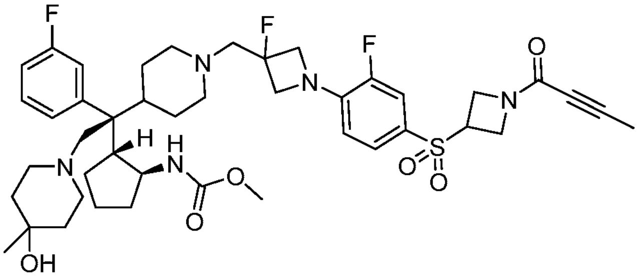
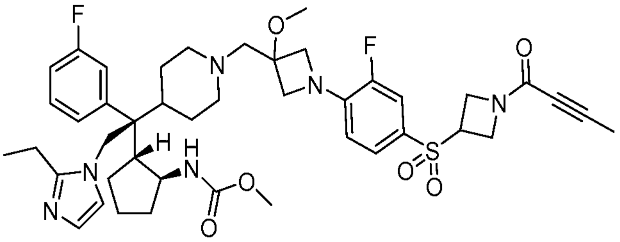
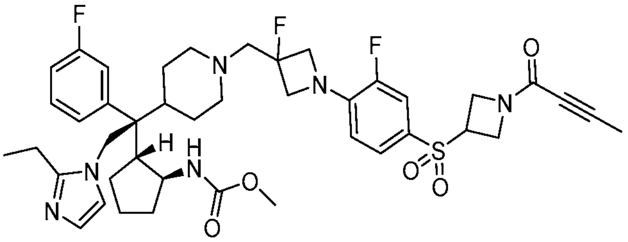
Cpd. No	**Structure**	**MS (ESI) m/z $[M+H]^+$**
37	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(dimethylamino)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	781.05
38	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	763.07
39	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	781.60

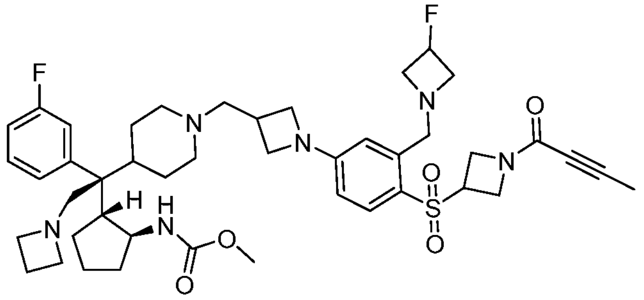
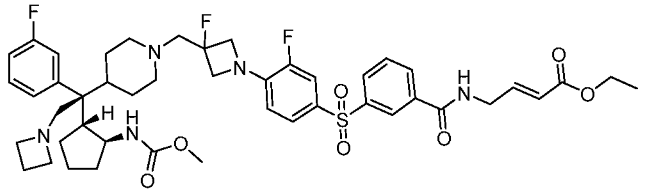
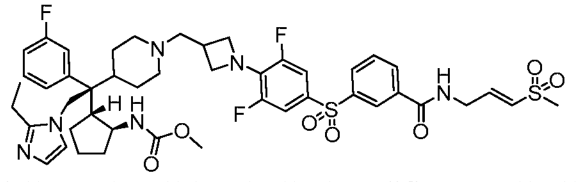
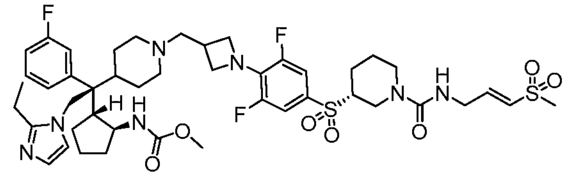
Cpd. No	**Structure**	**MS (ESI) m/z [M+H]$^+$**
40	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-((methoxycarbonyl)amino)ethyl)cyclopentyl)carbamate	811.40
41	 methyl ((1S,2R)-2-((S)-2-acetamido-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	795.45
42	 1-((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)-3-methylurea	810.48

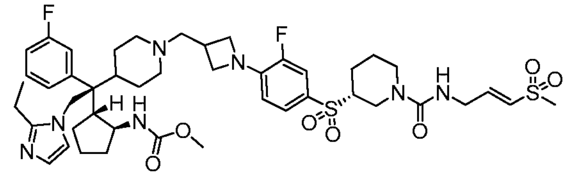
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
43	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	850.75
44	 3-((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)-1,1-dimethylurea	824.80
45	 3-((1S,2R)-2-((S)-1-(1-((1-(4-(((R)-4-acryloyl-1,4-oxazepan-6-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)-1,1-dimethylurea	827.58

Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
46	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((1S,4S)-5-((E)-but-2-enoyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	813.67
47	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-(((1S,4S)-5-methacryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	813.62
48	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-cyanoazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-(3-methylazetidin-1-yl)ethyl)cyclopentyl)carbamate	820.77

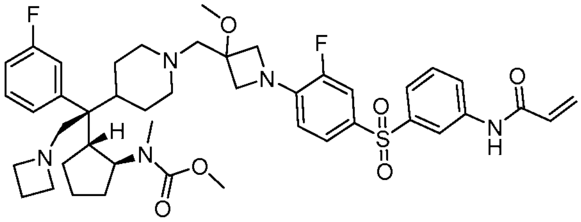
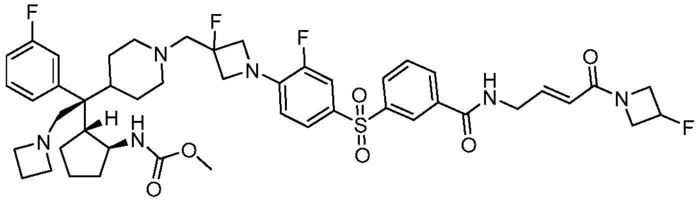
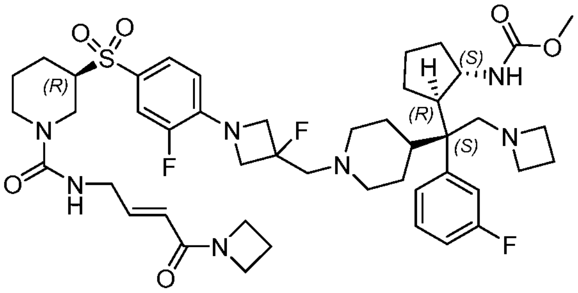
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
49	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-2-fluorophenyl)-3-cyanoazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	777.46
50	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-morpholinoethyl)cyclopentyl)carbamate	800.52
51	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-(1H-1,2,3-triazol-1-yl)ethyl)cyclopentyl)carbamate	782.56
52	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-(3-methylazetidin-1-yl)ethyl)cyclopentyl)carbamate	784.47

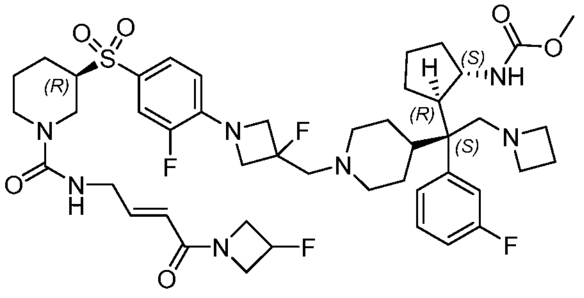
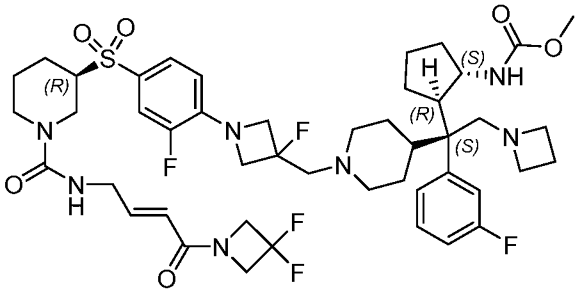
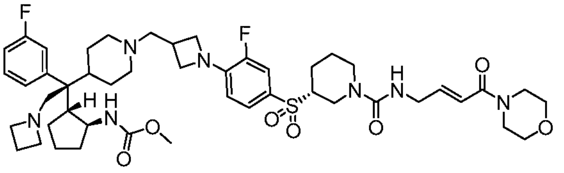
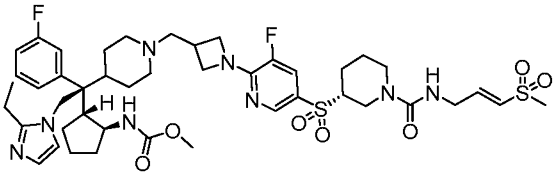
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
53	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)-2-(4-hydroxy-4-methylpiperidin-1-yl)ethyl)cyclopentyl)carbamate	828.52
54	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	820.98
55	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	809.48

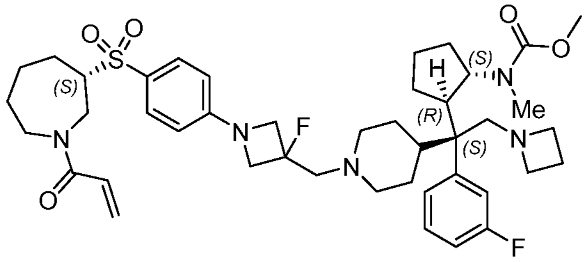
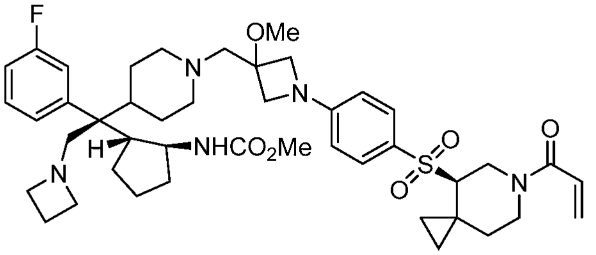
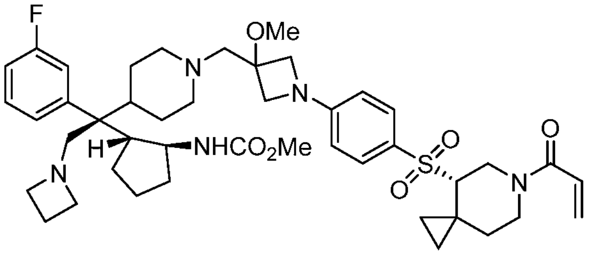
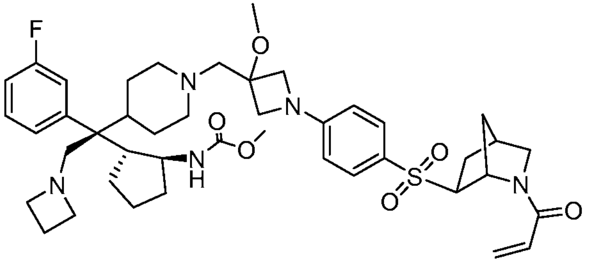
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
56	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-((1-(but-2-ynoyl)azetidin-3-yl)sulfonyl)-3-((3-fluoroazetidin-1-yl)methyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	821.34
57	 ethyl (E)-4-(3-((4-(3-((4-((S)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)ethyl)piperidin-1-yl)methyl)-3-fluoroazetidin-1-yl)-3-fluorophenyl)sulfonyl)benzamido)but-2-enoate	880.61
58	 methyl ((1S,2R)-2-((S)-1-(1-((1-(2,6-difluoro-4-((3-(((E)-3-(methylsulfonyl)allyl)carbamoyl)phenyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	925
59	 methyl ((1S,2R)-2-((S)-1-(1-((1-(2,6-difluoro-4-(((R)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)piperidin-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	932

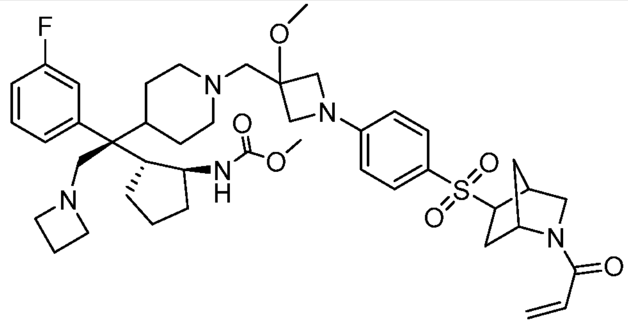
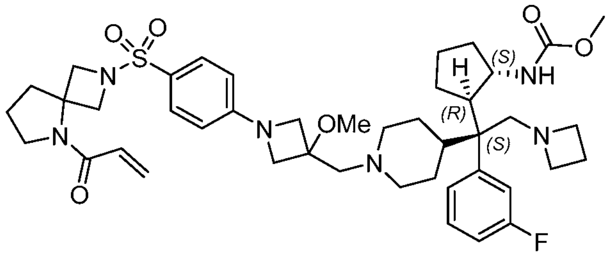
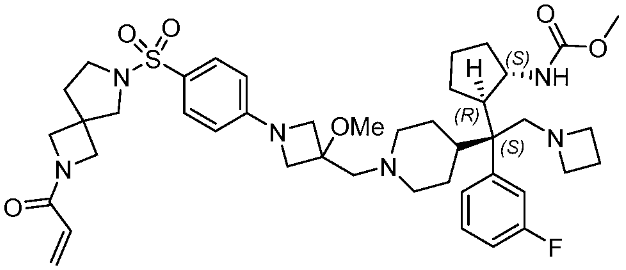
Cpd. No	Structure	MS (ESI) m/z $[M+H]^+$
60	 methyl ((1S,2R)-2-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(1-((1-(2-fluoro-4-(((R)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)piperidin-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	914

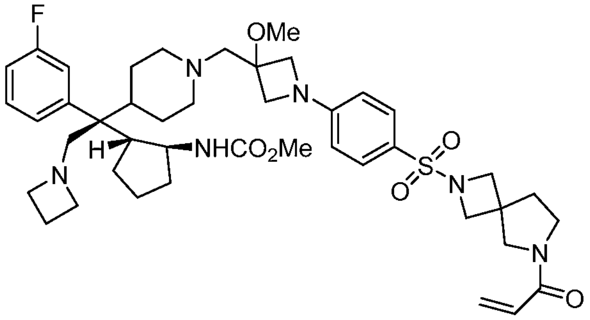
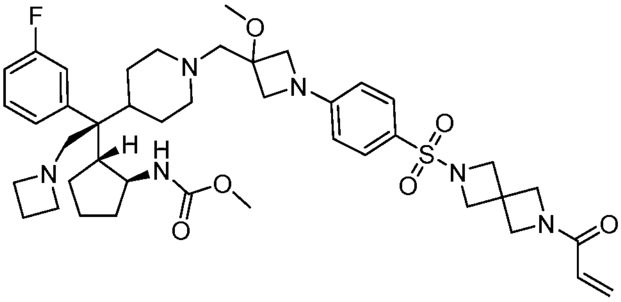
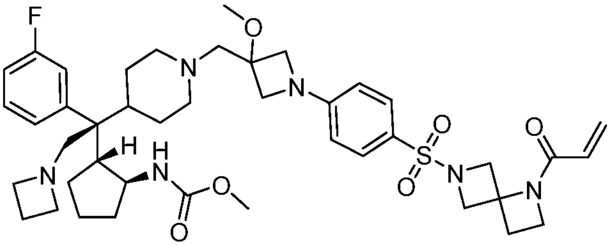
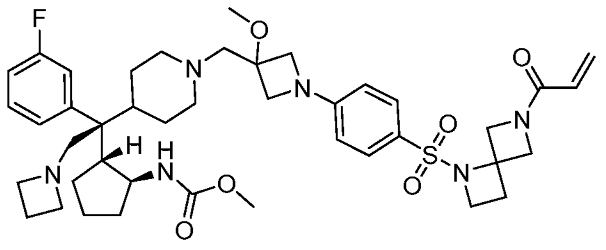
[000181] Table 1A

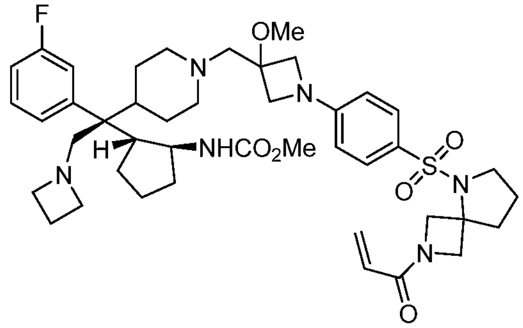
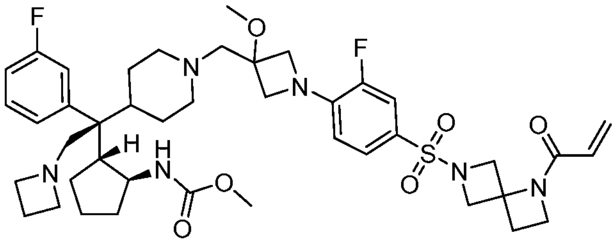
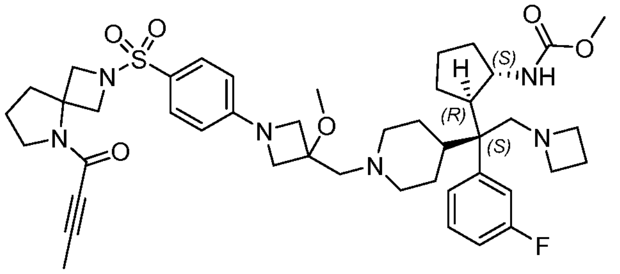
Cpd. No.	Structure/Name	MS (ESI) m/z $[M+H]^+$
61	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((3-acrylamidophenyl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)(methyl)carbamate	820.10
62	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-((3-(((E)-4-(3-fluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)carbamoyl)phenyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	909.27
64	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((R)-1-(((E)-4-(azetidin-1-yl)-4-oxobut-2-en-1-yl)carbamoyl)piperidin-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	898.10

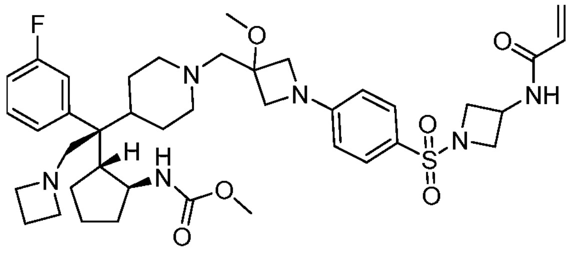
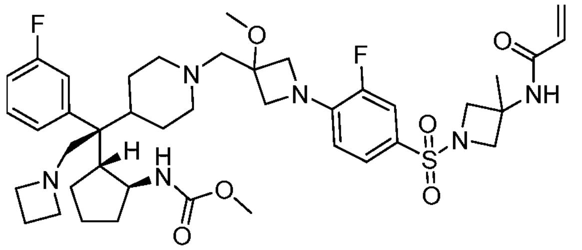
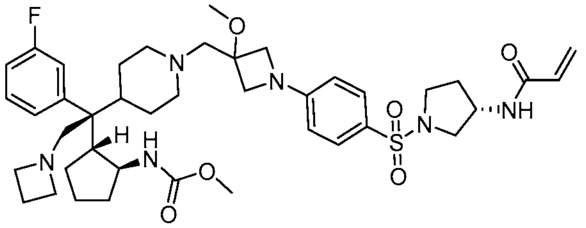
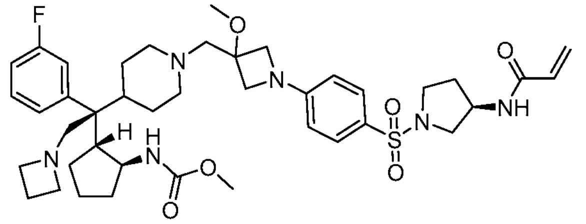
65	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-(((R)-1-(((E)-4-(3-fluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)carbamoyl)piperidin-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	916.64
66	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((R)-1-(((E)-4-(3,3-difluoroazetidin-1-yl)-4-oxobut-2-en-1-yl)carbamoyl)piperidin-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	934.67
67	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(2-fluoro-4-(((R)-1-(((E)-4-morpholino-4-oxobut-2-en-1-yl)carbamoyl)piperidin-3-yl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	910
70	 methyl ((1S,2R)-2-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(1-((1-(3-fluoro-5-(((R)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)piperidin-3-yl)sulfonyl)pyridin-2-yl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	915

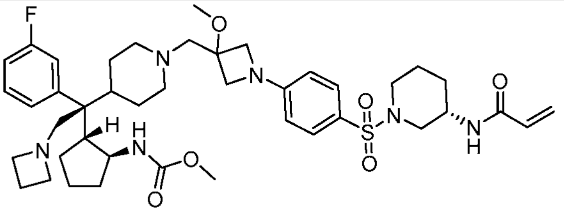
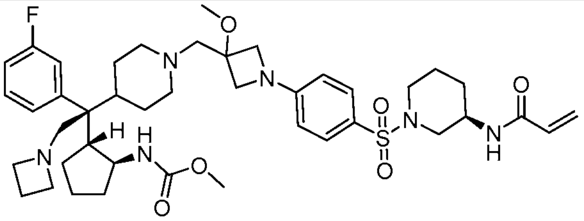
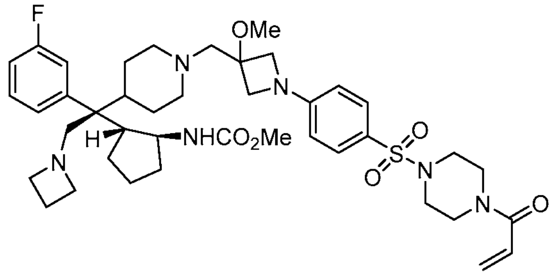
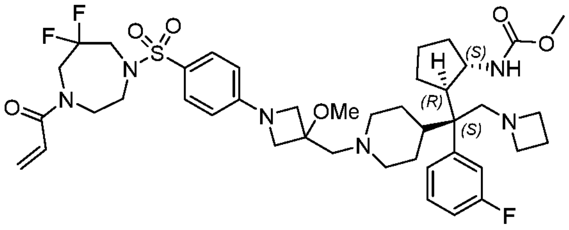
71	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((S)-1-acryloylazepan-3-yl)sulfonyl)phenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)(methyl)carbamate	796.71
72	 methyl ((1S,2R)-2-(1-(1-((1-(4-(((R)-6-acryloyl-6-azaspiro[2.5]octan-4-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	806.61
73	 methyl ((1S,2R)-2-(1-(1-((1-(4-(((S)-6-acryloyl-6-azaspiro[2.5]octan-4-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	806.60
74	 methyl ((1S,2R)-2-((S)1-(1-((1-(4-(((1S,4R,6S)-2-acryloyl-2-azabicyclo[2.2.1]heptan-6-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	792.28

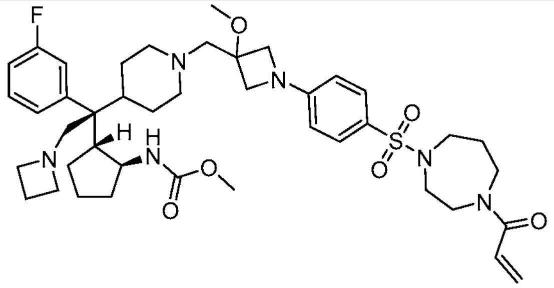
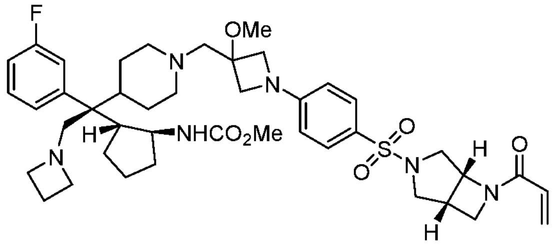
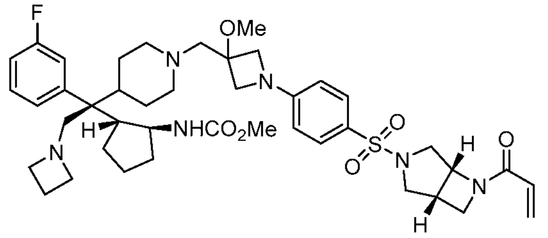
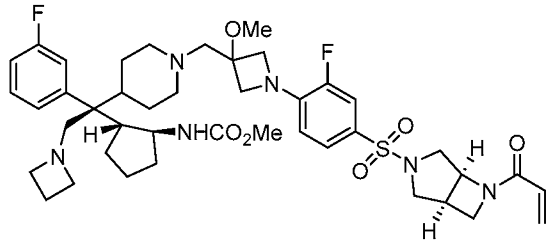
75	 methyl ((1RS,2SR)-2-((S)1-(1-((1-(4-(((1SR,4SR,5R)-2-acryloyl-2-azabicyclo[2.2.1]heptan-5-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	792.34
76	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((5-acryloyl-2,5-diazaspiro[3.4]octan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.10
77	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((2-acryloyl-2,6-diazaspiro[3.4]octan-6-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.11

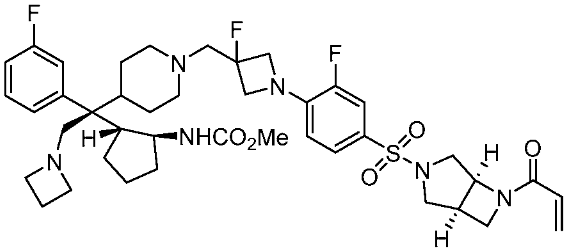
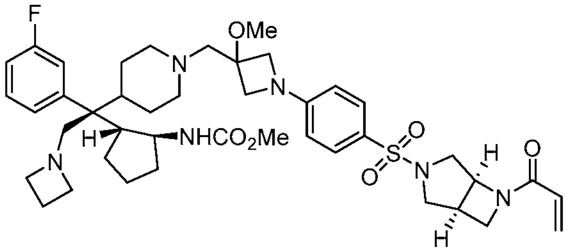
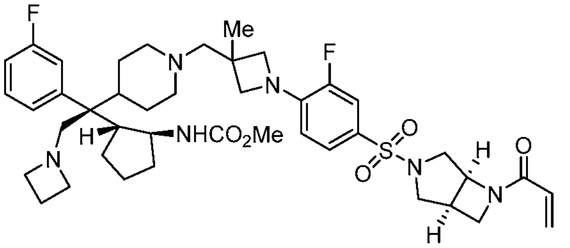
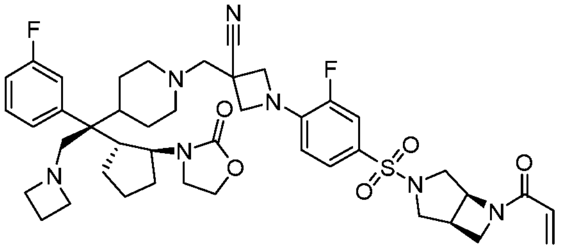
78	 methyl ((1S,2R)-2-(1-(1-((1-(4-((6-acryloyl-2,6-diazaspiro[3.4]octan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.66
79	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((6-acryloyl-2,6-diazaspiro[3.3]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	793.53
80	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((1-acryloyl-1,6-diazaspiro[3.3]heptan-6-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	793.47
81	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((6-acryloyl-1,6-diazaspiro[3.3]heptan-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	793.09

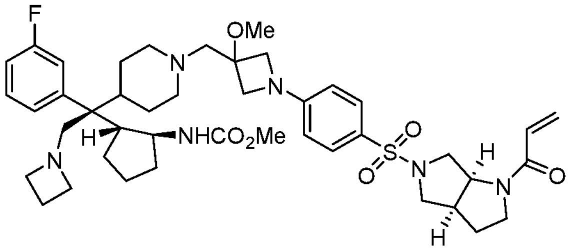
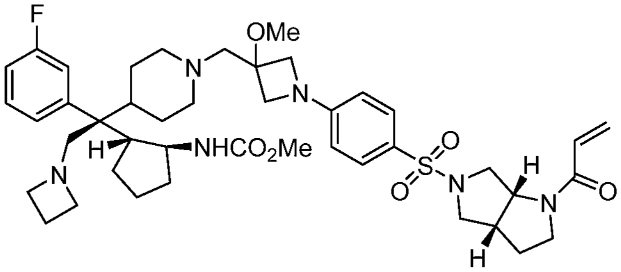
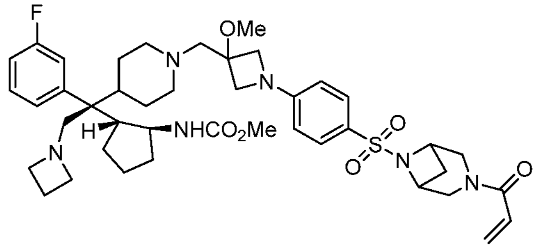
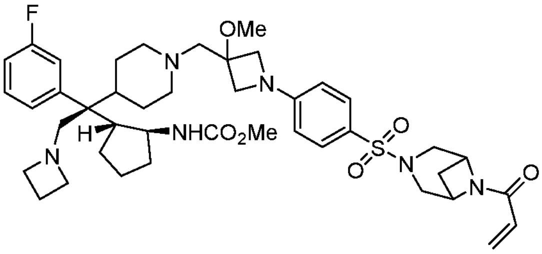
82	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((2-acryloyl-2,5-diazaspiro[3.4]octan-5-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.34
83	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((1-acryloyl-1,6-diazaspiro[3.3]heptan-6-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	811.12
84	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-((5-(but-2-ynoyl)-2,5-diazaspiro[3.4]octan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	819.64

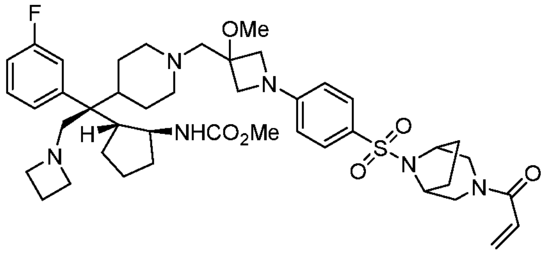
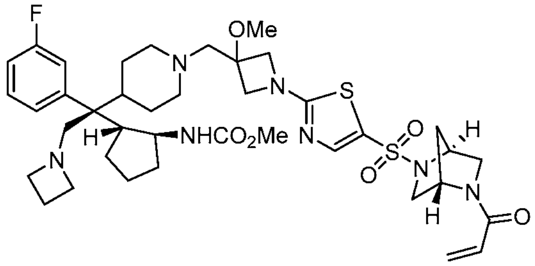
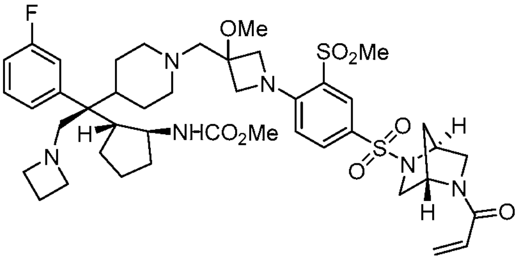
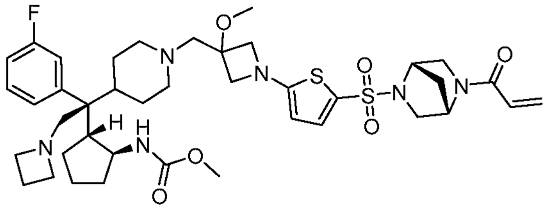
85	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((3-acrylamidoazetidin-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	767.54
86	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((3-acrylamido-3-methylazetidin-1-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	799.05
87	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((S)-3-acrylamidopyrrolidin-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	781.00
88	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((R)-3-acrylamidopyrrolidin-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	781.01

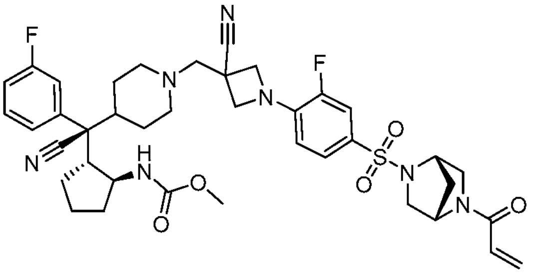
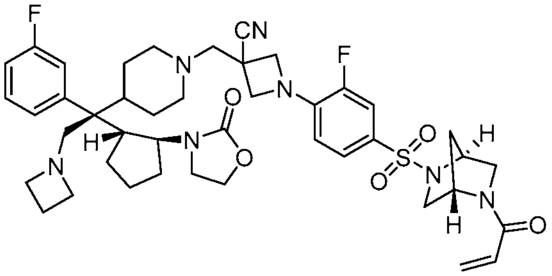
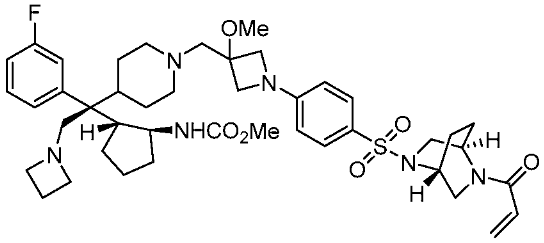
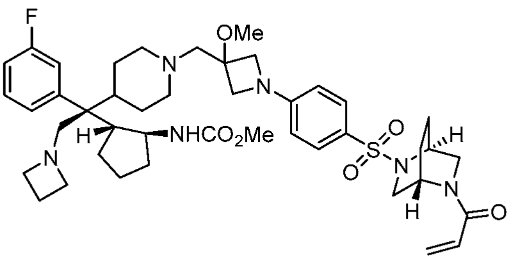
89	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((S)-3-acrylamidopiperidin-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	795.05
90	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((R)-3-acrylamidopiperidin-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	795.07
91	 methyl ((1S,2R)-2-(1-(1-((1-(4-((4-acryloylpiperazin-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	781.63
92	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((4-acryloyl-6,6-difluoro-1,4-diazepan-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	831.16

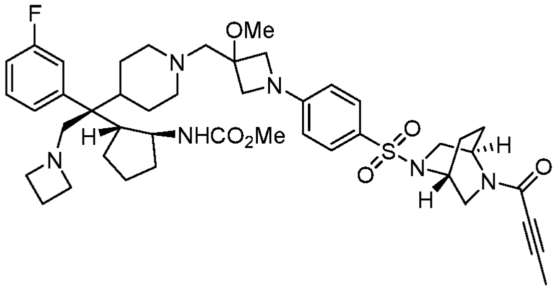
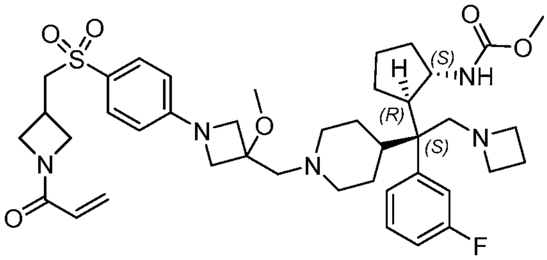
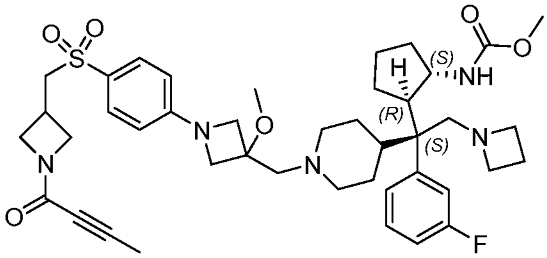
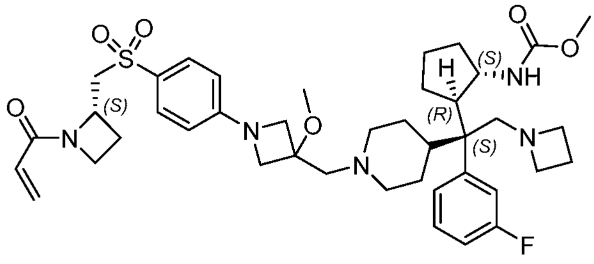
93	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((4-acryloyl-1,4-diazepan-1-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	795.47
94	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1R,5R)-6-acryloyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	793.30
95	 methyl ((1S,2R)-2-((S)2-(azetidin-1-yl)-1-(1-((1-(4-(((1S,4S)-5-(cyclopent-1-ene-1-carbonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	793.24
96	 methyl ((1S,2R)-2-((S)1-(1-((1-(4-(((1S,5S)-6-acryloyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)sulfonyl)-2-fluorophenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	811.24

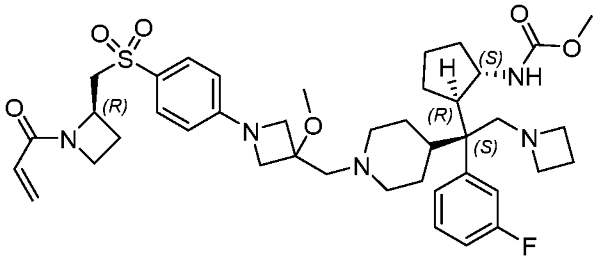
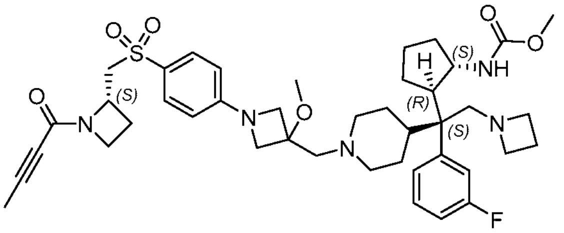
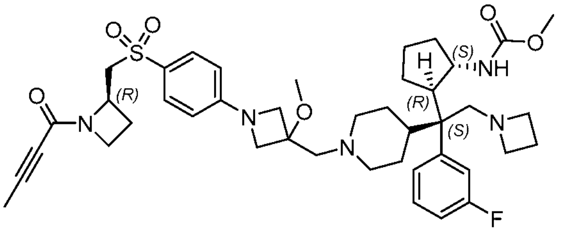
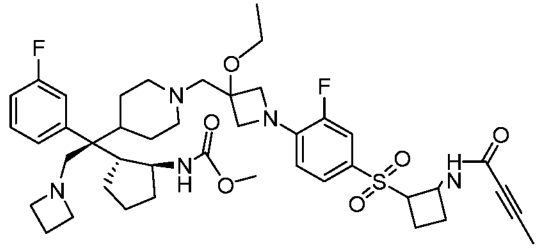
97	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,5S)-6-acryloyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)sulfonyl)-2-fluorophenyl)-3-fluoroazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	799.21
98	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,5S)-6-acryloyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	793.29
99	 methyl ((1S,2R)-2-((S)1-(1-((1-(4-(((1S,5S)-6-acryloyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)sulfonyl)-2-fluorophenyl)-3-methylazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	795.19
100	 1-(4-(((1S,5S)-6-acryloyl-3,6-diazabicyclo[3.2.0]heptan-3-yl)sulfonyl)-2-fluorophenyl)-3-((4-((R)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-(2-oxooxazolidin-3-yl)cyclopentyl)ethyl)piperidin-1-yl)methyl)azetidine-3-carbonitrile	818.19

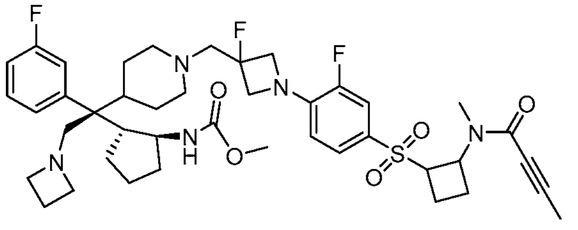
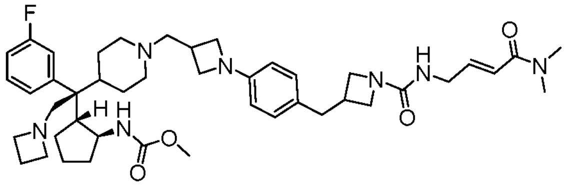
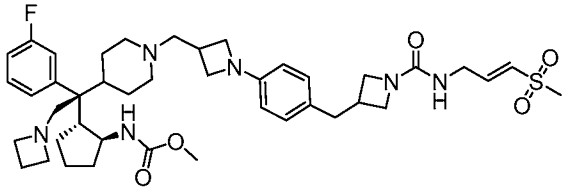
101	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((3aS,6aS)-1-acryloylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.31
102	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((3aR,6aR)-1-acryloylhexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.28
103	 methyl ((1S,2R)-2-(1-(1-((1-(4-((3-acryloyl-3,6-diazabicyclo[3.1.1]heptan-6-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	793.57
104	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1R,5S)-6-acryloyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	793.24

105	 methyl ((1S,2R)-2-(1-(1-((1-(4-((3-acryloyl-3,8-diazabicyclo[3.2.1]octan-8-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.46
106	 methyl ((1S,2R)-2-((S)-1-(1-((1-(5-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)thiazol-2-yl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	800.18
107	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-(methylsulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	871.25
108	 methyl ((1S,2R)-2-((S)-1-(1-((1-(5-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)thiophen-2-yl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	799.21

109	 methyl ((1S,2R)-2-((S)-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-cyanoazetidin-3-yl)methyl)piperidin-4-yl)(cyano)(3-fluorophenyl)methyl)cyclopentyl)carbamate	762.11
110	 1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)sulfonyl)-2-fluorophenyl)-3-((4-((R)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-(2-oxooxazolidin-3-yl)cyclopentyl)ethyl)piperidin-1-yl)methyl)azetidine-3-carbonitrile	818.14
111	 methyl ((1S,2R)-2-(1-(1-((1-(4-(((1R,4R)-5-acryloyl-2,5-diazabicyclo[2.2.2]octan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.59
112	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1S,4S)-5-acryloyl-2,5-diazabicyclo[2.2.2]octan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	807.20

113	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((1R,4R)-5-(but-2-ynoyl)-2,5-diazabicyclo[2.2.2]octan-2-yl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	819.27
114	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-(((1-acryloylazetidin-3-yl)methyl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	766.59
115	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(((1-(but-2-ynoyl)azetidin-3-yl)methyl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	778.60
116	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((((S)-1-acryloylazetidin-2-yl)methyl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	766.55

117	 methyl ((1S,2R)-2-((S)-1-(1-((1-(4-((((R)-1-acryloylazetidin-2-yl)methyl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-2-(azetidin-1-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	766.52
118	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-((((S)-1-(but-2-ynoyl)azetidin-2-yl)methyl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	778.55
119	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-((((R)-1-(but-2-ynoyl)azetidin-2-yl)methyl)sulfonyl)phenyl)-3-methoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	778.52
120	 methyl ((1S,2R)-2-((S)2-(azetidin-1-yl)-1-(1-((1-(4-((2-(but-2-ynamido)cyclobutyl)sulfonyl)-2-fluorophenyl)-3-ethoxyazetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	810.33

121	 methyl ((1S,2R)-2-((S)2-(azetidin-1-yl)-1-(1-((3-fluoro-1-(2-fluoro-4-((2-(N-methylbut-2-ynamido)cyclobutyl)sulfonyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	798.20
122	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-((1-(((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamoyl)azetidin-3-yl)methyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate	772
123	 methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-(1-((1-(4-((1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)azetidin-3-yl)methyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl)carbamate	779

[000182] Compounds of the Disclosure inhibit menin and are useful in the treatment of a variety of diseases and conditions. In particular, Compounds of the Disclosure are useful in methods of treating a disease or condition wherein inhibition of menin provides a benefit, for example, cancers and proliferative diseases. Methods of the disclosure comprise administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need thereof. The present methods also encompass administering a second therapeutic agent to the individual in addition to the Compound of the Disclosure. The second therapeutic agent is selected from drugs known as useful in treating the disease or condition afflicting the individual in need thereof, e.g., a chemotherapeutic agent and/or radiation known as useful in treating a particular cancer.

[000183] Salts of the Compounds of the Disclosure can also be used in the methods disclosed herein. The present disclosure further includes all possible stereoisomers and geometric isomers of Compounds of the Disclosure to include both racemic compounds and optically active isomers. When a Compound of the Disclosure is desired as a single enantiomer, it can be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or use of a chiral auxiliary reagent, for example, see Z. Ma et al., *Tetrahedron: Asymmetry, 8(6)*, pages 883-888 (1997). Resolution of the final product, an intermediate, or a starting material can be achieved by any suitable method known in the art. Additionally, in situations where tautomers of the Compounds of the Disclosure are possible, the present disclosure is intended to include all tautomeric forms of the compounds.

[000184] In one embodiment, Compounds of the Disclosure are enantiomerically enriched, e.g., the enantiomeric excess or "ee" of the compound is about 5% or more as measured by chiral HPLC. In another embodiment, the ee is about 10%. In another embodiment, the ee is about 20%. In another embodiment, the ee is about 30%. In another embodiment, the ee is about 40%. In another embodiment, the ee is about 50%. In another embodiment, the ee is about 60%. In another embodiment, the ee is about 70%. In another embodiment, the ee is about 80%. In another embodiment, the ee is about 85%. In another embodiment, the ee is about 90%. In another embodiment, the ee is about 91%. In another embodiment, the ee is about 92%. In another embodiment, the ee is about 93%. In another embodiment, the ee is about 94%. In another embodiment, the ee is about 95%. In another embodiment, the ee is about 96%. In another embodiment, the ee is about 97%. In another embodiment, the ee is about 98%. In another embodiment, the ee is about 99%.

[000185] The present disclosure encompasses the preparation and use of salts of Compounds of the Disclosure. As used herein, the pharmaceutical "pharmaceutically acceptable salt" refers to salts or zwitterionic forms of Compounds of the Disclosure. Salts of Compounds of the Disclosure can be prepared during the final isolation and purification of the compounds or separately by reacting the compound with an acid having a suitable cation. The pharmaceutically acceptable salts of Compounds of the

Disclosure can be acid addition salts formed with pharmaceutically acceptable acids. Examples of acids which can be employed to form pharmaceutically acceptable salts include inorganic acids such as nitric, boric, hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Nonlimiting examples of salts of compounds of the disclosure include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphosphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, paratoluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulfonate, and p-toluenesulfonate salts. In addition, available amino groups present in the compounds of the disclosure can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. In light of the foregoing, any reference Compounds of the Disclosure appearing herein is intended to include compounds of Compounds of the Disclosure as well as pharmaceutically acceptable salts thereof.

[000186] The present disclosure provides Compounds of the Disclosure as menin inhibitors for the treatment of diseases and conditions wherein inhibition of menin has a beneficial effect. Compounds of the Disclosure typically have a binding affinity (IC_{50}) to menin of less than 100 μM, e.g., less than 50 μM, less than 25 μM, and less than 5 μM, less than about 1 μM, less than about 0.5 μM, less than about 0.1 μM, less than about 0.05 μM, or less than about 0.01 μM. In one embodiment, the present disclosure relates to a method of treating an individual suffering from a disease or condition wherein inhibition of menin provides a benefit comprising administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need thereof.

[000187] Diseases and conditions mediated by menin can be treated by administering Compounds of the Disclosure because these compounds are inhibitors of menin. The present disclosure is thus directed generally to a method for treating a condition or disorder responsive to inhibition of menin, in an animal, e.g., a human, suffering from, or at risk of suffering from, the condition or disorder, the method comprising administering to the animal an effective amount of one or more Compounds of the Disclosure.

[000188] The present disclosure is further directed to a method of inhibiting menin in an animal in need thereof, said method comprising administering to the animal an effective amount of at least one Compound of the Disclosure.

[000189] The methods of the present disclosure can be accomplished by administering a Compound of the Disclosure as the neat compound or as a pharmaceutical composition. Administration of a pharmaceutical composition, or neat compound of a Compound of the Disclosure, can be performed during or after the onset of the disease or condition of interest. Typically, the pharmaceutical compositions are sterile, and contain no toxic, carcinogenic, or mutagenic compounds that would cause an adverse reaction when administered. Further provided are kits comprising a Compound of the Disclosure and, optionally, a second therapeutic agent, packaged separately or together, and an insert having instructions for using these active agents.

[000190] In one embodiment, a Compound of the Disclosure is administered in conjunction with a second therapeutic agent useful in the treatment of a disease or condition wherein inhibition of menin provides a benefit. The second therapeutic agent is different from the Compound of the Disclosure. A Compound of the Disclosure and the second therapeutic agent can be administered simultaneously or sequentially to achieve the desired effect. In addition, the Compound of the Disclosure and second therapeutic agent can be administered from a single composition or two separate compositions.

[000191] The second therapeutic agent is administered in an amount to provide its desired therapeutic effect. The effective dosage range for each second therapeutic agent is known in the art, and the second therapeutic agent is administered to an individual in need thereof within such established ranges.

[000192] A Compound of the Disclosure and the second therapeutic agent can be administered together as a single-unit dose or separately as multi-unit doses, wherein the Compound of the Disclosure is administered before the second therapeutic agent or vice versa. One or more doses of the Compound of the Disclosure and/or one or more dose of the second therapeutic agent can be administered. The Compound of the Disclosure therefore can be used in conjunction with one or more second therapeutic agents, for example, but not limited to, anticancer agents.

[000193] Diseases and conditions treatable by the methods of the present disclosure include, but are not limited to, cancer and other proliferative disorders, inflammatory diseases, sepsis, autoimmune disease, and viral infection. In one embodiment, a human patient is treated with a Compound of the Disclosure, or a pharmaceutical composition comprising a Compound of the Disclosure, wherein the compound is administered in an amount sufficient to inhibit menin activity in the patient. In another embodiment, the human patient is a human adult over 18 years old in need of treatment of a disease. In another embodiment, the human patient is a human child no more than 18 years old in need of treatment of a disease.

[000194] In another aspect, the present disclosure provides a method of treating cancer in a subject comprising administering a therapeutically effective amount of a Compound of the Disclosure. While not being limited to a specific mechanism, in some embodiments, Compounds of the Disclosure treat cancer by inhibiting menin. Examples of treatable cancers include, but are not limited to, any one or more of the cancers of Table 2.

[000195] Table 2

adrenal cancer	lymphoepithelioma
acinic cell carcinoma	lymphoma
acoustic neuroma	acute lymphocytic leukemia
acral lentigious melanoma	acute myelogeous leukemia
acrospiroma	chronic lymphocytic leukemia
acute eosinophilic leukemia	liver cancer
acute erythroid leukemia	small cell lung cancer
acute lymphoblastic leukemia	non-small cell lung cancer
acute megakaryoblastic leukemia	MALT lymphoma
acute monocytic leukemia	malignant fibrous histiocytoma
acute promyelocytic leukemia	malignant peripheral nerve sheath tumor
adenocarcinoma	malignant triton tumor
adenoid cystic carcinoma	mantle cell lymphoma
adenoma	marginal zone B-cell lymphoma
adenomatoid odontogenic tumor	mast cell leukemia
adenosquamous carcinoma	mediastinal germ cell tumor
adipose tissue neoplasm	medullary carcinoma of the breast
adrenocortical carcinoma	medullary thyroid cancer,
adult T-cell leukemia/lymphoma	medulloblastoma

aggressive NK-cell leukemia	melanoma,
AIDS-related lymphoma	meningioma,
alveolar rhabdomyosarcoma	merkel cell cancer
alveolar soft part sarcoma	mesothelioma
ameloblastic fibroma	metastatic urothelial carcinoma
anaplastic large cell lymphoma	mixed Mullerian tumor
anaplastic thyroid cancer	mucinous tumor
angioimmunoblastic T-cell lymphoma,	multiple myeloma
angiomyolipoma	muscle tissue neoplasm
angiosarcoma	mycosis fungoides
astrocytoma	myxoid liposarcoma
atypical teratoid rhabdoid tumor	myxoma
B-cell chronic lymphocytic leukemia	myxosarcoma
B-cell prolymphocytic leukemia	nasopharyngeal carcinoma
B-cell lymphoma	neurinoma
basal cell carcinoma	neuroblastoma
biliary tract cancer	neurofibroma
bladder cancer	neuroma
blastoma	nodular melanoma
bone cancer	ocular cancer
Brenner tumor	oligoastrocytoma
Brown tumor	oligodendroglioma
Burkitt's lymphoma	oncocytoma
breast cancer	optic nerve sheath meningioma
brain cancer	optic nerve tumor
carcinoma	oral cancer
carcinoma in situ	osteosarcoma
carcinosarcoma	ovarian cancer
cartilage tumor	Pancoast tumor
cementoma	papillary thyroid cancer
myeloid sarcoma	paraganglioma
chondroma	pinealoblastoma
chordoma	pineocytoma
choriocarcinoma	pituicytoma
choroid plexus papilloma	pituitary adenoma
clear-cell sarcoma of the kidney	pituitary tumor
craniopharyngioma	plasmacytoma
cutaneous T-cell lymphoma	polyembryoma
cervical cancer	precursor T-lymphoblastic lymphoma
colorectal cancer	primary central nervous system lymphoma
Degos disease	primary effusion lymphoma
desmoplastic small round cell tumor	preimary peritoneal cancer
diffuse large B-cell lymphoma	prostate cancer
dysembryoplastic neuroepithelial tumor	pancreatic cancer

dysgerminoma	pharyngeal cancer
embryonal carcinoma	pseudomyxoma periotonei
endocrine gland neoplasm	renal cell carcinoma
endodermal sinus tumor	renal medullary carcinoma
enteropathy-associated T-cell lymphoma	retinoblastoma
esophageal cancer	rhabdomyoma
fetus in fetu	rhabdomyosarcoma
fibroma	Richter's transformation
fibrosarcoma	rectal cancer
follicular lymphoma	sarcoma
follicular thyroid cancer	Schwannomatosis
ganglioneuroma	seminoma
gastrointestinal cancer	Sertoli cell tumor
germ cell tumor	sex cord-gonadal stromal tumor
gestational choriocarcinoma	signet ring cell carcinoma
giant cell fibroblastoma	skin cancer
giant cell tumor of the bone	small blue round cell tumors
glial tumor	small cell carcinoma
glioblastoma multiforme	soft tissue sarcoma
glioma	somatostatinoma
gliomatosis cerebri	soot wart
glucagonoma	spinal tumor
gonadoblastoma	splenic marginal zone lymphoma
granulosa cell tumor	squamous cell carcinoma
gynandroblastoma	synovial sarcoma
gallbladder cancer	Sezary's disease
gastric cancer	small intestine cancer
hairy cell leukemia	squamous carcinoma
hemangioblastoma	stomach cancer
head and neck cancer	T-cell lymphoma
hemangiopericytoma	testicular cancer
hematological malignancy	thecoma
hepatoblastoma	thyroid cancer
hepatosplenic T-cell lymphoma	transitional cell carcinoma
Hodgkin's lymphoma	throat cancer
non-Hodgkin's lymphoma	urachal cancer
invasive lobular carcinoma	urogenital cancer
intestinal cancer	urothelial carcinoma
kidney cancer	uveal melanoma
laryngeal cancer	uterine cancer
lentigo maligna	verrucous carcinoma
lethal midline carcinoma	visual pathway glioma
leukemia	vulvar cancer
leydig cell tumor	vaginal cancer
liposarcoma	Waldenstrom's macroglobulinemia
lung cancer	Warthin's tumor

lymphangioma	Wilms' tumor
lymphangiosarcoma	Ewing’s sarcoma
endometrial cancer	myelodysplastic syndrome
myelodysplastic/ myeloproliferative neoplasms	

[000196] In another embodiment, the cancer is a solid tumor. In another embodiment, the cancer is a hematological cancer. Exemplary hematological cancers include, but are not limited to, the cancers listed in Table 3. In another embodiment, the hematological cancer is acute lymphocytic leukemia, chronic lymphocytic leukemia (including B-cell chronic lymphocytic leukemia), or acute myeloid leukemia. In another embodiment, the hematological cancer is myelodysplastic syndrome.

[000197] Table 3

acute lymphocytic leukemia (ALL)	acute eosinophilic leukemia
acute myeloid leukemia (AML)	acute erythroid leukemia
chronic lymphocytic leukemia (CLL)	acute lymphoblastic leukemia
small lymphocytic lymphoma (SLL)	acute megakaryoblastic leukemia
multiple myeloma (MM)	acute monocytic leukemia
Hodgkin’s lymphoma (HL)	acute promyelocytic leukemia
non-Hodgkin's lymphoma (NHL)	acute myelogeous leukemia
mantle cell lymphoma (MCL)	B-cell prolymphocytic leukemia
marginal zone B-cell lymphoma	B-cell lymphoma
splenic marginal zone lymphoma	MALT lymphoma
follicular lymphoma (FL)	precursor T-lymphoblastic lymphoma
Waldenstrom's macroglobulinemia (WM)	T-cell lymphoma
diffuse large B-cell lymphoma (DLBCL)	mast cell leukemia
marginal zone lymphoma (MZL)	adult T cell leukemia/lymphoma
hairy cell leukemia (HCL)	aggressive NK-cell leukemia
Burkitt's lymphoma (BL)	angioimmunoblastic T-cell lymphoma
Richter's transformation	myelodysplastic syndromes

[000198] In another embodiment, the cancer is a leukemia, for example a leukemia selected from acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia (MLL). In another embodiment, the leukemia is NPM1c mutant acute myelogenous leukemia. In another embodiment, the leukemia is MLL-r acute myelogenous leukemia. In another embodiment, the leukemia is MLL-r acute lymphocytic leukemia. In another embodiment the cancer is NUT-midline carcinoma. In another embodiment the cancer is multiple myeloma. In another embodiment the cancer is a lung cancer such as small cell lung cancer (SCLC). In another embodiment the cancer is a neuroblastoma. In another embodiment the cancer is Burkitt's lymphoma. In another embodiment the cancer is cervical cancer. In another embodiment the cancer is esophageal cancer. In another embodiment the cancer is ovarian cancer. In another embodiment the cancer is colorectal cancer. In another embodiment, the cancer is prostate cancer. In another embodiment, the cancer is breast cancer. In another embodiment, the cancer is Ewing’s sarcoma.

[000199] In another embodiment, the present disclosure provides a method of treating a benign proliferative disorder, such as, but are not limited to, benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, meningioma, multiple endocrine neoplasia, nasal polyps, pituitary tumors, prolactinoma, pseudotumor cerebri, seborrheic keratoses, stomach polyps, thyroid nodules, cystic neoplasms of the pancreas, hemangiomas, vocal cord nodules, polyps, and cysts, Castleman disease, chronic pilonidal disease, dermatofibroma, pilar cyst, pyogenic granuloma, and juvenile polyposis syndrome.

[000200] Compounds of the Disclosure can also treat infectious and noninfectious inflammatory events and autoimmune and other inflammatory diseases by administration of an effective amount of a present compound to a mammal, in particular a human in need of such treatment. Examples of autoimmune and inflammatory diseases, disorders, and syndromes treated using the compounds and methods described herein include inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholocystitus, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, Type I diabetes, septic shock, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituatarism, Guillain-Barre syndrome, Behcet's disease, scleracierma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[000201] In another embodiment, the present disclosure provides a method of treating systemic inflammatory response syndromes, such as LPS-induced endotoxic shock and/or bacteria-induced sepsis by administration of an effective amount of a Compound of the Disclosure to a mammal, in particular a human in need of such treatment.

[000202] In another embodiment, the present disclosure provides a method for treating viral infections and diseases. Examples of viral infections and diseases treated using the compounds and methods described herein include episome-based DNA viruses including, but not limited to, human papillomavirus, Herpesvirus, Epstein-Barr virus, human immunodeficiency virus, hepatis B virus, and hepatitis C virus.

[000203] In another embodiment, the present disclosure provides therapeutic method of modulating protein methylation, gene expression, cell proliferation, cell differentiation and/or apoptosis *in vivo* in diseases mentioned above, in particular cancer, inflammatory disease, and/or viral disease is provided by administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need of such therapy.

[000204] In another embodiment, the present disclosure provides a method of regulating endogenous or heterologous promoter activity by contacting a cell with a Compound of the Disclosure.

[000205] In methods of the present disclosure, a therapeutically effective amount of a Compound of the Disclosure, typically formulated in accordance with pharmaceutical practice, is administered to a human being in need thereof. Whether such a treatment is indicated depends on the individual case and is subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

[000206] A Compound of the Disclosure can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, intracisternal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site) administration. Parenteral administration can be accomplished using a needle and syringe or using a high pressure technique.

[000207] Pharmaceutical compositions include those wherein a Compound of the Disclosure is administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by an individual physician in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of a Compound of the Disclosure that is sufficient to maintain therapeutic effects.

[000208] Toxicity and therapeutic efficacy of the Compounds of the Disclosure can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) of a compound, which defines as the highest dose that causes no toxicity in animals. The dose ratio between the maximum tolerated dose and therapeutic effects (e.g. inhibiting of tumor growth) is the therapeutic index. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[000209] A therapeutically effective amount of a Compound of the Disclosure required for use in therapy varies with the nature of the condition being treated, the length of time that activity is desired, and the age and the condition of the patient, and ultimately is determined by the attendant physician. Dosage amounts and intervals can be adjusted individually to provide plasma levels of the menin inhibitor that are sufficient to maintain the desired therapeutic effects. The desired dose conveniently can be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four or more subdoses per day. In one embodiment, a Compound of the Disclosure is administered once daily (QD). In another embodiment, a Compound of the Disclosure is administered twice daily (BID). Multiple doses often are desired, or required. For example, a Compound of the Disclosure can be administered at a frequency of: four doses delivered as one dose per day at four-day intervals (q4d x 4); four doses delivered as one dose per day at three-day intervals (q3d x 4); one dose delivered per day at five-day intervals (qd x 5); one dose per week for three weeks (qwk3); five daily doses, with two days rest, and another five daily doses (5/2/5); or, any dose regimen determined to be appropriate for the circumstance.

[000210] A Compound of the Disclosure used in a method of the present disclosure can be administered in an amount of about 0.005 to about 500 milligrams per dose, about 0.05 to about 250 milligrams per dose, or about 0.5 to about 100 milligrams per dose. For example, a Compound of the Disclosure can be administered, per dose, in an amount of about 0.005, about 0.05, about 0.5, about 5, about 10, about 20, about 30, about 40, about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, or about 500 milligrams, including all doses between 0.005 and 500 milligrams.

[000211] The dosage of a composition containing a Compound of the Disclosure, or a composition containing the same, can be from about 1 ng/kg to about 200 mg/kg, about 1 µg/kg to about 100 mg/kg, or about 1 mg/kg to about 50 mg/kg. The dosage of a composition can be at any dosage including, but not limited to, about 1 µg/kg. The dosage of a composition may be at any dosage including, but not limited to, about 1 µg/kg, about 10 µg/kg, about 25 µg/kg, about 50 µg/kg, about 75 µg/kg, about 100 µg/kg, about 125 µg/kg, about 150 µg/kg, about 175 µg/kg, about 200 µg/kg, about 225 µg/kg, about 250 µg/kg, about 275 µg/kg, about 300 µg/kg, about 325 µg/kg, about 350 µg/kg, about 375 µg/kg, about 400 µg/kg, about 425 µg/kg, about 450 µg/kg, about 475 µg/kg, about 500 µg/kg, about 525 µg/kg, about 550 µg/kg, about 575 µg/kg, about 600 µg/kg, about 625 µg/kg, about 650 µg/kg, about 675 µg/kg, about 700 µg/kg, about 725 µg/kg, about 750 µg/kg, about 775 µg/kg, about 800 µg/kg, about 825 µg/kg, about 850 µg/kg, about 875 µg/kg, about 900 µg/kg, about 925 µg/kg, about 950 µg/kg, about 975 µg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg, about 90 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, or more. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this disclosure. In practice, the physician determines the actual dosing regimen that is most suitable for an individual patient, which can vary with the age, weight, and response of the particular patient.

[000212] As stated above, a Compound of the Disclosure can be administered in combination with a second therapeutically active agent. In some embodiments, the second therapeutic agent is an epigenetic drug. As used herein, the term "epigenetic drug" refers to a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, but are not limited to, vorinostat.

[000213] In another embodiment, chemotherapeutic agents or other anti-proliferative agents can be combined with Compound of the Disclosure to treat proliferative diseases and cancer. Examples of therapies and anticancer agents that can be used in combination with Compounds of the Disclosure include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, a biologic response modifier (e.g., an interferon, an interleukin, tumor necrosis factor (TNF), hyperthermia and cryotherapy, an agent to attenuate any adverse effect (e.g., an antiemetic), and any other approved chemotherapeutic drug.

[000214] In another embodiment, a Compound of the Disclosure and pharmaceutical compositions described herein can be used in combination with one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, antiproliferative agents, glycolysis inhibitors, autophagy inhibitors, demethylating agents, DOT1L inhibitors, IDH1 inhibitors, IDH2 inhibitors, IDH1/IDH2 dual inhibitors, LSD1 inhibitors, XPO1 inhibitors, or dastinib. In another embodiment, the Compound of the Disclosure can be used in combination a second therapeutic agent selected from a demethylating agent, DOT1L inhibitor, IDH1 inhibitor, IDH2 inhibitor, IDH1/IDH2 dual inhibitor, an LSD1 inhibitor, an XPO1 inhibitors, and dastinib.

[000215] Demethylating agents include substances that inhibit or interfere with DNA methylation. In some examples, a demethylating agent is a DNA methyltransferase inhibitor. Exemplary nonlimiting demethylating agents include 5-azacytidine, decitabine, methotrexate, edatrexate, 2’-deoxy-5-azacytidine, 6-

thioguanine, 5-fluoro-2'-deoxycytidine, pseudoisocytidine, 5,6-dihydro-5-azacytidine, fazarabine, zebularine, 2'-deoxy-5,6-dihydro-5-azacytidine, 4'-thio-2'-deoxycytidine, 5-aza-4'-thio-2'-deoxycytidine, RX-3117, SGI-110, NPEOC-DAC, CP-4200, and 2'3'5'triacetyl-5-azacytidine.

[000216] Exemplary nonlimiting examples of inhibitors of the histone methyltransferase DOTlL include EPZ-5676, SGC-0946, and EPZ004777.

[000217] Exemplary nonlimiting IDH1 inhibitors include tibsovo (ivosidnib), AG-881, AG-120, FT-2102 (olutasidenib), BAY1436032, IDH-305, and ZX-06. Exemplary nonlimiting examples of IDH2 inhibitors include idhifa (enasidenib; AG-221), AG-881, AGl-6780, SH1573, and TQ05310. Exemplary nonlimiting IDH1/IDH2 dual inhibitors include HMPL-306.

[000218] Exemplary nonlimiting examples of a LSD1 inhibitor include ORY-1001, OG-L002, SP2509, 4SC-202, GSK2879552, T-3775440, and RN-1.

[000219] Exemplary nonlimiting examples of an XPO1 inhibitor include selinexor (KPT-330), KPT-8602, KPT25 l, and SL-801.

[000220] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrixmetalloproteinase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a Compound of the Disclosure and pharmaceutical compositions described herein. Exemplary nonlimiting anti-angiogenesis agents include rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Exemplary nonlimiting COX-II inhibitors include CELEBREXTM (alecoxib), valdecoxib, and rofecoxib. Exemplary nonlimiting matrix metalloproteinase inhibitors include those described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No.

PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. In certain embodiments, the MMP-2 and MMP-9 inhibitors have little or no activity inhibiting MMP-1. In certain embodiments, the MMP-2 and MMP-9 inhibitors selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (e.g., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-11, MMP-12, andMMP-13). Exemplary nonlimiting MMP inhibitors include AG-3340, RO 32-3555, and RS 13-0830.

[000221] Exemplary nonlimiting autophagy inhibitors include chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), may also be used.

[000222] Examples of antiproliferative compounds include, but are not limited to, an aromatase inhibitor; an anti-estrogen; an anti-androgen; a gonadorelin agonist; a topoisomerase I inhibitor; a topoisomerase II inhibitor; a microtubule active agent; an alkylating agent; a retinoid, a carontenoid, or a tocopherol; a cyclooxygenase inhibitor; an MMP inhibitor; an mTOR inhibitor; an antimetabolite; a platin compound; a methionine aminopeptidase inhibitor; a bisphosphonate; an antiproliferative antibody; a heparanase inhibitor; an inhibitor of Ras oncogenic isoforms; a telomerase inhibitor; a proteasome inhibitor; a compound used in the treatment of hematologic malignancies; a Flt-3 inhibitor; an Hsp90 inhibitor; a kinesin spindle protein inhibitor; a MEK inhibitor; an antitumor antibiotic; a nitrosourea; a mitotic inhibitor, a compound targeting/decreasing protein or lipid kinase activity, a compound targeting/decreasing protein or lipid phosphatase activity, or any further anti-angiogenic compound.

[000223] Nonlimiting exemplary aromatase inhibitors include, but are not limited to, steroids, such as atamestane, exemestane, and formestane, and non-steroids, such as aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole, and letrozole.

[000224] Nonlimiting anti-estrogens include, but are not limited to, tamoxifen, fulvestrant, raloxifene, and raloxifene hydrochloride. Anti-androgens include, but are not limited to, bicalutamide. Gonadorelin agonists include, but are not limited to, abarelix, goserelin, and goserelin acetate.

[000225] Exemplary topoisomerase I inhibitors include, but are not limited to, topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin, and the macromolecular camptothecin conjugate PNU-166148. Topoisomerase II inhibitors include, but are not limited to, anthracyclines, such as doxorubicin, daunorubicin, epirubicin, idarubicin, and nemorubicin; anthraquinones, such as mitoxantrone and losoxantrone; and podophillotoxines, such as etoposide and teniposide.

[000226] Microtubule active agents include microtubule stabilizing, microtubule destabilizing compounds, and microtubulin polymerization inhibitors including, but not limited to, taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine, vinblastine sulfate, vincristine, and vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof.

[000227] Exemplary nonlimiting alkylating agents include cyclophosphamide, ifosfamide, melphalan, and nitrosoureas, such as carmustine and lomustine.

[000228] Exemplary nonlimiting cyclooxygenase inhibitors include Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib, rofecoxib, etoricoxib, valdecoxib, or a 5-alkyl-2-arylaminophenylacetic acid, such as lumiracoxib.

[000229] Exemplary nonlimiting matrix metalloproteinase inhibitors ("MMP inhibitors") include collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, batimastat, marimastat, prinomastat, metastat, BMS-279251, BAY 12-9566, TAA211, MMI270B, and AAJ996.

[000230] Exemplary nonlimiting mTOR inhibitors include compounds that inhibit the mammalian target of rapamycin (mTOR) and possess antiproliferative activity such as sirolimus, everolimus, CCI-779, and ABT578.

[000231] Exemplary nonlimiting antimetabolites include 5-fluorouracil (5-FU), capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists, such as pemetrexed.

[000232] Exemplary nonlimiting platin compounds include carboplatin, cis-platin, cisplatinum, and oxaliplatin.

[000233] Exemplary nonlimiting methionine aminopeptidase inhibitors include bengamide or a derivative thereof and PPI-2458.

[000234] Exemplary nonlimiting bisphosphonates include etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, and zoledronic acid.

[000235] Exemplary nonlimiting antiproliferative antibodies include trastuzumab, trastuzumab-DM1, cetuximab, bevacizumab, rituximab, PR064553, and 2C4. The term “antibody" is meant to include intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity.

[000236] Exemplary nonlimiting heparanase inhibitors include compounds that target, decrease, or inhibit heparin sulfate degradation, such as PI-88 and OGT2115.

[000237] The term "an inhibitor of Ras oncogenic isoforms," such as H-Ras, K-Ras, or N-Ras, as used herein refers to a compound which targets, decreases, or inhibits the oncogenic activity of Ras, for example, a farnesyl transferase inhibitor, such as L-744832, DK8G557, tipifarnib, and lonafarnib.

[000238] Exemplary nonlimiting telomerase inhibitors include compounds that target, decrease, or inhibit the activity of telomerase, such as compounds that inhibit the telomerase receptor, such as telomestatin.

[000239] Exemplary nonlimiting proteasome inhibitors include compounds that target, decrease, or inhibit the activity of the proteasome including, but not limited to, bortezomid.

[000240] The phrase "compounds used in the treatment of hematologic malignancies" as used herein includes FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, I-β-D-arabinofuransylcytosine (ara-c), and bisulfan; ALK inhibitors, which are compounds that target, decrease, or inhibit anaplastic lymphoma kinase; and BH3 mimetics, which are compounds that target, decrease, or inhibit antiapoptotic proteins from the BCL-2 family.

[000241] Exemplary nonlimiting Flt-3 inhibitors include gilteritinib, PKC412, midostaurin, a staurosporine derivative, SU11248, and MLN518.

[000242] Exemplary nonlimiting HSP90 inhibitors include compounds targeting, decreasing, or inhibiting the intrinsic ATPase activity of HSP90; or degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins, or antibodies that inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[000243] Exemplary nonlimiting BH3 mimetics include venetoclax.

[000244] The phrase "a compound targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or any further anti-angiogenic compound" as used herein includes a protein tyrosine kinase and/or serine and/or threonine kinase inhibitor or lipid kinase inhibitor, such as a) a compound targeting, decreasing, or inhibiting the activity of the platelet- derived growth factor-receptors (PDGFR), such as a compound that targets, decreases, or inhibits the activity of PDGFR, such as an N-phenyl-2-pyrimidine-amine derivatives, such as imatinib, SUlOl, SU6668, and GFB-111; b) a compound targeting, decreasing, or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) a compound targeting, decreasing, or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as a compound that targets, decreases, or inhibits the activity of IGF-IR; d) a compound targeting, decreasing, or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) a compound targeting, decreasing, or inhibiting the activity of the Axl receptor tyrosine kinase family; f) a compound targeting, decreasing, or inhibiting the activity of the Ret receptor tyrosine kinase; g) a compound targeting, decreasing, or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) a compound targeting, decreasing, or inhibiting the activity of the c-Kit receptor tyrosine kinases, such as imatinib; i) a compound targeting, decreasing, or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. Bcr-Abl kinase) and mutants, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib; PD180970; AG957; NSC 680410; PD173955; or dasatinib; j) a compound targeting, decreasing, or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK), such as a staurosporine derivative disclosed in U.S. Patent No. 5,093,330, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, bryostatin 1, perifosine; ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; a isochinoline compound; a farnesyl transferase inhibitor; PD184352 or QAN697, or AT7519; k) a compound targeting, decreasing or inhibiting the activity of a protein-tyrosine kinase, such as imatinib mesylate or a tyrphostin, such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); l) a compound targeting, decreasing, or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as CP 358774, ZD 1839, ZM 105180; trastuzumab, cetuximab, gefitinib, erlotinib, OSI-774, Cl-1033, EKB-569, GW-2016, antibodies E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; and m) a compound targeting, decreasing, or inhibiting the activity of the c-Met receptor.

[000245] Exemplary compounds that target, decrease, or inhibit the activity of a protein or lipid phosphatase include inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[000246] Further anti-angiogenic compounds include compounds having another mechanism for their activity unrelated to protein or lipid kinase inhibition, e.g., thalidomide and TNP-470.

[000247] Additional, nonlimiting, exemplary chemotherapeutic compounds, one or more of which may be used in combination with a Compound of the Disclosure, include: daunorubicin, adriamycin, Ara-C, VP-16, teniposide, mitoxantrone, idarubicin, carboplatinum, PKC412, 6-mercaptopurine (6-MP), fludarabine phosphate, octreotide, SOM230, FTY720, 6-thioguanine, cladribine, 6-mercaptopurine, pentostatin, hydroxyurea, 2-hydroxy-lH-isoindole-l,3-dione derivatives, l-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate, angiostatin, endostatin, anthranilic acid amides, ZD4190, ZD6474, SU5416, SU6668, bevacizumab, rhuMAb, rhuFab, macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, RPI 4610, bevacizumab, porfimer sodium, anecortave, triamcinolone, hydrocortisone, 11-a-epihydrocotisol, cortex olone, 17a-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone, dexamethasone, fluocinolone, a plant alkaloid, a hormonal compound and/or antagonist, a biological response modifier, such as a lymphokine or interferon, an antisense oligonucleotide or oligonucleotide derivative, shRNA, and siRNA.

[000248] Other examples of second therapeutic agents, one or more of which a Compound of the Disclosure also can be combined, include, but are not limited to: a treatment for Alzheimer's Disease, such as donepezil and rivastigmine; a treatment for Parkinson's Disease, such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; an agent for treating multiple sclerosis (MS) such as beta interferon (e.g., AVONEX® and REBIF®), glatiramer acetate, and mitoxantrone; a treatment for asthma, such as albuterol and montelukast; an agent for treating schizophrenia, such as zyprexa, risperdal, seroquel, and haloperidol; an anti-inflammatory agent, such as a corticosteroid, a TNF blocker, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; an immunomodulatory agent, including immunosuppressive agents, such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, an interferon, a corticosteroid, cyclophosphamide, azathioprine, and sulfasalazine; a neurotrophic factor, such as an acetylcholinesterase inhibitor, an MAO inhibitor, an interferon, an anti-convulsant, an ion channel blocker, riluzole, or an anti-Parkinson's agent; an agent for treating cardiovascular disease, such as a beta-blocker, an ACE inhibitor, a diuretic, a nitrate, a calcium channel blocker, or a statin; an agent for treating liver disease, such as a corticosteroid, cholestyramine, an interferon, and an anti-viral agent; an agent for treating blood disorders, such as a corticosteroid, an anti-leukemic agent, or a growth factor; or an agent for treating immunodeficiency disorders, such as gamma globulin.

[000249] The above-mentioned second therapeutically active agents, one or more of which can be used in combination with a Compound of the Disclosure, are prepared and administered as described in the art.

[000250] Compounds of the Disclosure typically are administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present disclosure are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of Compound of the Disclosure.

[000251] These pharmaceutical compositions can be manufactured, for example, by conventional mixing, dissolving, granulating, dragee-making, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of the Compound of the Disclosure is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition additionally can contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 0.01% to about 95%, and preferably from about 1% to about 50%, of a Compound of the Disclosure. When administered in liquid form, a liquid carrier, such as water, petroleum, or oils of animal or plant origin, can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.1% to about 90%, and preferably about 1% to about 50%, by weight, of a Compound of the Disclosure.

[000252] When a therapeutically effective amount of a Compound of the Disclosure is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, an isotonic vehicle.

[000253] Compounds of the Disclosure can be readily combined with pharmaceutically acceptable carriers well-known in the art. Standard pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995. Such carriers enable the active agents to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding the Compound of the Disclosure to a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

[000254] Compound of the Disclosure can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[000255] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active agent in water-soluble form. Additionally, suspensions of a Compound of the Disclosure can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[000256] Compounds of the Disclosure also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the Compound of the Disclosure also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the Compound of the Disclosure can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins.

[000257] In particular, the Compounds of the Disclosure can be administered orally, buccally, or sublingually in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. Compound of the Disclosure also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the Compound of the Disclosure are typically used in the form of a sterile aqueous solution which can contain other substances, for example, salts or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

[000258] The disclosure provides the following particular embodiments in connection with treating a disease in a subject.

[000259] Embodiment 1. A method of treating a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount a Compound of the Disclosure, wherein the subject has cancer.

[000260] Embodiment 2. The method of Embodiment 1, wherein the cancer is any one or more of the cancers of Table 2.

[000261] Embodiment 3. The method of Embodiment 2, wherein the cancer is a hematological cancer.

[000262] Embodiment 4. The method of Embodiment 3, wherein the hematological cancer is any one or more of the cancers of Table 3.

[000263] Embodiment 5. The method of any one of Embodiments 1-4 further comprising administering a therapeutically effective amount of a second therapeutic agent useful in the treatment of cancer.

[000264] Embodiment 6. A pharmaceutical composition comprising a Compound of the Disclosure and a pharmaceutically acceptable carrier for use in treating cancer.

[000265] Embodiment 7. The pharmaceutical composition of Embodiment 6, wherein the cancer is any one or more of the cancers of Table 2.

[000266] Embodiment 8. The pharmaceutical composition of Embodiment 7, wherein the cancer is a hematological cancer.

[000267] Embodiment 9. The pharmaceutical composition of Embodiment 8, wherein the hematological cancer is any one or more of the cancers of Table 3.

[000268] Embodiment 10. A Compound of the Disclosure for use in treatment of cancer.

[000269] Embodiment 11. The compound for use of Embodiment 10, wherein the cancer is any one or more of the cancers of Table 2.

[000270] Embodiment 12. The compound for use of Embodiment 11, wherein the cancer is a hematological cancer.

[000271] Embodiment 13. The compound for use of Embodiment 12, wherein the hematological cancer is any one or more of the cancers of Table 3.

[000272] Embodiment 14. Use of a Compound of the Disclosure for the manufacture of a medicament for treatment of cancer.

[000273] Embodiment 15. The use of Embodiment 14, wherein the cancer is any one or more of the cancers of Table 2.

[000274] Embodiment 16. The use of Embodiment 15, wherein the cancer is a hematological cancer.

[000275] Embodiment 17. The use of Embodiment 16, wherein the hematological cancer is any one or more of the cancers of Table 3.

[000276] In another embodiment, the present disclosure provides kits which comprise a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a manner that facilitates their use to practice methods of the present disclosure. In one embodiment, the kit includes a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of the compound or composition to practice the method of the disclosure. In one embodiment, the compound or composition is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

[000277] To facilitate an understanding of the present disclosure, a number of terms and phrases are defined below.

[000278] In the present disclosure, the term "halo" as used by itself or as part of another group refers to -Cl, -F, -Br, or -I.

[000279] In the present disclosure, the term "nitro" as used by itself or as part of another group refers to $-NO_2$.

[000280] In the present disclosure, the term "cyano" as used by itself or as part of another group refers to -CN.

[000281] In the present disclosure, the term "hydroxy" as used by itself or as part of another group refers to -OH.

[000282] In the present disclosure, the term "alkyl" as used by itself or as part of another group refers to unsubstituted straight- or branched-chain aliphatic hydrocarbons containing from one to twelve carbon atoms, i.e., C_{1-12} alkyl or C_1-C_{12} alkyl, or the number of carbon atoms designated, e.g., a C_1 alkyl such as methyl, a C_2 alkyl such as ethyl, a C_3 alkyl such as propyl or isopropyl, a C_{1-3} alkyl such as methyl, ethyl, propyl, or isopropyl, and so on. In one embodiment, the alkyl is a C_{1-10} alkyl. In another embodiment, the alkyl is a C_{1-6} alkyl. In another embodiment, the alkyl is a C_{1-4} alkyl. In another embodiment, the alkyl is a straight chain C_{1-10} alkyl. In another embodiment, the alkyl is a branched chain C_{3-10} alkyl. In another embodiment, the alkyl is a straight chain C_{1-6} alkyl. In another embodiment, the alkyl is a branched chain C_{3-6} alkyl. In another embodiment, the alkyl is a straight chain C_{1-4} alkyl. In another embodiment, the alkyl is a branched chain C_{3-4} alkyl. In another embodiment, the alkyl is a straight or branched chain C_{3-4} alkyl. Non-limiting exemplary C_{1-10} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, and decyl. Non-limiting exemplary C_{1-4} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, and *iso*-butyl.

[000283] In the present disclosure, the term "optionally substituted alkyl" as used by itself or as part of another group refers to an alkyl that is either unsubstituted or substituted with one, two, or three substituents independently selected from the group consisting of nitro, haloalkoxy, aryloxy, aralkyloxy, alkylthio, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, and alkylcarbonyloxy. In one embodiment, the optionally substituted alkyl is substituted with two substituents. In another embodiment, the optionally substituted alkyl is substituted with one substituent. In another embodiment, the optionally substituted alkyl is unsubstituted. Non-limiting exemplary substituted alkyl groups include $-CH_2CH_2NO_2$, $-CH_2SO_2CH_3$,

$CH_2CH_2SO_2CH_3$,-$CH_2CH_2CO_2H$, -CH_2SCH_3, -$CH_2CH_2SO_2CH_3$, -CH_2CH_2COPh, and -$CH_2OC(=O)CH_3$.

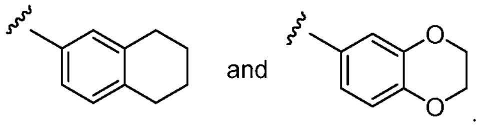
[000284] In the present disclosure, the term "cycloalkyl" as used by itself or as part of another group refers to unsubstituted saturated or partially unsaturated, e.g., containing one or two double bonds, cyclic aliphatic hydrocarbons containing one to three rings having from three to twelve carbon atoms, i.e., C_{3-12} cycloalkyl, or the number of carbons designated. In one embodiment, the cycloalkyl has two rings. In another embodiment, the cycloalkyl has one ring. In another embodiment, the cycloalkyl is saturated. In another embodiment, the cycloalkyl is unsaturated. In another embodiment, the cycloalkyl is a C_{3-8} cycloalkyl. In another embodiment, the cycloalkyl is a C_{3-6} cycloalkyl. The term "cycloalkyl" is meant to include groups wherein a ring -CH_2- is replaced with a -C(=O)-. Non-limiting exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, cyclopentenyl, and cyclopentanone.

[000285] In the present disclosure, the term "optionally substituted cycloalkyl" as used by itself or as part of another group refers to a cycloalkyl that is either unsubstituted or substituted with one, two, or three substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, (heterocyclo)alkyl, -OC(=O)-amino, -$N(R^{19a})C(=O)-R^{19b}$, and -$N(R^{20a})SO_2-R^{20b}$, wherein R^{19a} is selected from the group consisting of hydrogen and alkyl, R^{19b} is selected from the group consisting of amino, alkoxy, alkyl, and optionally substituted aryl, R^{20a} is selected from the group consisting of hydrogen and alkyl, and R^{20b} is selected from the group consisting of amino, alkyl, and optionally substituted aryl. The term optionally substituted cycloalkyl includes cycloalkyl groups having a fused optionally substituted aryl, e.g., phenyl, or fused optionally substituted heteroaryl, e.g., pyridyl. An optionally substituted cycloalkyl having a fused optionally substituted aryl or fused optionally substituted heteroaryl group may be attached to the remainder of the molecule at any available carbon atom on the cycloalkyl ring. In one embodiment, the optionally substituted cycloalkyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkyl is substituted with one substituent. In another embodiment, the optionally substituted cycloalkyl is unsubstituted.

[000286] In the present disclosure, the term "aryl" as used by itself or as part of another group refers to unsubstituted monocyclic or bicyclic aromatic ring systems having from six to fourteen carbon atoms, i.e., a C_{6-14} aryl. Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph"), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups. In one embodiment, the aryl group is phenyl or naphthyl.

[000287] In the present disclosure, the term "optionally substituted aryl" as used herein by itself or as part of another group refers to an aryl that is either unsubstituted or substituted with one to five substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, haloalkylsulfonyl cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heterocyclosulfonyl, carboxy, carboxyalkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxycarbonyl, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, and (heterocyclo)alkyl.

[000288] In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In another embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. In another embodiment, the optionally substituted phenyl has one substituent. In another embodiment, the optionally substituted phenyl is unsubstituted. Non-limiting exemplary substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-dimethoxyphenyl, 3,5-di-fluorophenyl 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, 3-chloro-4-fluorophenyl, 4-(pyridin-4-ylsulfonyl)phenyl The term optionally substituted aryl includes phenyl groups having a fused optionally substituted cycloalkyl or fused optionally substituted heterocyclo group. An optionally substituted phenyl having a fused optionally substituted cycloalkyl or fused optionally substituted heterocyclo group may be attached to the remainder of the molecule at any available carbon atom on the phenyl ring. Non-limiting examples include:



[000289] In the present disclosure, the term "alkenyl" as used by itself or as part of another group refers to an alkyl containing one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl has one carbon-to-carbon double bond. In another embodiment, the alkenyl is a C_{2-6} alkenyl. In another embodiment, the alkenyl is a C_{2-4} alkenyl. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

[000290] In the present disclosure, the term "optionally substituted alkenyl" as used herein by itself or as part of another group refers to an alkenyl that is either unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, heteroaryl, and optionally substituted heterocyclo.

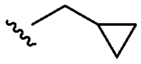
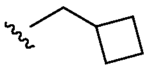
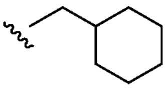
[000291] In the present disclosure, the term "alkynyl" as used by itself or as part of another group refers to an alkyl containing one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-to-carbon triple bond. In another embodiment, the alkynyl is a C_{2-6} alkynyl. In another embodiment, the alkynyl is a C_{2-4} alkynyl. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

[000292] In the present disclosure, the term "optionally substituted alkynyl" as used herein by itself or as part refers to an alkynyl that is either unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, and heterocyclo.

[000293] In the present disclosure, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl substituted by one or more fluorine, chlorine, bromine and/or iodine atoms. In one embodiment, the alkyl group is substituted by one, two, or three fluorine and/or chlorine atoms. In another embodiment, the haloalkyl group is a C_{1-4} haloalkyl group. Non-limiting exemplary haloalkyl groups include fluoromethyl, 2-fluoroethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

[000294] In the present disclosure, the term "hydroxyalkyl" as used by itself or as part of another group refers to an alkyl substituted with one, two, or three hydroxy groups. In one embodiment, the hydroxyalkyl is a monohydroxyalkyl, i.e., a hydroxyalkyl substituted with one hydroxy group. In another embodiment, the hydroxyalkyl is a dihydroxyalkyl, i.e., a hydroxyalkyl substituted with two hydroxy groups. Non-limiting exemplary hydroxyalkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, such as 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

[000295] In the present disclosure, the term "(cycloalkyl)alkyl," as used by itself or as part of another group refers to an alkyl substituted with an optionally substituted cycloalkyl. In one embodiment, the (cycloalkyl) alkyl, is a "(C_{3-6} cycloalkyl)C_{1-4} alkyl," i.e., a C_{1-4} alkyl substituted with an optionally substituted C_{3-6} cycloalkyl. Non-limiting exemplary (cycloalkyl) alkyl groups include:

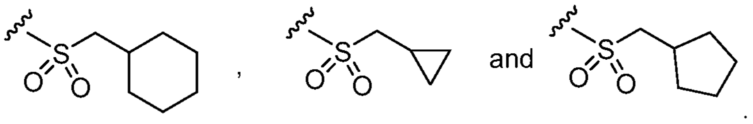
 ,  and  .

[000296] In the present disclosure, the term "alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., $-SO_2-$, substituted with an optionally substituted alkyl. In one embodiment, the alkyl is a C_{1-6} alkyl. In another embodiment, the alkyl is a C_{1-4} alkyl. A non-limiting exemplary alkylsulfonyl group is $-SO_2CH_3$.

[000297] In the present disclosure, the term "haloalkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., $-SO_2-$, substituted with a haloalkyl. A non-limiting exemplary alkylsulfonyl group is $-SO_2CF_3$.

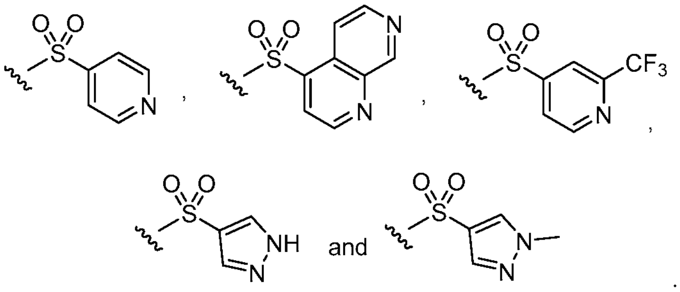
[000298] In the present disclosure, the term "cycloalkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., $-SO_2-$, substituted with an optionally substituted cycloalkyl. Non-limiting exemplary alkylsulfonyl group include $-SO_2$-cyclopropyl and $-SO_2$-cyclopenyl.

[000299] In the present disclosure, the term "(cycloalkyl)alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., $-SO_2-$, substituted with a (cycloalkyl)alkyl. Non-limiting exemplary (cycloalkyl)alkylsulfonyl groups include:

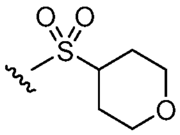


[000300] In the present disclosure, the term "arylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., $-SO_2-$, substituted with an optionally substituted aryl. A non-limiting exemplary arylsulfonyl group is $-SO_2Ph$.

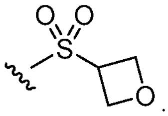
[000301] In the present disclosure, the term "heteroarylsulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., $-SO_2-$, substituted with an optionally substituted heteroaryl group. Non-limiting exemplary heteroarylsulfonyl groups include:



[000302] In the present disclosure, the term "heterocyclosulfonyl" as used by itself or as part of another group refers to a sulfonyl, i.e., $-SO_2-$, substituted with an optionally substituted heterocyclo group. A non-limiting exemplary heterocyclosulfonyl group is:



and



.

[000303] In the present disclosure, the term "sulfonamido" as used by itself or as part of another group refers to a radical of the formula $-SO_2NR^{21a}R^{21b}$, wherein R^{21a} and R^{21b} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, and optionally substituted aryl, or R^{21a} and R^{21b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. Non-limiting exemplary sulfonamido groups include $-SO_2NH_2$, $-SO_2N(H)CH_3$, $-SO_2N(CH_3)_2$, and $-SO_2N(H)Ph$.

[000304] In the present disclosure, the term "alkoxy" as used by itself or as part of another group refers to an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, or optionally substituted alkynyl attached to a terminal oxygen atom. In one embodiment, the alkoxy is an optionally substituted alkyl attached to a terminal oxygen atom. In one embodiment, the alkoxy group is a C_{1-6} alkyl attached to a terminal oxygen atom. In another embodiment, the alkoxy group is a C_{1-4} alkyl attached to a terminal oxygen atom. Non-limiting exemplary alkoxy groups include methoxy, ethoxy, *tert*-butoxy, and $-OCH_2SO_2CH_3$.

[000305] In the present disclosure, the term "alkylthio" as used by itself or as part of another group refers to an optionally substituted alkyl attached to a terminal sulfur atom. In one embodiment, the alkylthio group is a C_{1-4} alkylthio group. Non-limiting exemplary alkylthio groups include $-SCH_3$ and $-SCH_2CH_3$.

[000306] In the present disclosure, the term "alkoxyalkyl" as used by itself or as part of another group refers to an optionally alkyl substituted with an alkoxy group. Non-limiting exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, propoxymethyl, iso-propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl.

[000307] In the present disclosure, the term "haloalkoxy" as used by itself or as part of another group refers to a haloalkyl attached to a terminal oxygen atom. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

[000308] In the present disclosure, the term "aryloxy" as used by itself or as part of another group refers to an optionally substituted aryl attached to a terminal oxygen atom. A non-limiting exemplary aryloxy group is PhO-.

[000309] In the present disclosure, the term "aralkyloxy" as used by itself or as part of another group refers to an aralkyl attached to a terminal oxygen atom. Non-limiting exemplary aralkyloxy groups include $PhCH_2O$- and $PhCH_2CH_2O$-.

[000310] In the present disclosure, the term "heteroaryl" refers to unsubstituted monocyclic and bicyclic aromatic ring systems having 5 to 14 ring atoms, i.e., a 5- to 14-membered heteroaryl, wherein at least one carbon atom of one of the rings is replaced with a heteroatom independently selected from the group consisting of oxygen, nitrogen and sulfur. In one embodiment, the heteroaryl contains 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of oxygen, nitrogen and sulfur. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. In another embodiment, the heteroaryl is a 5- to 10-membered heteroaryl. In another embodiment, the heteroaryl is a 5- or 6-membered heteroaryl. In another embodiment, the heteroaryl has 5 ring atoms, e.g., thienyl, a 5-membered heteroaryl having four carbon atoms and one sulfur atom. In another embodiment, the heteroaryl has 6 ring atoms, e.g., pyridyl, a 6-membered heteroaryl having five carbon atoms and one nitrogen atom. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranyl, isobenzofuranyl, benzooxazonyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. In one embodiment, the heteroaryl is selected from the group consisting of thienyl (e.g., thien-2-yl and thien-3-yl), furyl (e.g., 2-furyl and 3-furyl), pyrrolyl (e.g., 1H-pyrrol-2-yl and 1H-pyrrol-3-yl), imidazolyl (e.g., 2H-imidazol-2-yl and 2H-imidazol-4-yl), pyrazolyl (e.g., 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, and 1H-pyrazol-5-

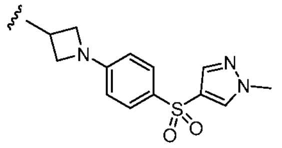
yl), pyridyl (e.g., pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (e.g., pyrimidin-2-yl, pyrimidin-4-yl, and pyrimidin-5-yl), thiazolyl (e.g., thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (*e.g.*, isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (*e.g.*, oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl), isoxazolyl (e.g., isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl), and indazolyl (e.g., 1H-indazol-3-yl). The term "heteroaryl" is also meant to include possible N-oxides. A non-limiting exemplary N-oxide is pyridyl N-oxide.

[000311] In one embodiment, the heteroaryl is a 5- or 6-membered heteroaryl. In one embodiment, the heteroaryl is a 5-membered heteroaryl, i.e., the heteroaryl is a monocyclic aromatic ring system having 5 ring atoms wherein at least one carbon atom of the ring is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. Non-limiting exemplary 5-membered heteroaryl groups include thienyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, and isoxazolyl. In another embodiment, the heteroaryl is a 6-membered heteroaryl, e.g., the heteroaryl is a monocyclic aromatic ring system having 6 ring atoms wherein at least one carbon atom of the ring is replaced with a nitrogen atom. Non-limiting exemplary 6-membered heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl.

[000312] In the present disclosure, the term "optionally substituted heteroaryl" as used by itself or as part of another group refers to a heteroaryl that is either unsubstituted or substituted with one two, three, or four substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, haloalkylsulfonyl cycloalkylsulfonyl, (cycloalkyl)alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, carboxy, carboxyalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, and (heterocyclo)alkyl. In one embodiment, the optionally substituted heteroaryl has one substituent. In another embodiment, the optionally substituted heteroaryl is unsubstituted. Any available carbon or nitrogen atom can be substituted. The term optionally substituted heteroaryl includes heteroaryl groups having a fused optionally substituted cycloalkyl or fused optionally substituted heterocyclo group. An optionally substituted heteroaryl having a fused optionally substituted cycloalkyl or fused optionally substituted heterocyclo group may be attached to the remainder of the molecule at any available carbon atom on the heteroaryl ring.

[000313] In the present disclosure, the term "heterocyclo" as used by itself or as part of another group refers to unsubstituted saturated and partially unsaturated, e.g., containing one or two double bonds, cyclic groups containing one, two, or three rings having from three to fourteen ring members, i.e., a 3- to 14-membered heterocyclo, wherein at least one carbon atom of one of the rings is replaced with a heteroatom. Each heteroatom is independently selected from the group consisting of oxygen, sulfur, including sulfoxide and sulfone, and/or nitrogen atoms, which can be oxidized or quaternized. The term "heterocyclo" includes groups wherein a ring -CH_2- is replaced with a -C(=O)-, for example, cyclic ureido groups such as 2-imidazolidinone and cyclic amide groups such as β-lactam, γ-lactam, δ-lactam, ε-lactam, and piperazin-2-one. The term "heterocyclo" also includes groups having fused optionally substituted aryl groups, e.g., indolinyl or chroman-4-yl. In one embodiment, the heterocyclo group is a C_{4-6} heterocyclo, i.e., a 4-, 5- or 6-membered cyclic group, containing one ring and one or two oxygen and/or nitrogen atoms. In one embodiment, the heterocyclo group is a C_{4-6} heterocyclo containing one ring and one nitrogen atom. The heterocyclo can be optionally linked to the rest of the molecule through any available carbon or nitrogen atom. Non-limiting exemplary heterocyclo groups include azetidinyl, dioxanyl, tetrahydropyranyl, 2-oxopyrrolidin-3-yl, piperazin-2-one, piperazine-2,6-dione, 2-imidazolidinone, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, and indolinyl.

[000314] In the present disclosure, the term "optionally substituted heterocyclo" as used herein by itself or part of another group refers to a heterocyclo that is either unsubstituted or substituted with one, two, three, or four substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, cycloalkylcarbonyl, alkoxycarbonyl, $CF_3C(=O)$-, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, (carboxamido)alkyl, or (heterocyclo)alkyl. Substitution may occur on any available carbon or nitrogen atom, or both. Non-limiting exemplary substituted heterocyclo groups include: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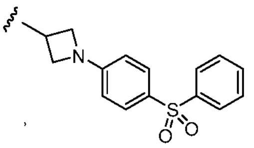
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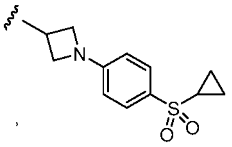
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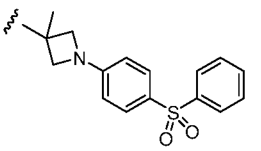
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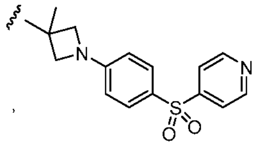
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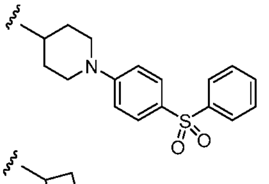
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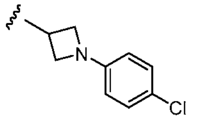
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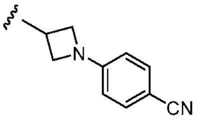
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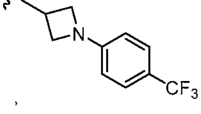
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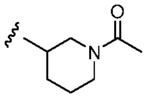
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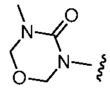
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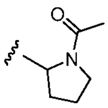
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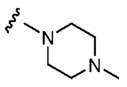
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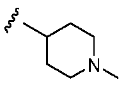
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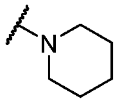
[000315] In the present disclosure, the term "amino" as used by itself or as part of another group refers to a radical of the formula $-NR^{22a}R^{22b}$, wherein R^{22a} and R^{22b} are independently selected from the group consisting of hydrogen, alkyl, aralkyl, hydroxyalkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, and optionally substituted heteroaryl, or R^{22a} and R^{22b} are taken together to form a 3- to 8-membered optionally substituted heterocyclo. Non-limiting exemplary amino groups include $-NH_2$, $-N(H)(CH_3)$,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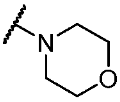
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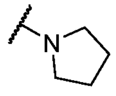
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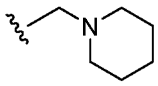
[000316] In the present disclosure, the term "(amino)alkyl" as used by itself or as part of another group refers to a C_{1-6} alkyl substituted with an amino. In one embodiment, the (amino)alkyl is $-CH_2NR^{22a}R^{22b}$, wherein R^{22a} and R^{22b} are independently selected from the group consisting of hydrogen, alkyl, aralkyl, hydroxyalkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, and optionally substituted heteroaryl, or R^{22a} and R^{22b} are taken together to form a 3- to 8-membered optionally substituted heterocyclo. In another embodiment, R^{22a} and R^{22b} are independently hydrogen or C_{1-4} alkyl. Non-limiting exemplary (amino)alkyl groups include $-CH_2NH_2$, $-CH_2N(H)CH_3$, $-CH_2N(CH_3)_2$, $-CH_2CH_2N(CH_3)_2$,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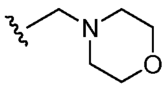
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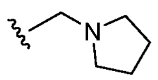
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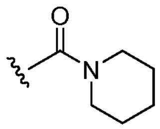
[000317] In the present disclosure, the term "dialkylaminoalkyl" as used by itself or as part of another group refers to a C_{1-4} alkyl attached to a di-(C_{1-6} alkyl) substituted amino. Non-limiting exemplary dialkylaminoalkyl groups include $-CH_2N(CH_3)_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_2N(CH_3)_2$, $-CH_2CH_2CH_2CH_2N(CH_3)_2$, and $-CH_2N(CH_2CH_3)_2$.

[000318] In the present disclosure, the term "carboxamido" as used by itself or as part of another group refers to a radical of formula $-C(=O)NR^{23a}R^{23b}$, wherein R^{23a} and R^{23b} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, hydroxyalkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, and optionally substituted heteroaryl, or R^{23a} and R^{23b} taken together with the nitrogen to which they are attached form a 3- to 8-membered optionally substituted heterocyclo group. In one embodiment, R^{23a} and R^{23b} are each independently hydrogen or optionally substituted alkyl. In one embodiment, R^{23a} and R^{23b} are taken together to taken together with the nitrogen to which they are attached form a 3- to 8-membered optionally substituted heterocyclo group. Non-limiting exemplary carboxamido groups include $-CONH_2$, $-CON(H)CH_3$, $-CON(CH_3)_2$, $-CON(H)Ph$,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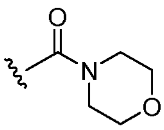
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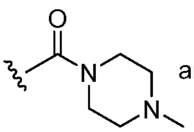
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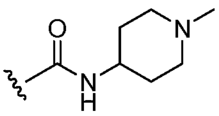
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[000319] In the present disclosure, the term "alkylamide" as used by itself or as part of another group refers to a radical of formula $-C(=O)NR^{24a}R^{24b}$, wherein R^{24a} is selected from the group consisting of hydrogen and alkyl and R^{24b} is alkyl. In one embodiment, R^{24a} is hydrogen and R^{24b} is C_{1-6} alkyl. In another embodiment, R^{24a} is hydrogen and R^{24b} is C_{1-4} alkyl. In another embodiment, R^{24a} and R^{24b} are each independently C_{1-6} alkyl. In another embodiment, R^{24a} and R^{24b} are each independently C_{1-4} alkyl. Non-limiting exemplary alkylamide groups include $-CON(H)CH_3$, $-CON(CH_3)_2$, $-CON(H)CH_2CH_3$, and $-CON(CH_2CH_3)_2$.

[000320] In the present disclosure, the term "alkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted with an alkyl. Non-limiting exemplary alkylcarbonyl groups include $-C(=O)CH_3$ and $-C(=O)CH_2CH_2CH_2CH_3$.

[000321] In the present disclosure, the term "cycloalkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted with a cycloalkyl. A non-limiting exemplary cycloalkylcarbonyl group is -C(=O)-cyclopropyl.

[000322] In the present disclosure, the term "arylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted with an optionally substituted aryl. A non-limiting exemplary arylcarbonyl group is -COPh.

[000323] In the present disclosure, the term "alkoxycarbonyl" as used by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted with an alkoxy. In one embodiment, the alkoxy is a C_{1-4} alkoxy. In another embodiment, the alkoxy is a C_{1-6} alkoxy. Non-limiting exemplary alkoxycarbonyl groups include -C(=O)OMe, -C(=O)OEt, and -C(=O)OtBu.

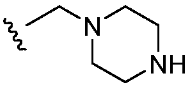
[000324] In the present disclosure, the term "(alkoxycarbonyl)alkyl" as used by itself or as part of another group refers to an alkyl substituted by an alkoxycarbonyl group. Non-limiting exemplary (alkoxycarbonyl)alkyl groups include $-CH_2C(=O)OMe$, $-CH_2C(=O)OEt$, and $-CH_2C(=O)OtBu$.

[000325] In the present disclosure, the term "carboxy" as used by itself or as part of another group refers to a radical of the formula $-CO_2H$.

[000326] In the present disclosure, the term "carboxyalkyl" as used by itself or as part of another group refers to an alkyl substituted with a $-CO_2H$. A non-limiting exemplary carboxyalkyl group is $-CH_2CO_2H$.

[000327] In the present disclosure, the term "aralkyl" as used by itself or as part of another group refers to an alkyl substituted with one, two, or three optionally substituted aryl groups. In one embodiment, aralkyl is a C_{1-4} alkyl substituted with one optionally substituted C_5 or C_6 aryl group. In another embodiment, the aralkyl is a C_1 alkyl substituted with one optionally substituted aryl group. In another embodiment, the aralkyl is a C_2 alkyl substituted with one optionally substituted aryl group. In another embodiment, the aralkyl is a C_3 alkyl substituted with one optionally substituted aryl group. In one embodiment, the aralkyl is a C_1 or C_2 alkyl substituted with one optionally substituted phenyl group. Non-limiting exemplary aralkyl groups include benzyl, phenethyl, -CHPh$_2$, -CH(CH$_3$)Ph, -CH$_2$(4-F-Ph), -CH$_2$(4-Me-Ph), -CH$_2$(4-CF$_3$-Ph), and -CH(4-F-Ph)$_2$.

[000328] In the present disclosure, the term "(heterocyclo)alkyl" as used by itself or part of another group refers to an alkyl substituted with an optionally substituted heterocyclo group. In one embodiment, the (heterocyclo)alkyl is a C$_{1-4}$ alkyl substituted with one optionally substituted heterocyclo group. Non-limiting exemplary (heterocyclo)alkyl groups include: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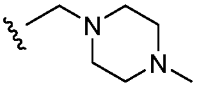
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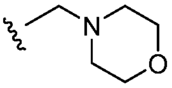
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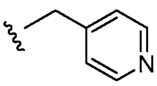
[000329] In the present disclosure, the term "(heteroaryl)alkyl" as used by itself or part of another group refers to an alkyl substituted with an optionally substituted heteroaryl group. In one embodiment, the (heteroaryl)alkyl is a C$_{1-4}$ alkyl substituted with one optionally substituted heteroaryl group. In another embodiment, the (heteroaryl)alkyl is a C$_1$ alkyl substituted with one optionally substituted heteroaryl group Non-limiting exemplary (heteroaryl)alkyl groups include: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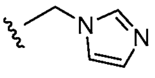
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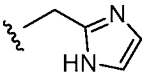
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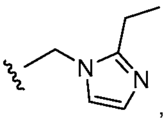
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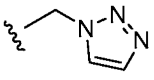
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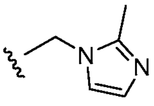
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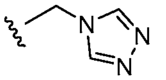
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[000330] In the present disclosure, the term "(carboxamido)alkyl" as used by itself or as part of another group refers to an alkyl substituted with one or two carboxamido groups. In one embodiment, the (carboxamido)alkyl is a C$_{1-4}$ alkyl substituted with one carboxamido group, i.e., a (carboxamido)C$_{1-4}$ alkyl. In another embodiment, the (carboxamido)alkyl is a C$_{1-4}$ alkyl substituted with two carboxamido groups. Non-limiting exemplary (carboxamido)alkyl groups include -CH$_2$CONH$_2$, -C(H)CH$_3$-CONH$_2$, and -CH$_2$CON(H)CH$_3$.

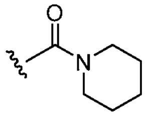
[000331] In the present disclosure, the term "(aryloxy)alkyl" as used by itself or as part of another group refers to an alkyl substituted with an aryloxy group. In one embodiment, the "(aryloxy)alkyl" is a C$_{1-4}$ alkyl substituted with an aryloxy. In one embodiment, the "(aryloxy)alkyl" is a C$_{2-4}$ alkyl substituted with an aryloxy.

Non-limiting exemplary (aryloxy)alkyl groups include $-CH_2CH_2OPh$ and $-CH_2CH_2CH_2OPh$.

[000332] In the present disclosure, the term "alkylcarbonyloxy" as used by itself or as part of another group refers to an oxy, e.g., -O-, substituted with an alkylcarbonyl group. Non-limiting exemplary "alkylcarbonyloxy" groups include $-OC(=O)CH_2CH_3$, $-OC(=O)CH_3$, i.e., acetoxy, $-OC(=O)CH_2CH_2CH_3$, and $-OC(=O)CH(CH_3)_2$.

[000333] In the present disclosure, the term "cycloalkylcarbonyloxy" as used by itself or as part of another group refers to an oxy, e.g., -O-, substituted with an cycloalkylcarbonyl group. Non-limiting exemplary "cycloalkylcarbonyloxy" groups include -OC(=O)-cyclopropyl, -OC(=O)-cyclobutyl, and -OC(=O)-cyclopentyl.

[000334] In the present disclosure, the term "heterocyclylcarbonyl" as used by itself or as part of another group refers to a carbonyl, i.e., -C(=O)-, substituted with an optionally substituted heterocyclo group. Non-limiting exemplary heterocyclylcarbonyl groups include: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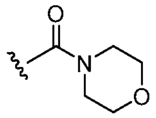
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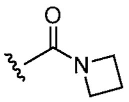
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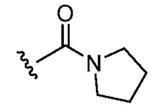
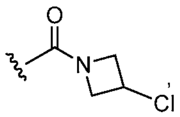


[000335] In the present disclosure, the term "halo-substituted heterocyclylcarbonyl" as used by itself or as part of another group refers to a carbonyl, i.e., -(C=O)-, attached to a heterocyclo group substituted with at least one halo group. In one embodiment, the heterocyclo group is substituted with one halo group. In another embodiment, the heterocyclo group is substituted with two halo groups. Non-limiting exemplary halo-substituted heterocyclylcarbonyl groups include: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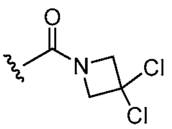
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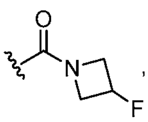
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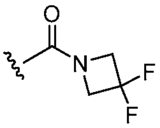
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[000336] The term "menin inhibitor" or "inhibitor of menin" as used herein refers to a compound that disrupts, e.g., inhibits, the menin-MLL fusion protein interaction.

[000337] The term "a disease or condition wherein inhibition of menin provides a benefit" pertains to a disease or condition in which menin and/or the interaction of menin with a menin-interacting protein is important or necessary, e.g., for the onset, progress, or expression of that disease or condition, or a disease or a condition which is known to be treated by a menin inhibitor. Examples of such conditions include, but are not limited to, a cancer, a chronic autoimmune disease, an inflammatory disease, a proliferative disease, sepsis, and a viral infection. One of ordinary skill in the art is readily able to determine whether a compound treats a disease or condition mediated by menin for any particular cell type, for example, by assays which conveniently can be used to assess the activity of particular compounds.

[000338] The term "second therapeutic agent" refers to a therapeutic agent different from a Compound of the Disclosure and that is known to treat the disease or condition of interest. For example when a cancer is the disease or condition of interest, the second therapeutic agent can be a known chemotherapeutic drug, like taxol, or radiation, for example.

[000339] The term "disease" or “condition” denotes disturbances and/or anomalies that as a rule are regarded as being pathological conditions or functions, and that can manifest themselves in the form of particular signs, symptoms, and/or malfunctions. As demonstrated below, Compounds of the Disclosure are menin inhibitors and can be used in treating diseases and conditions wherein menin inhibition provides a benefit.

[000340] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need of such treatment.

[000341] Within the meaning of the disclosure, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy.

[000342] The term "therapeutically effective amount" or "effective dose" as used herein refers to an amount of the active ingredient(s) that is(are) sufficient, when administered by a method of the disclosure, to efficaciously deliver the active ingredient(s) for the treatment of condition or disease of interest to an individual in need thereof. In the case of a cancer or other proliferation disorder, the therapeutically effective amount of the agent may reduce (i.e., retard to some extent and preferably stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., retard to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., retard to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; reduce menin interactions in the target cells; and/or relieve, to some extent, one or more of the symptoms associated with the cancer. To the extent the administered compound or composition prevents growth and/or kills existing cancer cells, it may be cytostatic and/or cytotoxic.

[000343] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[000344] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[000345] "Concurrent administration," "administered in combination," "simultaneous administration," and similar phrases mean that two or more agents are administered concurrently to the subject being treated. By "concurrently," it is meant that each agent is administered either simultaneously or sequentially in any order at different points in time. However, if not administered simultaneously, it is meant that they are administered to an individual in a sequence and sufficiently close in time so as to provide the desired therapeutic effect and can act in concert. For example, a Compound of the Disclosure can be administered at the same time or sequentially in any order at different points in time as a second therapeutic agent. A Compound of the Disclosure and the second therapeutic agent can be administered separately, in any appropriate form and by any suitable route. When a Compound of the Disclosure and the second therapeutic agent are not administered concurrently, it is understood that they can be administered in any order to a subject in need thereof. For example, a Compound of the Disclosure can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapeutic agent treatment modality (e.g., radiotherapy), to an individual in need thereof. In various embodiments, a Compound of the Disclosure and the second therapeutic agent are administered 1 minute apart, 10 minutes apart, 30 minutes apart, less than 1 hour apart, 1 hour apart, 1 hour to 2 hours apart, 2 hours to 3 hours apart, 3 hours to 4 hours apart, 4 hours to 5 hours apart, 5 hours to 6 hours apart, 6 hours to 7 hours apart, 7 hours to 8 hours apart, 8 hours to 9 hours apart, 9 hours to 10 hours apart, 10 hours to 11 hours apart, 11 hours to 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In one embodiment, the components of the combination therapies are administered at about 1 minute to about 24 hours apart.

[000346] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[000347] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[000348] The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

[000349] The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive. In one embodiment, Compounds of the Disclosure are racemic.

[000350] The term "absolute configuration" refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, e.g., R or S.

[000351] The stereochemical terms and conventions used in the specification are meant to be consistent with those described in *Pure & Appl. Chem 68*:2193 (1996), unless otherwise indicated.

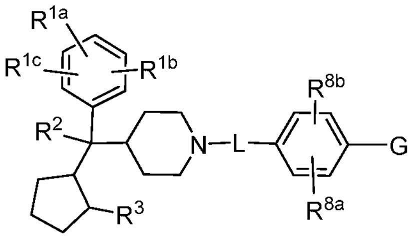
[000352] The term "enantiomeric excess" or "ee" refers to a measure for how much of one enantiomer is present compared to the other. For a mixture of R and S enantiomers, the percent enantiomeric excess is defined as $|R - S|*100$, where R and S are the respective mole or weight fractions of enantiomers in a mixture such that $R + S = 1$. With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as $([\alpha]_{obs}/[\alpha]_{max})*100$, where $[\alpha]_{obs}$ is the optical rotation of the mixture of enantiomers and $[\alpha]_{max}$ is the optical rotation of the pure enantiomer. Determination of enantiomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography or optical polarimetry.

[000353] The use of the terms "a", "an", "the", and similar referents in the context of this disclosure (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended to better illustrate the disclosure and is not a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosure.

[000354] The term "about," as used herein, when used in combination with a numeric value or range of values means the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art.

[000355] Aspects I

[000356] Aspect 1. A compound having Formula **I**:



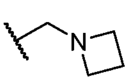
I,

[000357] and the pharmaceutically acceptable salts thereof, wherein:

[000358] R^{1a}, R^{1b}, and R^{1c} are each independently selected from the group consisting of hydrogen and halo;

[000359] G is $-SO_2-X-Z^2$;

[000360] R^2 is selected from the group consisting of:



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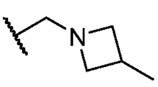

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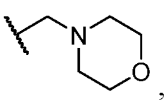

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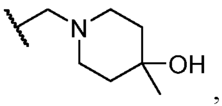

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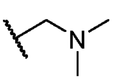

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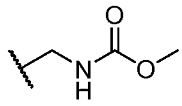

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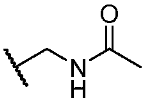

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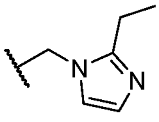

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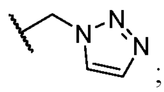
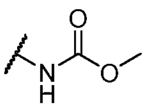


;

[000361] R^3 is selected from the group consisting of:



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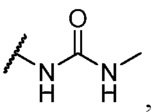

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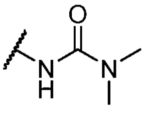

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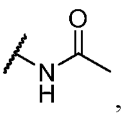

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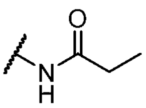

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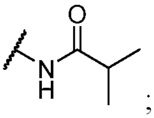
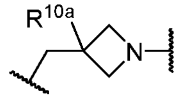
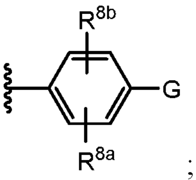


;

[000362] L is


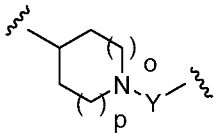
, wherein the nitrogen atom of L is attached to



;

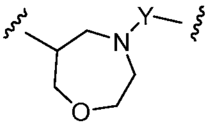
[000363] R^{10a} is selected from the group consisting of hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and hydroxy;

[000364] X is selected from the group consisting of:



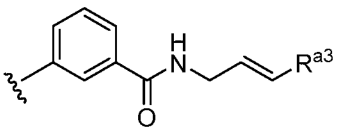
X-1

,



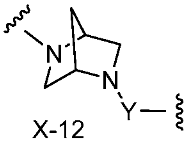
X-9

,



X-10

, and



X-12

;

[000365] wherein Y is attached to Z^2;

[000366] Y is -C(=O)- ;

[000367] o and p are each independently 0, 1, 2, or 3;

[000368] Z^2 is selected from the group consisting of $-C(R^{13a})=C(R^{13b})(R^{13c})$, $-C\equiv CR^{13d}$, and R^{a4}, wherein Z^2 is absent when X is X-10;

[000369] R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and halo;

[000370] R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen, methyl, and dimethylaminomethyl;

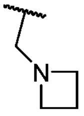
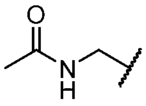
[000371] R^{a3} is selected from the group consisting of alkoxycarbonyl and alkylsulfonyl;

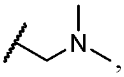
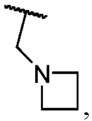
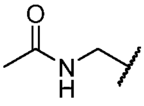
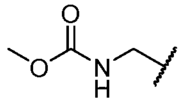
[000372] R^{a4} is $-N(H)CH_2CH=CH-R^{a5}$; and

[000373] R^{a5} is selected from the group consisting of alkoxycarbonyl and alkylsulfonyl;

[000374] provided:

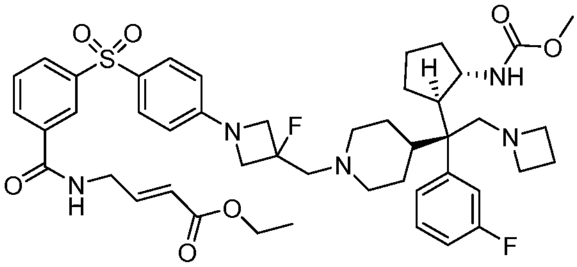
[000375] when X is X-1, o and p are each 0, and Z^2 is $C(R^{13a})=C(R^{13b})(R^{13c})$, then none of R^{13a}, R^{13b} and R^{13c} is dimethylaminomethyl;

[000376] when X is X-1, R^{10a} is hydrogen, F, OH, methyl or methoxy, Z^2 is $-C\equiv CR^{13d}$, and R^2 is  or , then R^{13d} is not hydrogen or methyl;

[000377] when X is X-1, Z^2 is CH=CH2, and R^2 is , , , or , then R^{10a} is not hydrogen, F, OH, fluoromethyl, methyl or methoxy;

[000378] when X is X-9 and Z^2 is CH=CH2, then R^{10a} is not hydrogen, F, or methyl; and

[000379] the compound of formula (I) is not



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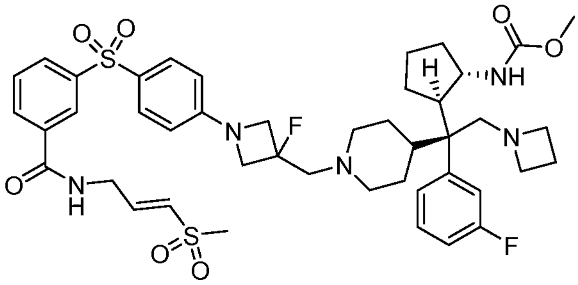

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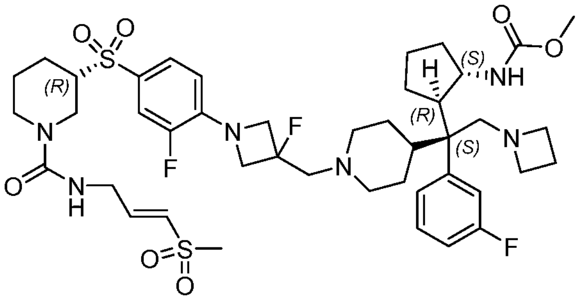

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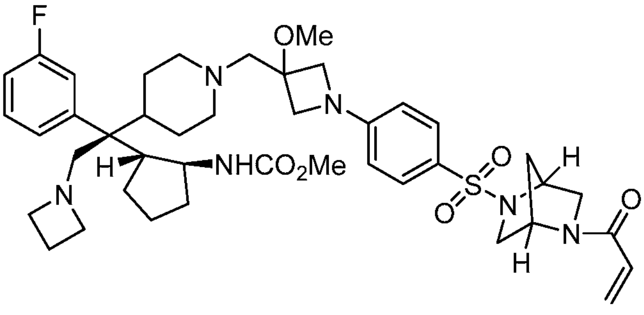
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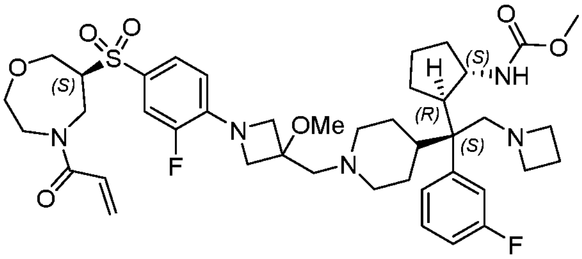
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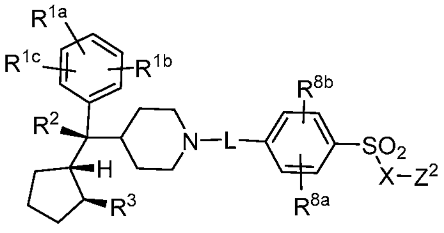
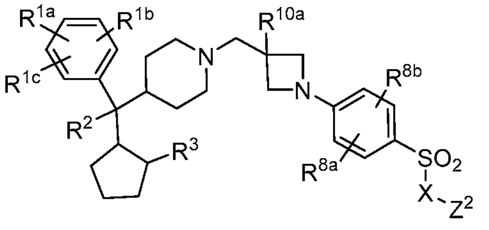
[000380] Aspect 2. The compound of Aspect 1 having Formula **II**:


II,

[000381] or a pharmaceutically acceptable salt thereof.

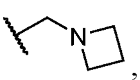
[000382] Aspect 3. The compound of Aspect 1 having Formula **XI**


XI.

[000383] or a pharmaceutically acceptable salt thereof.

[000384] Aspect 4. The compound of any of Aspects 1 to 3, wherein:

[000385] R^2 is selected from the group consisting of: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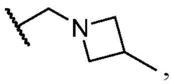
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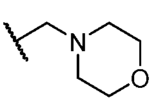
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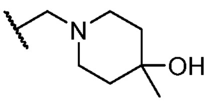
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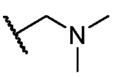
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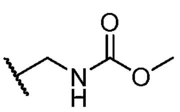
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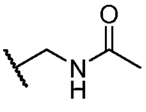
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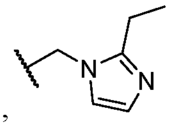
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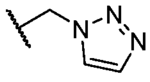

;

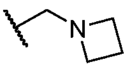
[000386] R^{10a} is selected from the group consisting of hydrogen, fluoro, cyano, methyl, methoxy, ethoxy, and hydroxy;

[000387] Z^2 is selected from the group consisting of $-C(R^{13a})=C(R^{13b})(R^{13c})$, and $-C\equiv CR^{13d}$;

[000388] R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and fluoro; and

[000389] R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen, methyl, and dimethylaminomethyl.

[000390] Aspect 5. The compound of any one of Aspects 1-4, wherein R^2 is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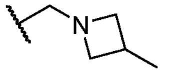
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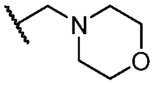
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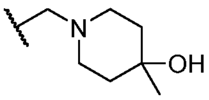
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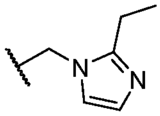
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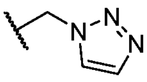
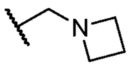

;

[000391] or a pharmaceutically acceptable salt thereof.

[000392] Aspect 6. The compound of Aspects 1-4, or a pharmaceutically acceptable salt thereof, wherein R^2 is

[000393]

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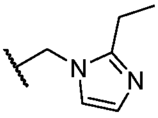
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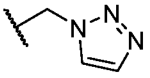
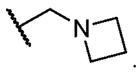

;

[000394] or a pharmaceutically acceptable salt thereof.

[000395] Aspect 7. The compound of Aspect 4, or a pharmaceutically acceptable salt thereof, wherein R^2 is

.

[000396] Aspect 8. The compound of any one of Aspects 1-7, wherein R^{8a} and R^{8b} are hydrogen, or a pharmaceutically acceptable salt thereof.

[000397] Aspect 9. The compound of any one of Aspects 1-7, wherein R^{8a} is fluoro, or a pharmaceutically acceptable salt thereof.

[000398] Aspect 10. The compound of any one of Aspects 1-9, wherein at least one of R^{1a}, R^{1b} and R^{1c} is a fluoro, or a pharmaceutically acceptable salt thereof.

[000399] Aspect 11. The compound of any one of Aspects 1-10, wherein R^{10a} is hydrogen, or a pharmaceutically acceptable salt thereof.

[000400] Aspect 12. The compound of any one of Aspects 1-10, wherein R^{10a} is fluoro, or a pharmaceutically acceptable salt thereof.

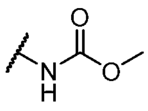
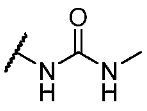
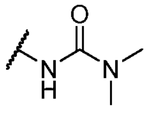
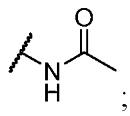
[000401] Aspect 13. The compound of any one of Aspects 1-12, wherein X is X-1, X-9, or X-12, or a pharmaceutically acceptable salt thereof.

[000402] Aspect 14. The compound of any one of Aspects 1-13, wherein X is X-1, or a pharmaceutically acceptable salt thereof.

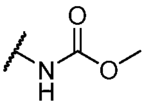
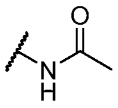
[000403] Aspect 15. The compound of any one of Aspects 1-13, wherein X is X-9, or a pharmaceutically acceptable salt thereof.

[000404] Aspect 16. The compound of any one of Aspects 1-12, wherein X is X-10, or a pharmaceutically acceptable salt thereof.

[000405] Aspect 17. The compound of any one of Aspects 1-13, wherein X is X-12, or a pharmaceutically acceptable salt thereof.

[000406] Aspect 18. The compound of any one of Aspects 1-17, wherein R^3 is , , , or ;

[000407] or a pharmaceutically acceptable salt thereof.

[000408] Aspect 19. The compound of any one of Aspects 1-18, wherein R^3 is  or ;

[000409] or a pharmaceutically acceptable salt thereof.

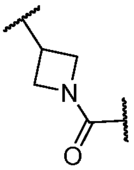
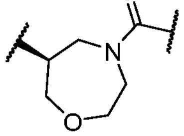
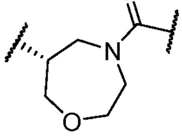
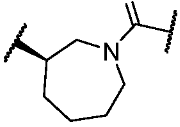
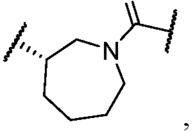
[000410] Aspect 20. The compound of any one of Aspects 1-19, wherein Z^2 is $-C(R^{13a})=C(R^{13b})(R^{13c})$, or a pharmaceutically acceptable salt thereof.

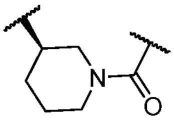
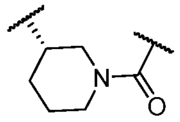
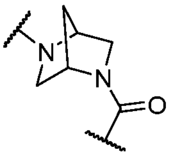
[000411] Aspect 21. The compound of Aspect 20, wherein R^{13a} and R^{13b} are hydrogen and R^{13c} is dimethylaminomethyl, or a pharmaceutically acceptable salt thereof.

[000412] Aspect 22. The compound of Aspect 20, wherein R^{13c} is methyl and R^{13a} and R^{13b} are hydrogen, or a pharmaceutically acceptable salt thereof.

[000413] Aspect 23. The compound of Aspect 20, wherein each of R^{13a}, R^{13b}, and R^{13c} is hydrogen, or a pharmaceutically acceptable salt thereof.

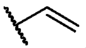
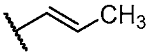
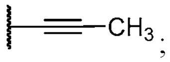
[000414] Aspect 25. The compound of any one of Aspects 1-12 and 18-24, wherein X is selected from the group consisting of:

, , , , ,

, , ,

[000415] wherein the carbonyl is attached to Z^2, or a pharmaceutically acceptable salt thereof.

[000416] Aspect 26. The compound of any one of Aspects 1-19, wherein Z^2 is selected from the group consisting of:

, , and ;

[000417] or a pharmaceutically acceptable salt thereof.

[000418] Aspect 27. The compound of Aspect 1, wherein the compound is any one or more of the compounds of Table 1, or a pharmaceutically acceptable salt thereof.

[000419] Aspect 28. A pharmaceutical composition comprising the compound of any one of Aspects 1-27, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[000420] Aspect 29. A method of treating a patient, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of Aspects 1-27, or a pharmaceutically acceptable salt thereof, wherein the patient has cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

[000421] Aspect 30. The method of Aspect 29, wherein the patient has cancer.

[000422] Aspect 31. The method of Aspect 30, wherein the cancer is any one or more of the cancers of Table 2.

[000423] Aspect 32. The method of Aspect 31, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

[000424] Aspect 33. The method of any one of Aspects 29-32 further comprising administering a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition.

[000425] Aspect 34. The pharmaceutical composition of Aspect 28 for use in treating cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

[000426] Aspect 35. The pharmaceutical composition of Aspect 34 for use in treating cancer.

[000427] Aspect 36. The pharmaceutical composition of Aspect 35, wherein the cancer is any one or more of the cancers of Table 2.

[000428] Aspect 37. The pharmaceutical composition of Aspect 36, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

[000429] Aspect 38. A compound of any one of Aspects 1-27, or a pharmaceutically acceptable salt thereof, for use in treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

[000430] Aspect 39. The compound of Aspect 38 for use in treating cancer.

[000431] Aspect 40. The compound of Aspect 39, wherein the cancer is any one or more of the cancers of Table 2.

[000432] Aspect 41. The compound of Aspect 40, wherein` the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

[000433] Aspect 42. Use of a compound of any one of Aspects 1-27, or a pharmaceutically acceptable salt 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.

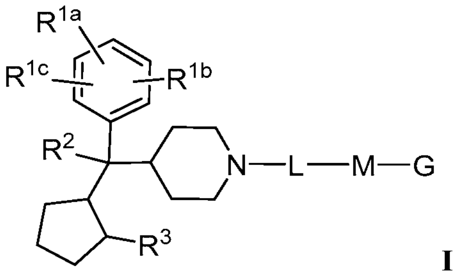
[000434] Aspect 43. The use of Aspect 42 for treatment of cancer.

[000435] Aspect 44. The use of Aspect 43, wherein the cancer is any one or more of the cancers of Table 2.

[000436] Aspect 45. The use of Aspect 44, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, and breast cancer.

[000437] Aspects II

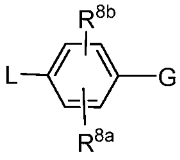
[000438] Aspect 1. A compound having Formula **Ia**,



Ia

[000439] or a pharmaceutically acceptable salt thereof, wherein

[000440] L-M-G is



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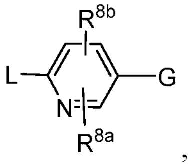

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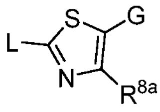

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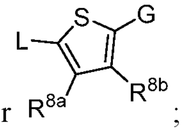


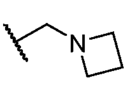
;

M-1 M-2 M-3 M-4

[000441] R^{1a}, R^{1b}, and R^{1c} are each independently selected from the group consisting of hydrogen and halo;

[000442] G is $-SO_2-X-Z^2$ or $-CH_2-X-Z^2$;

[000443] R^2 is selected from the group consisting of:



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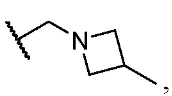

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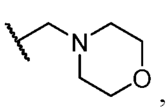

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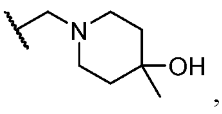

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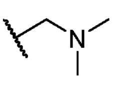

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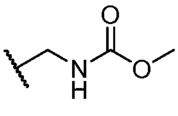

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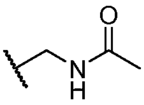

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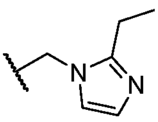

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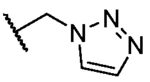
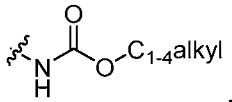
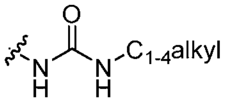
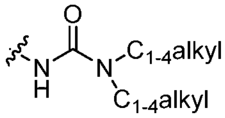


;

[000444] R^3 is selected from the group consisting of:

[000445] 

, 

, 

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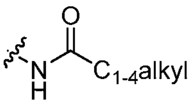
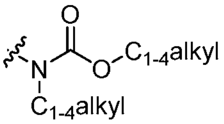
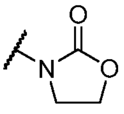
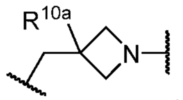


, 

, and 

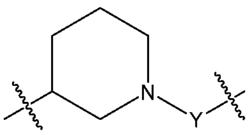
;

[000446] L is 

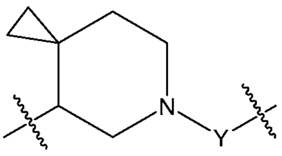
, wherein the nitrogen atom of L is attached to the M;

[000447] each R^{10a} is independently selected from the group consisting of hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, and hydroxy;

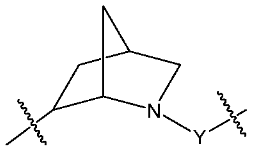
[000448] X is selected from the group consisting of:



X-20,



X-21,



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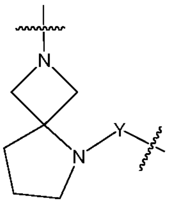

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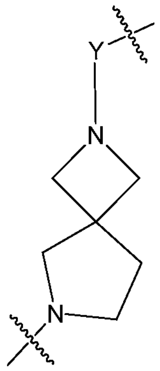

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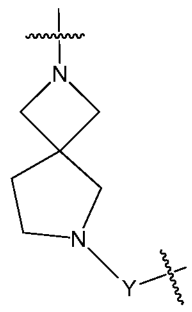

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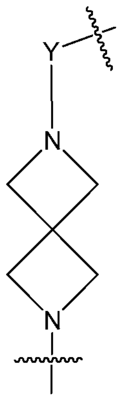
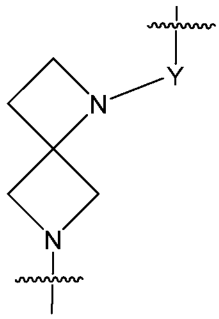
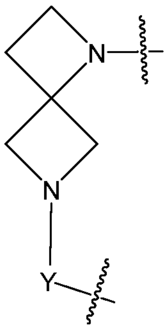


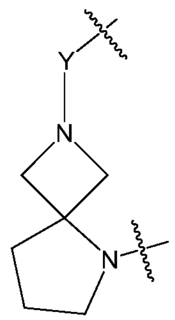
X-26,



X-27,



X-28,



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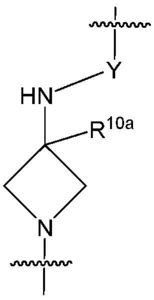

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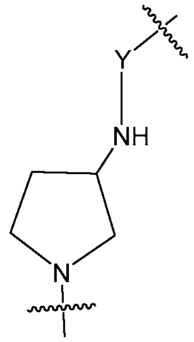

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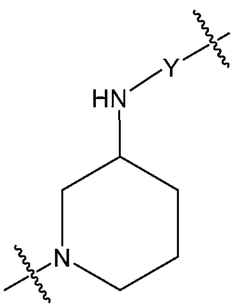

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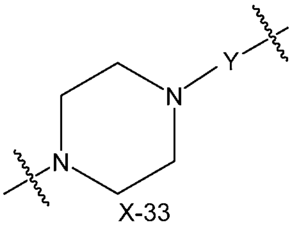
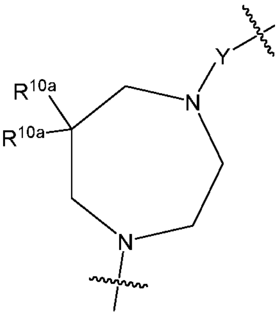
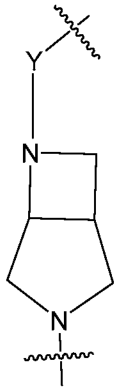


X-33 ,



X-34 ,



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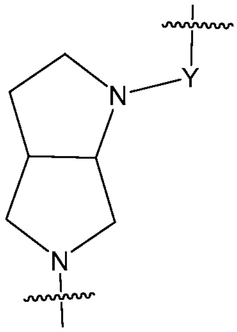

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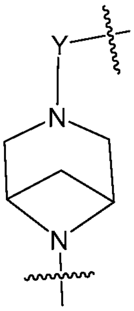

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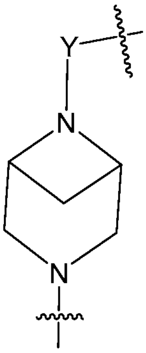

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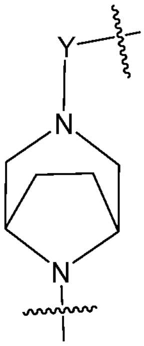

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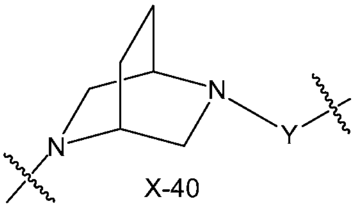

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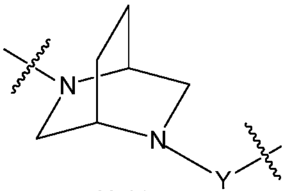

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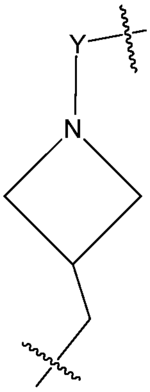

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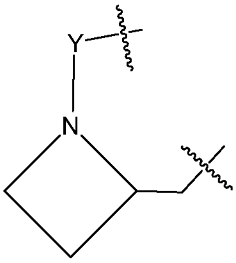

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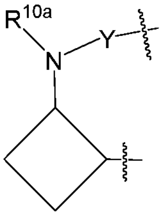

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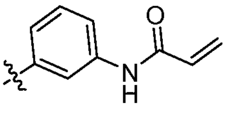

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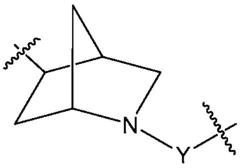
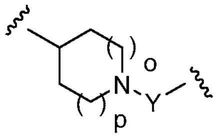
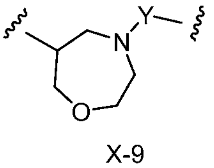


X-46



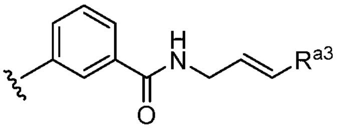
X-1

,



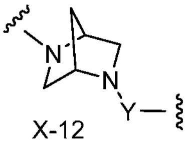
X-9

,



X-10

, and



X-12

;

[000449] wherein Y is attached to Z^2;

[000450] Y is -C(=O)- ;

[000451] o and p are each independently 0, 1, 2, or 3;

[000452] Z^2 is selected from the group consisting of -C(R^{13a})=C(R^{13b})(R^{13c}), -C≡CR^{13d}, and R^{a4},

[000453] Z^2 is absent when X is X-10 or when X is X-45;

[000454] R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen, -SO_2-C_1-C_6 alkyl and halo;

[000455] R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and di-C_1-C_6 alkylaminoC_1-C_4 alkyl;

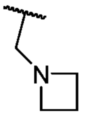
[000456] R^{a3} is selected from the group consisting of C_1-C_6 alkoxycarbonyl-, heterocyclyl-carbonyl-, halo-substituted heterocyclyl-carbonyl-, C_1-C_6 alkylamide and C_1-C_6 alkylsulfonyl;

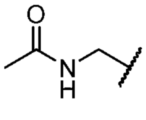
[000457] R^{a4} is -N(H)CH_2CH=CH-R^{a5}; and

[000458] R^{a5} is selected from the group consisting of C_1-C_6 alkoxycarbonyl-, heterocyclyl-carbonyl-, halo-substituted heterocyclyl-carbonyl-, C_1-C_6 alkylamide and C_1-C_6 alkylsulfonyl;

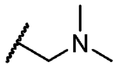
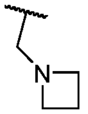
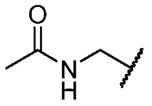
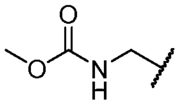
[000459] provided:

[000460] when X is X-1, o and p are each 0, and Z^2 is C(R^{13a})=C(R^{13b})(R^{13c}), then none of R^{13a}, R^{13b} and R^{13c} is dimethylaminomethyl;

[000461] when X is X-1, R^{10a} is hydrogen, F, OH, methyl or methoxy, Z^2 is -C≡CR^{13d}, and R^2 is 

or 

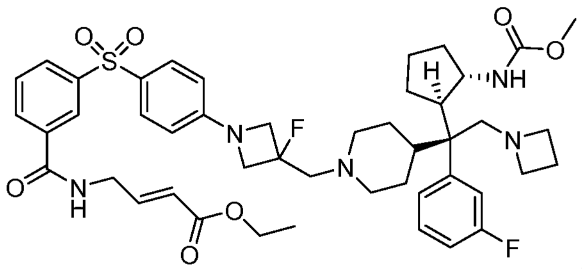
, then R^{13d} is not hydrogen or methyl;

[000462] when X is X-1, Z^2 is $CH=CH_2$, and R^2 is , , , or , then R^{10a} is not hydrogen, F, OH, fluoromethyl, methyl or methoxy;

[000463] when X is X-9 and Z^2 is $CH=CH_2$, then R^{10a} is not hydrogen, F, or methyl;

[000464] R^2 is -CN only when X is X-12; and

[000465] the compound of formula (I) is not



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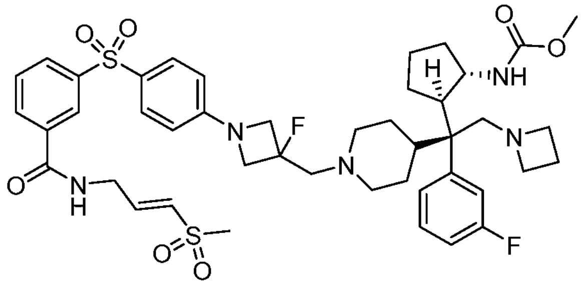

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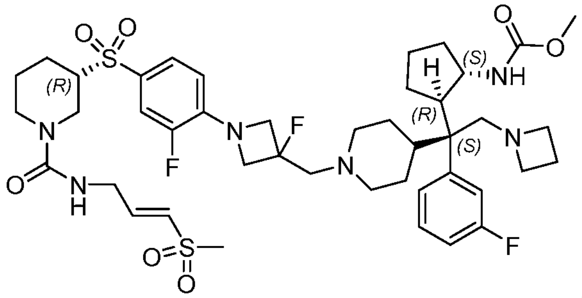

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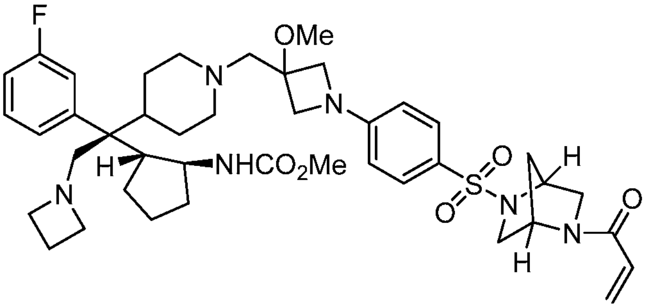

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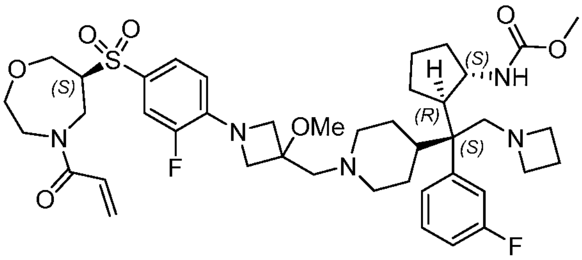
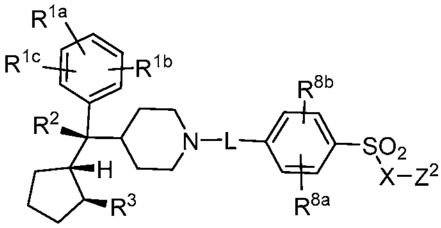


.

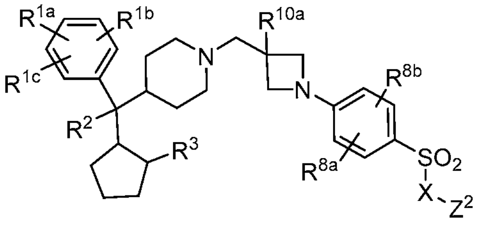
[000466] Aspect 2. The compound of Aspect 1 having Formula **II**:



II,

[000467] or a pharmaceutically acceptable salt thereof.

[000468] Aspect 3. The compound of Aspect 1 having Formula **XI**

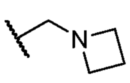


XI.

[000469] or a pharmaceutically acceptable salt thereof.

[000470] Aspect 4. The compound of any of Aspects 1 to 3, wherein:

[000471] R^2 is selected from the group consisting of:



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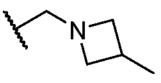

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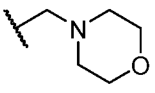

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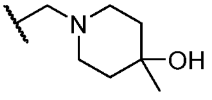

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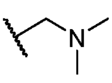

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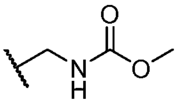

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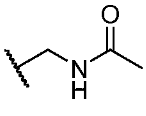

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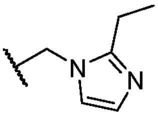

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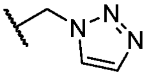


;

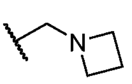
[000472] R^{10a} is selected from the group consisting of hydrogen, fluoro, cyano, methyl, methoxy, ethoxy, and hydroxy;

[000473] Z^2 is selected from the group consisting of $-C(R^{13a})=C(R^{13b})(R^{13c})$, and $-C\equiv CR^{13d}$;

[000474] R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and fluoro; and

[000475] R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen, methyl, and dimethylaminomethyl.

[000476] Aspect 5. The compound of any one of Aspects 1-4, wherein R^2 is



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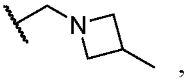

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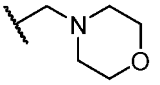

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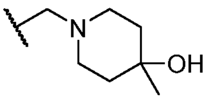

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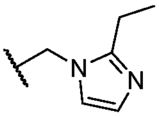

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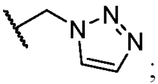
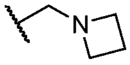


;

[000477] or a pharmaceutically acceptable salt thereof.

[000478] Aspect 6. The compound of Aspect 1-4, or a pharmaceutically acceptable salt thereof, wherein R^2 is

[000479]


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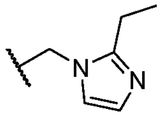

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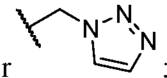
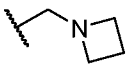


;

[000480] or a pharmaceutically acceptable salt thereof.

[000481] Aspect 7. The compound of Aspect 4, or a pharmaceutically acceptable salt thereof, wherein R^2 is


.

[000482] Aspect 8. The compound of any one of Aspects 1-7, wherein R^{8a} and R^{8b} are hydrogen, or a pharmaceutically acceptable salt thereof.

[000483] Aspect 9. The compound of any one of Aspects 1-7, wherein R^{8a} is fluoro, or a pharmaceutically acceptable salt thereof.

[000484] Aspect 10. The compound of any one of Aspects 1-9, wherein at least one of R^{1a}, R^{1b} and R^{1c} is a fluoro, or a pharmaceutically acceptable salt thereof.

[000485] Aspect 11. The compound of any one of Aspects 1-10, wherein R^{10a} is hydrogen, or a pharmaceutically acceptable salt thereof.

[000486] Aspect 12. The compound of any one of Aspects 1-10, wherein R^{10a} is fluoro, or a pharmaceutically acceptable salt thereof.

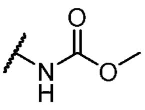
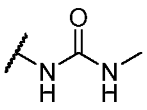
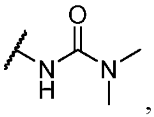
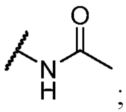
[000487] Aspect 13. The compound of any one of Aspects 1-12, wherein X is X-1, X-9, or X-12, or a pharmaceutically acceptable salt thereof.

[000488] Aspect 14. The compound of any one of Aspects 1-13, wherein X is X-1, or a pharmaceutically acceptable salt thereof.

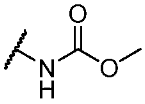
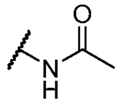
[000489] Aspect 15. The compound of any one of Aspects 1-13, wherein X is X-9, or a pharmaceutically acceptable salt thereof.

[000490] Aspect 16. The compound of any one of Aspects 1-12, wherein X is X-10, or a pharmaceutically acceptable salt thereof.

[000491] Aspect 17. The compound of any one of Aspects 1-13, wherein X is X-12, or a pharmaceutically acceptable salt thereof.

[000492] Aspect 18. The compound of any one of Aspects 1-17, wherein R^3 is , , , or ;

[000493] or a pharmaceutically acceptable salt thereof.

[000494] Aspect 19. The compound of any one of Aspects 1-18, wherein R^3 is  or ;

[000495] or a pharmaceutically acceptable salt thereof.

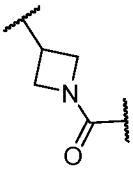
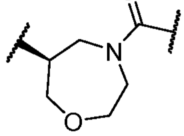
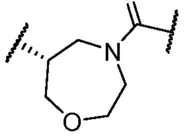
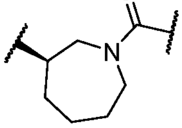
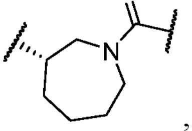
[000496] Aspect 20. The compound of any one of Aspects 1-19, wherein Z^2 is $-C(R^{13a})=C(R^{13b})(R^{13c})$, or a pharmaceutically acceptable salt thereof.

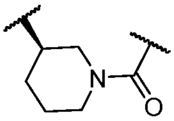
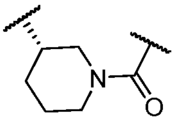
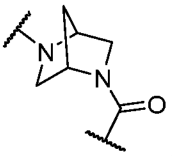
[000497] Aspect 21. The compound of Aspect 20, wherein R^{13a} and R^{13b} are hydrogen and R^{13c} is dimethylaminomethyl, or a pharmaceutically acceptable salt thereof.

[000498] Aspect 22. The compound of Aspect 20, wherein R^{13c} is methyl and R^{13a} and R^{13b} are hydrogen, or a pharmaceutically acceptable salt thereof.

[000499] Aspect 23. The compound of Aspect 20, wherein each of R^{13a}, R^{13b}, and R^{13c} is hydrogen, or a pharmaceutically acceptable salt thereof.

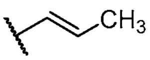
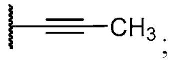
[000500] Aspect 24. The compound of any one of Aspects 1-12 and 18-23, wherein X is selected from the group consisting of:

,
,
,
,
,

,
,
,

[000501] wherein the carbonyl is attached to Z^2, or a pharmaceutically acceptable salt thereof.

[000502] Aspect 25. The compound of any one of 1-19, wherein Z^2 is selected from the group consisting of:

, , and ;

[000503] or a pharmaceutically acceptable salt thereof.

[000504] Aspect 26. The compound of Aspect 1, wherein the compound is any one or more of the compounds of Table 1, or a pharmaceutically acceptable salt thereof.

[000505] Aspect 27. A pharmaceutical composition comprising the compound of any one of Aspects 1-26, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[000506] Aspect 28. A method of treating a patient, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of Aspects 1-26, or a pharmaceutically acceptable salt thereof, wherein the patient has cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

[000507] Aspect 29. The method of Aspect 28, wherein the patient has cancer.

[000508] Aspect 30. The method of Aspect 29, wherein the cancer is any one or more of the cancers of Table 2.

[000509] Aspect 31. The method of Aspect 30, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.

[000510] Aspect 32. The method of any one of Aspects 28-31 further comprising administering a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition.

[000511] Aspect 33. The pharmaceutical composition of Aspect 27 for use in treating cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

[000512] Aspect 34. The pharmaceutical composition of Aspect 33 for use in treating cancer.

[000513] Aspect 35. The pharmaceutical composition of Aspect 34, wherein the cancer is any one or more of the cancers of Table 2.

[000514] Aspect 36. The pharmaceutical composition of Aspect 34, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.

[000515] Aspect 37. A compound of any one of Aspects 1-26, or a pharmaceutically acceptable salt thereof, for use in treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

[000516] Aspect 38. The compound of Aspect 37 for use in treating cancer.

[000517] Aspect 39. The compound of Aspect 38, wherein the cancer is any one or more of the cancers of Table 2.

[000518] Aspect 40. The compound of Aspect 38, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.

[000519] Aspect 41. Use of a compound of any one of Aspect 1-26, or a pharmaceutically acceptable salt 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.

[000520] Aspect 42. The use of Aspect 41 for treatment of cancer.

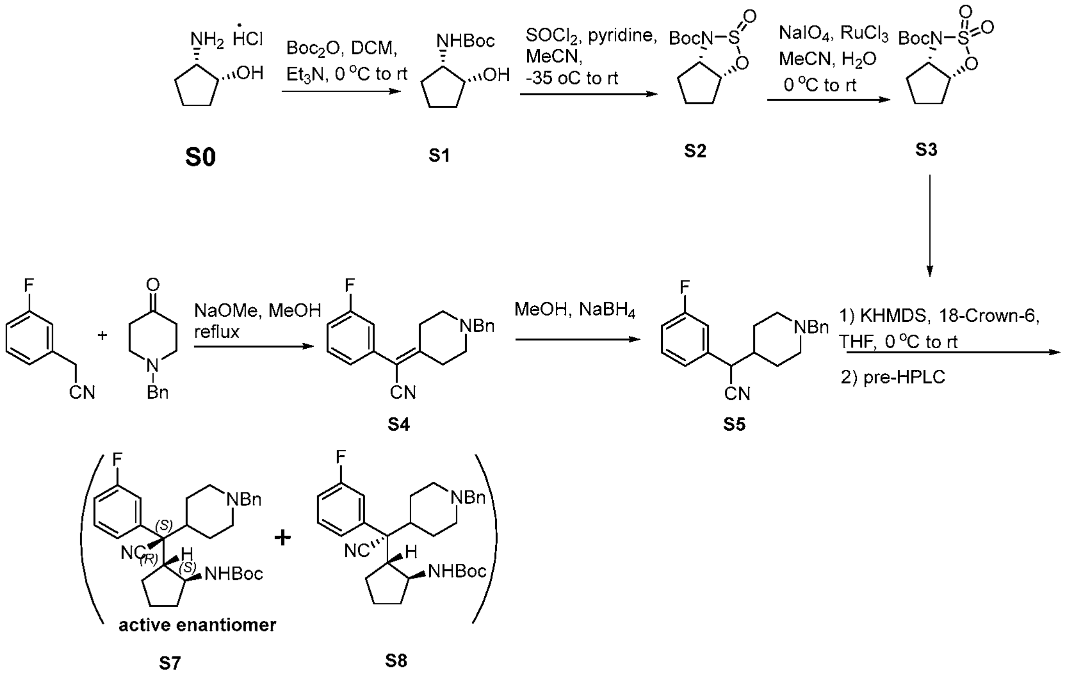
[000521] Aspect 43. The use of Aspect 42, wherein the cancer is any one or more of the cancers of Table 2.

[000522] Aspect 44. The use of Aspect 42, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.

[000523] Examples

[000524] Example 1

[000525] **Synthesis of S7**



[000315] **Synthesis of S1**

[000316] To a solution of (1R,2S)-2-aminocyclopentanol hydrochloride **S0** (11 g, 79.9 mmol) and Boc_2O (20.9 g, 95.9 mmol) in dichloromethane (200 mL) was added dropwise Et_3N (20.9 mL, 119.9 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring overnight, the reaction mixture was washed with saturated brine and the water phase was extracted with dichloromethane twice. The combined organic solvent was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography to give the intermediate **S1** as oil (15.5 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (s, 1H), 4.16 (s, 1H), 3.80 (s, 1H), 2.02-1.95 (m, 1H), 1.93-1.87 (m, 1H), 1.86-1.77 (m, 2H), 1.70-1.65 (m, 1H), 1.59-1.51 (m, 2H), 1.45 (s, 9H).

[000317] **Synthesis of S2**

[000318] To a solution of thionyl chloride (7 mL, 96.3 mmol) in dry acetonitrile (150 mL) was added a solution of the intermediate **S1** (15.5g, 77.0 mmol) in

acetonitrile (150mL) at -35°C. Then, pyridine (18.7 mL, 231 mmol) was added dropwise and the reaction mixture was allowed to slowly warm to room temperature. After stirring overnight, the reaction mixture was concentrated, and water and ethyl acetate were added. The organic layer was separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic solvent was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to produce the intermediate **S2** as oil (18.8 g, 98%). 1H NMR (400 MHz, CDC13) δ 5.74 (t, J = 4.6 Hz, 1H), 4.46 (s, 1H), 2.14-2.09 (m, 1H), 1.90-1.68 (m, 5H), 1.52 (s, 9H).

[000319] **Synthesis of S3**

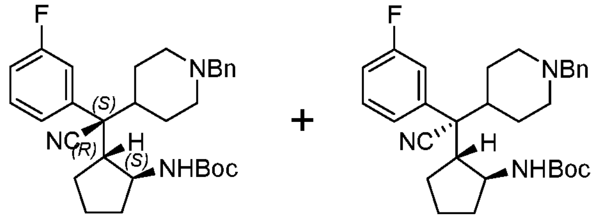
[000320] To a solution of the intermediate **S2** (18.8 g, 76 mmol) in acetonitrile (100 mL) and H_2O (100 mL) was added $NaIO_4$ (24.4 g, 114 mmol) in portions, followed by addition of $RuCl_3.3H_2O$ (315 mg, 1.5 mmol) at 0 °C. The reaction was stirred at room temperature for 2 hours. Then, the aqueous layer was extracted with diethyl ether three times. The combined organic solvent was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to produce the title compound **S3** as a white solid (19 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.18-5.15 (m, 1H), 4.56-4.53 (m, 1H), 2.23-2.18 (m, 1H), 2.06-1.95 (m, 3H), 1.87-1.77 (m, 2H), 1.55 (s, 9H). ESI-MS calculated for $C_{10}H_{17}NO_5S$ $[M + Na]^+ = 286.07$, found: 286.10.

[000321] **Synthesis of S5**

[000322] Sodium methoxide (12 mL, 55.52 mmol of 25% wt in methanol) was added to a solution of 2-(3-fluorophenyl)acetonitrile (5g, 37.01 mmol) in MeOH (50 mL) and stirred briefly. To this solution was added 1-benzylpiperidin-4-one (7.01 g, 37.01 mmol) and reaction was refluxed. After overnight, the solvent was removed, water and EtOAc were added and separated. The aqueous layer was extracted two more times with EtOAc, dried over Na_2SO_4, filtered and concentrated to give **S4** that was used without further purification.

[000323] Crude **S4** (37.01 mmol) was redissolved in MeOH (50 mL) and $NaBH_4$ (4.2 g, 111.03 mmol) was slowly added. After overnight, the reaction was checked by TLC (if the reaction is not complete more $NaBH_4$ was added). After complete conversion of **S4** to **S5**, 8 mL of water was added and the reaction was concentrated then more H_2O and EtOAc were added and separated. The aqueous layer was extracted three times with EtOAc, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (DCM/EtOAc gradient) to produce **S5** as an oil. ^1H NMR (400 MHz, MeOD) δ 7.44-7.38 (m, 1H), 7.32-7.28 (m, 4H), 7.27-7.22 (m, 1H), 7.18-7.16 (m, 1H), 7.13-7.05 (m, 2H), 3.98 (d, J = 7.1 Hz, 1H), 3.48 (s, 2H), 2.96-2.87 (m, 2H), 2.00-1.92 (m, 2H), 1.87-1.80 (m, 1H), 1.79-1.72 (m, 1H), 1.59-1.52 (m, 1H), 1.50-1.39 (m, 2H); ESI-MS calculated for $C_{20}H_{21}FN_2$ $[M + H]^+$ = 309.17, found: 309.16.

[000324] Synthesis of S7 and S8

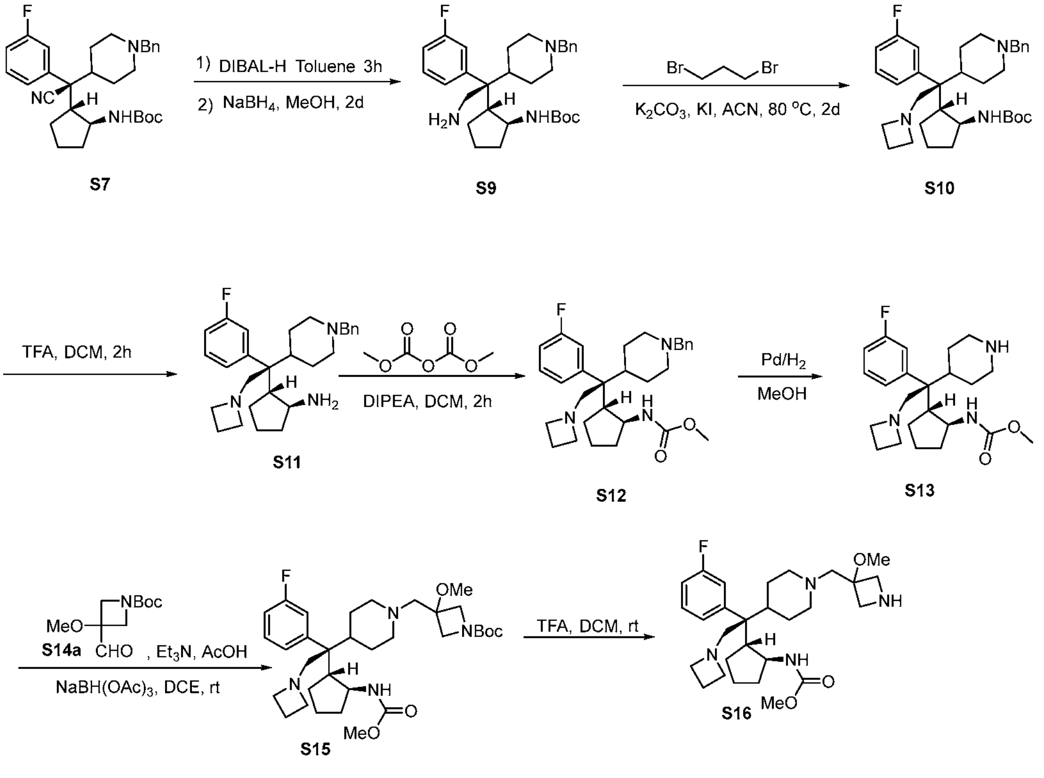


S7 S8

[000325] Compound **S5** (2.18 g, 7.07 mmol), 18-Crown-6 (5.61 g, 21.21 mmol), and compound **S3** (5.58 g, 21.21 mmol) were added to a dry round-bottom flask. Then, the flask was covered with a kimwipe and dried in a desiccator under vacuum for 1-2 days. After the drying step, the flask was removed from the desiccator and quickly capped with a septum. The system was vacuumed and protected under nitrogen atmosphere. The contents in the flask were then dissolved completely with 60 mL of freshly distilled THF. The solution was then briefly vacuumed then put under nitrogen atmosphere (This purging was repeated two more times). The reaction was cooled to 0 °C, KHMDS (0.5M in toluene, 42.4 mL, 21.21 mmol) was added dropwise and then the reaction was allowed to warm to room temperature and stirred overnight. After overnight, a solution of concentrated H_2SO_4 (0.6 mL, 11.31 mmol) in H_2O (10 mL) was added (Note: PH of solution should be < 7) and the solution was vigorously stirred overnight. Then, the reaction mixture was slowly quenched and basified with saturated $NaHCO_3$, extracted with ethyl acetate three times. The combined organic solvent was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatograph to give the mixture of diastereomers in a ratio of 3:2 as a yellow solid (2.5 g, 73%). Then, the diastereomers were separated by reverse phase preparative HPLC to give the enantiopure title compounds **S7** (1.2 g, 36%) and **S8** (0.8 g, 24%) as salts of trifluoroacetic acid, respectively.

[000326] The enantiopure compound **S7** is isolated by recrystallization in a solution of hexane and dichloromethane with a ratio of 4:1. Data for S7: ^{1}H NMR (400 MHz, MeOD) δ 7.44-7.39 (m, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.31-7.22 (m, 6H), 7.11-7.06 (m, 1H), 3.82-3.77 (m, 1H), 3.46 (s, 2H), 2.91 (t, *J* = 12.5 Hz, 2H), 2.81-2.76 (m, 1H), 2.07-1.93 (m, 5H), 1.80-1.72 (m, 1H), 1.62-1.46 (m, 5H), 1.33 (s, 9H), 1.27-1.17 (m, 2H); ESI-MS calculated for $C_{30}H_{38}FN_3O_2$ $[M + H]^+$ = 492.29, found: 492.36. $[\alpha]_D^{20}$ = + 23.1, (c 1.17×10^{-3} g/mL, MeOH); t_R (UPLC) = 4.46 min. Data for **S8:** ^{1}H NMR (400 MHz, MeOD) δ 7.50-7.43 (m, 6H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 9.9 Hz, 1H), 7.14 (t, *J* = 8.3 Hz, 1H), 4.24 (s, 2H), 4.02-3.98 (m, 1H), 3.54-3.45 (m, 2H), 3.08 (t, *J* = 11.4 Hz, 2H), 2.88-2.83 (m, 2H), 2.59 (t, *J* = 11.8 Hz, 1H), 2.25 (d, *J* = 14.0 Hz, 1H), 1.99-1.87 (m, 2H), 1.79-1.74 (m, 1H), 1.67-1.57 (m, 3H), 1.46 (s, 9H), 1.43-1.37 (m, 2H), 1.33-1.18 (m, 1H); ESI-MS calculated for $C_{30}H_{38}FN_3O_2$ $[M + H]^+$ = 492.29, found: 492.36. $[\alpha]_D^{20}$ = + 9.4, (c 1.07×10^{-3} g/mL, MeOH); t_R (UPLC) = 4.63 min.

[000327] Synthesis of **S13** and **S16**



[000328] Synthesis of S9

[000329] S7 (3g, 6.1 mmol) was added to a dry RB-flask, covered with a kimwipe and put in a desiccator that was put under vacuum for 1-2 days. After the vacuuming step, the flask was removed from the desiccator and quickly capped with a septum and the system was vacuumed under N2 atmosphere. Anhydrous toluene (30 ml, Sigma catalog no. 244511) was added to the flask, then was cooled to 0 °C in the ice-bath. Diisobutylaluminiumhydride (25% in toluene, 16.4 mL, 24.4 mmol, 4 eq) was injected into the reaction mixture with syringe slowly at 0 °C with stirring. Then the ice-bath was removed, the reaction was monitored using UPLC-Mass (about 4h). After the mass (492) of **S7** disappeared, 20 ml of NaOH (1M) solution was added slowly into the reaction mixture at 0 °C to quench the reaction. After stirring for 5 min, the ice-bath was removed and additional 20 ml saturated brine was added. Then about 50 mL EA was added, the gel forms. The gel was filtered with celite, and was washed with EA, combine the solvent. The solution was extracted with EA, dichloromethane (DCM) twice respectively. The organic solvent was dried with Na_2SO_4, filtered, and concentrated under rotatory vacuum. Then DCM (50 ml) was added, and concentrated again (repeat twice to remove EA completely).

[000330] Then the residue was redissolved in MeOH (100 mL), $NaBH_4$ (461 mg, 12.2 mmol, 4 eq) was added slowly at 0 °C. After completion of the addition of $NaBH_4$, the reaction mixture was stirred at room temperature while monitoring it using UPLC-Mass (Ultra-Performance Liquid Chromatography- Mass spectrometry) (about 2 days). $NaBH_4$ (1 eq) was added every 12 hour if there is still imine intermediate (mass: 495). After the imine intermediate disappeared, the reaction mixture was concentrated, and diluted with water. The solution was extracted with EA, DCM twice respectively. The organic solvent was dried with Na_2SO_4, filter, and concentrated under rotatory vacuum to give crude product **S9** (mass: 496) without further purification. 1H NMR (400 MHz, MeOD) δ 7.41-7.35 (m, 1H), 7.33-7.23 (m, 6H), 7.18 (d, J = 11.6 Hz, 1H), 6.99-6.95 (m, 1H), 4.07-4.02 (m, 1H), 3.52-3.44 (m, 2H), 3.24 (d, J = 14.4 Hz, 1H), 3.09 (d, J = 14.4 Hz, 1H), 2.98 (d, J = 11.2 Hz, 1H), 2.91 (d, J = 10.8 Hz, 1H), 2.35-2.29 (m, 1H), 2.12-2.04 (m, 2H), 2.01-1.94 (m, 2H), 1.77-1.69 (m, 1H), 1.61-1.58 (m, 1H), 1.54-1.47 (m, 2H), 1.44 (s, 9H), 1.41-1.29 (m, 3H), 1.22-1.14 (m, 2H); ESI-MS calculated for $C_{30}H_{42}FN_3O_2$ [M + H]+ = 496.33, found: 496.48.

[000331] **Synthesis of S10**

[000332] To a solution of the intermediate **S9** (3 g, 6.05 mmol) in acetonitrile (150 mL) was added 1,3-dibromopropane (1.47 g, 0.74 ml, 7.26 mmol, 1.2 eq), K_2CO_3 (2.51 g, 18 mmol, 3 eq) and KI (100 mg, 0.6 mmol, 0.1 eq). The mixture was stirred at 80 °C for 1~2 days. Then, the mixture was filtered with celite to remove the most of

K_2CO_3 solid. The mixture was concentrated, and dissolved in the water, extracted with ethyl acetate and DCM twice respectively, dried over Na_2SO_4, and the solvent was evaporated under vacuum to give crude product **S10** without further purification. 1H NMR (400 MHz, MeOD) δ 7.47-7.40 (m, 6H), 7.16-7.03 (m, 3H), 4.52-4.46 (m, 2H), 4.38-4.31 (m, 1H), 4.19-4.10 (m, 2H), 4.19 (s, 2H), 3.70-3.66 (m, 1H), 3.44-3.40 (m, 3H), 3.01-2.90 (m, 2H), 2.79-2.73 (m, 1H), 2.56-2.46 (m, 1H), 2.42-2.36 (m, 1H), 2.05-1.93 (m, 4H), 1.82-1.73 (m, 2H), 1.68-1.57 (m, 3H), 1.37-1.29 (m, 1H), 1.22 (s, 9H), 1.06-0.98 (m, 1H). ESI-MS calculated for $C_{33}H_{46}FN_3O_2$ [M + H]+ = 536.36, found: 536.44.

[000333] **Synthesis of S11**

[000334] Compound **S10** (2.55 g, 4.76 mmol) was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (10 mL) was added slowly at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was concentrated under vacuum, and redissolved in 100 mL of DCM. Amberlyst® A21 (3g) (resin, Sigma catalog no. 216410) was added and stirred for 30 min to neutralized the TFA. Then, the resin was filtered, and the organic solvent was concentrated to give the crude product **S11** without further purification. ESI-MS calculated for $C_{28}H_{38}FN_3$ [M + H]+ = 436.30, found: 436.32.

[000335] **Synthesis of S12**

[000336] **S11** (2.07 g, 4.75 mmol) was dissolved in dry dichloromethane (50 mL). Then, N, N-diisopropylethylamine (3.31 mL, 19 mmol) and dimethyl dicarbonate (764 mg, 5.7 mmol, 1.2 eq) were added at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was concentrated under vacuum. The residue was purified by reverse phase preparative HPLC to give the title compound **S12** as a salt of trifluoroacetic acid. 1H NMR (400 MHz, MeOD) δ 7.48-7.40 (m, 6H), 7.14-7.10 (m, 2H), 7.02 (d, J = 7.6 Hz, 1H), 4.52-4.47 (m, 2H), 4.38-4.31 (m, 2H), 4.21 (s, 2H), 4.11 (d, J = 15. 6 Hz, 1H), 3.76 (d, J = 15.6 Hz, 1H), 3.46-3.41 (m, 3H), 3.29 (s, 3H), 3.02-2.90 (m, 2H), 2.77-2.71 (m, 1H), 2.55-2.48 (m, 1H), 2.46-2.40 (m, 1H), 2.05-2.02 (m, 2H), 1.99-1.95 (m, 2H), 1.88-1.82 (m, 1H), 1.77-1.73 (m, 1H), 1.69-1.61 (m, 3H), 1.43-1.34 (m, 1H), 1.07-0.97 (m, 1H); ESI-MS calculated for $C_{30}H_{40}FN_3O_2$ [M + H]+ = 494.31, found: 494.45.

[000337] **Synthesis of S13**

[000338] To a solution of the salt of trifluoroacetic acid **S12** (1.6 g, 3.24 mmol) in methanol (50 mL) was added 10% Pd/C (344 mg, 0.1 eq, Sigma catalog no. 205699) under N2 atmosphere. Then, the flask was degassed three times with stirring. Then the mixture was stirred for 2 h at room temperature under hydrogen atmosphere (normal pressure). After the Pd/C catalyst was filtered off, the solvent was removed by rotary evaporation to give the title compound **S13**. 1H NMR (400 MHz, MeOD) δ 7.48-7.43 (m, 1H), 7.16-7.06 (m, 3H), 4.51-4.45 (m, 2H), 4.38-4.27 (m, 2H), 4.10 (d, J = 15.6 Hz, 1H), 3.77 (d, J = 15.2 Hz, 1H), 3.55-3.52 (m, 1H), 3.40-3.33 (m, 2H), 3.31 (s, 3H), 3.01-2.89 (m, 2H), 2.78-2.72 (m, 1H), 2.58-2.48 (m, 1H), 2.46-2.39 (m, 1H), 2.05-1.93 (m, 5H), 1.78-1.70 (m, 1H), 1.68-1.54 (m, 3H), 1.39-1.30 (m, 1H), 1.08-1.02 (m, 1H); ESI-MS calculated for $C_{23}H_{34}FN_3O_2$ [M + H]+ = 404.26, found: 404.42.

[000339] **S13** may be converted to various intermediate compounds that are suitable for preparing some of the claimed compounds (e.g., compounds 27-29 and 35). Groups in other compounds corresponding to **S13** can similarly be prepared by choosing appropriate **S7** starting material. Following a variant of the procedure described below for converting **S13** to **S15**, analogs of **S15** may be prepared. For example, using appropriate **S14**a analogs (in which the group corresponding to R^{10a} is, for example, H, methyl, F, CN, etc.), analogs of **S15** may be prepared.

[000340] **Synthesis of S14a**

[000341] To a solution of DMSO (0.78 mL, 11.0 mmol) in DCM (30 mL) was added $(COCl)_2$ (2.8 mL, 2M in DCM) under an argon atmosphere at -78 °C. After 0.5 h, **S14** (800 mg, 3.68 mmol) was added and the mixture was stirred at -78 °C for 2h. Et_3N (3.1 mL, 22.0 mmol) was then added and the mixture was stirred for another 0.5h before it was quenched with saturated NH_4Cl (aq). The solution was extracted with DCM 3 times. The combined organic solvent was washed with brine and dried with Na_2SO_4, filtered, and concentrated under rotatory vacuum to give crude product **S14**a without further purification.

[000342] **Synthesis of S15**

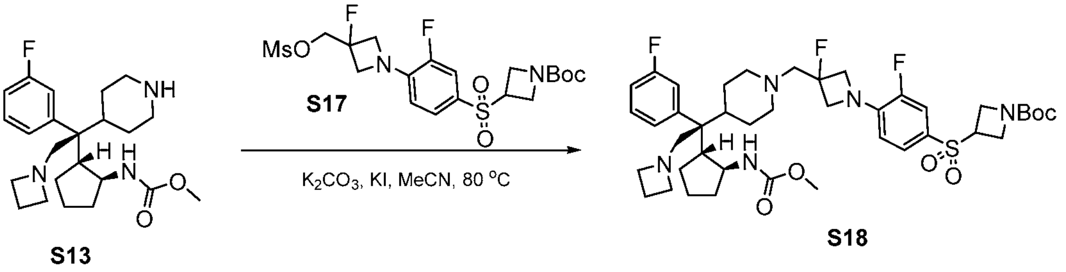
[000343] To a solution of **S13** (1.40 g, 3.48 mmol) in DCE (30 mL) was added Et_3N (1.2 mL, 8.70 mmol), AcOH (0.8 mL, 13.9 mmol) and **S14**a (748 mg, 3.48 mmol) subsequently. After 3h, $NaBH(OAc)_3$ (2.21 g, 10.4 mmol) was added. The mixture was stirred overnight, quenched with water and concentrated under vacuum. The residue was purified by reverse phase preparative HPLC to give the title compound **S15** as a salt of trifluoroacetic acid. 1H NMR (400 MHz, Methanol-d4) δ 7.37 (td, J = 8.4, 6.2 Hz, 1H), 7.10 – 7.01 (m, 2H), 6.97 (d, J = 8.0 Hz, 1H), 4.40 (m, 1H), 4.32 – 4.15 (m, 1H), 4.14 – 3.93 (m, 4H), 3.86 – 3.68 (m, 4H), 3.64 (d, J = 8.0 Hz, 2H), 3.38 (m, 4H), 3.28 – 3.14 (m, 6H), 2.99 (tp, J = 23.5, 11.8, 11.2 Hz, 2H), 2.70 (q, J = 9.1 Hz, 1H), 2.46 (dq, J = 11.5, 9.2 Hz, 1H), 2.34 (m, 1H), 2.00 – 1.83 (m, 4H), 1.78 (d, J = 5.8 Hz, 1H), 1.70 (dt, J = 8.8, 4.4 Hz, 1H), 1.64 – 1.47 (m, 3H), 1.36 (m, 11H). ESI-MS calculated for $C_{33}H_{52}FN_4O_5$ [M + H]+ = 603.39, found: 603.13.

[000344] **Synthesis of S16**

[000345] Compound **S15** (2.20 g, 3.48 mmol) was dissolved in DCM (50 mL), then trifluoroacetic acid (5.0 mL, 73.1 mmol) was added. After stirring for 2 h at rt, the reaction mixture was evaporated to give the crude title product **S16** without further purification.

[000346] Example 2

[000347] Alternatively, **S13** or its analogs may be converted to **S18** or its analogs in accordance with the following scheme:

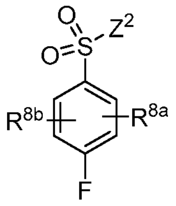


[000348] **Synthesis of S18**

[000349] To a solution of the intermediate **S13** (400 mg, 0.991 mmol) in acetonitrile (5 mL) is added compound **S17** (548 mg, 1.19 mmol), K_2CO_3 (274 mg, 0.198 mmol) and KI (16 mg, 0.099 mmol). The mixture is stirred at 80 °C overnight. Then, the mixture is extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and the solvent is evaporated under vacuum. The residue is purified by reverse phase preparative HPLC to give the trifluoroacetic acid salt of **S18**. **S18** may be used to prepare compound 35.

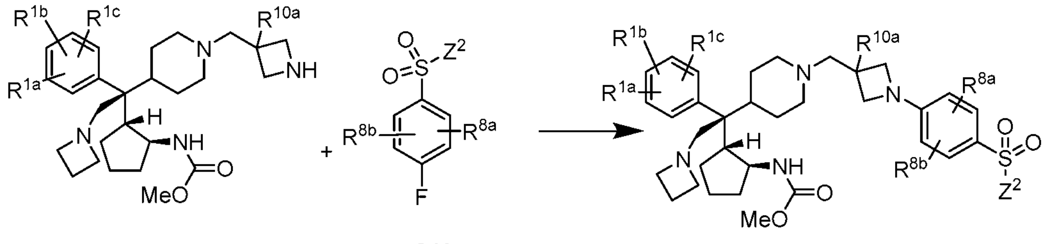
[000350] Example 3

[000351] **S16** or its analogs (in which, for example, the group corresponding to R^{10a} is H, F, cyano, etc.) may be converted to a final product by reacting it with various compounds that can structurally be summarized as:



S19

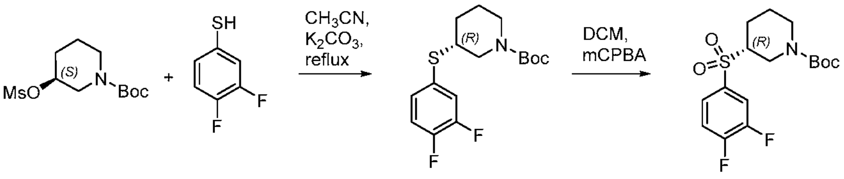
in accordance with the following scheme:



S16a **S19** **S20**

[000352] Various analogs of **S19** compounds may be prepared in accordance with various methods known to those skilled in the art.

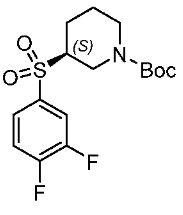
[000353] Synthesis of S19-1



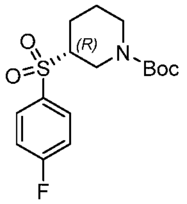
A1 **A2** **A3** **S19-1**

[000354] **A1** (3.63 g, 13.00 mmol) and **A2** (1.58 g, 10.84 mmol) were dissolved in 50 mL of acetonitrile then K_2CO_3 (2.39g, 17.34 mmol) was added and the reaction was refluxed. After overnight, the reaction was cooled, water was added and the solution was extracted three times with ethyl acetate. After column purification, 3.26 g of **A3** was obtained.

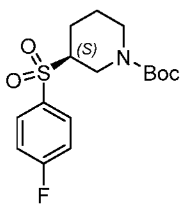
[000355] mCPBA (77% w/w, 1.40g, 6.25 mmol) was added to a cooled solution, 0°C, of **A3** (3.27g, 2.50 mmol) dissolved in 10 mL of DCM. The solution was allowed to warm up to room temperature then after 4 hours it was quenched with saturated $NaHCO_3$ solution and extracted three times with ethyl acetate. After column purification 3.1 g of **S19-1** was obtained.



S19-2



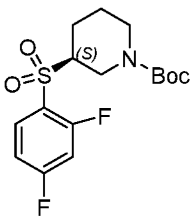
S19-3



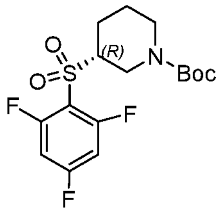
S19-4

[000356] Intermediates **S19-2 to S19-4** were synthesized according to the procedure used to make **S19-1**.

[000357] Intermediates **S20-1** to **S20-2** were also synthesized according to the procedure used to make **S19-1**.

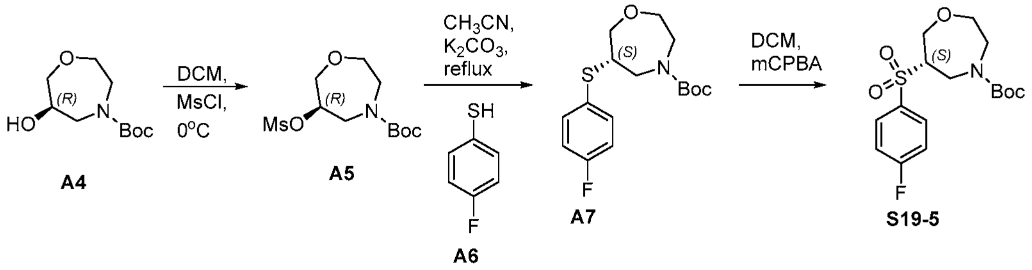


S20-1



S20-2

[000358] **Synthesis of S19-5**

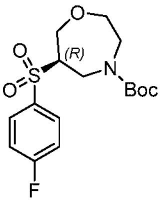


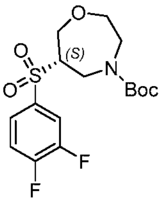
[000359] Methanesulfonyl chloride (213 μL, 2.76 mmol) was added to a cold solution, 0°C, of **A4** (500 mg, 2.30 mmol) and trimethylamine (960 μL, 6.90 mmol) dissolved in 4 mL of DCM. After 1h, water was added and the reaction was extracted three times with DCM, concentrated and purified by column to give 714 mg of **A5**.

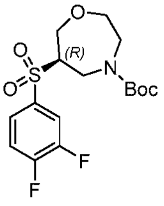
[000360] Potassium carbonate (432 mg, 3.129 mmol) was added to a solution of **A5** (308 mg, 1.18 mmol) and **A6** (267 mg, 2.08 mmol) in 3 mL of acetonitrile and refluxed. After overnight, the reaction was cooled, water was added and the solution was extracted three times with ethyl acetate. After column purification, 307 mg of **A7** was obtained.

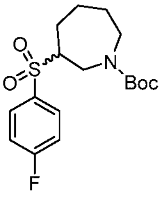
[000361] mCPBA (77% w/w, 526 mg, 2.35 mmol) was added to a cooled solution, 0°C, of **A7** (307 mg, 0.939 mmol) dissolved in 5 mL of DCM. The solution

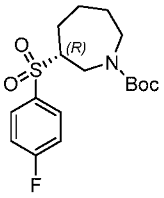
was allowed to warm up to room temperature then after 4 hours it was quenched with saturated NaHCO3 solution and extracted three times with ethyl acetate. After column purification, 305 mg of **S19-5** was obtained.

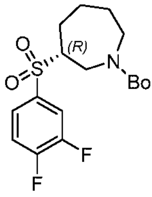

S19-6


S19-7


S19-8

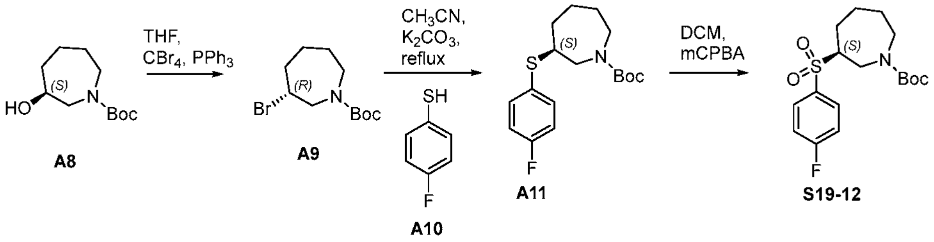

S-19-9


S19-10


S19-11

[000362] Intermediates **S19-6** to **S19-11** were synthesized according to the procedure used to make **S19-5**.

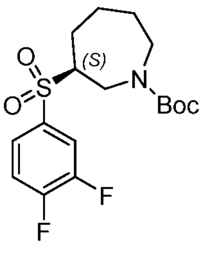
[000363] Synthesis of S19-12



[000364] Triphenyl phosphine (1.83g, 6.967 mmol), and CBr_4 (2.31g, 6.967 mmol) were added to a solution of **A8** (1.0g, 4.645 mmol) in 16 mL of THF. After stirring overnight, the reaction was diluted with water, extracted with diethyl ether, concentrated and purified by column chromatography to yield 588 mg of **A9**.

[000365] Potassium carbonate (436 mg, 3.162 mmol) was added to a solution of **A9** (293 mg, 1.054 mmol) and **A10** (270 mg, 2.108 mmol) in 3 mL of acetonitrile and refluxed. After overnight, the reaction was cooled, water was added and the solution was extracted three times with ethyl acetate. After column purification, 325 mg of **A11** was obtained.

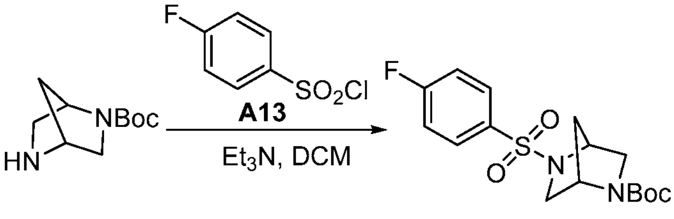
[000366] mCPBA (77% w/w, 559 mg, 2.497 mmol) was added to a cooled solution, 0°C, of **A11** (325mg, 0.999 mmol) dissolved in 5 mL of DCM. The solution was allowed to warm up to room temperature then, after 4 hours, it was quenched with saturated NaHCO3 solution and extracted three times with ethyl acetate. After column purification 303 mg of **S19-12** was obtained.



S19-13

[000367] Intermediate **S19-13** was synthesized according to the procedure used to make **S19-12**.

[000368] **Synthesis of S19-14**

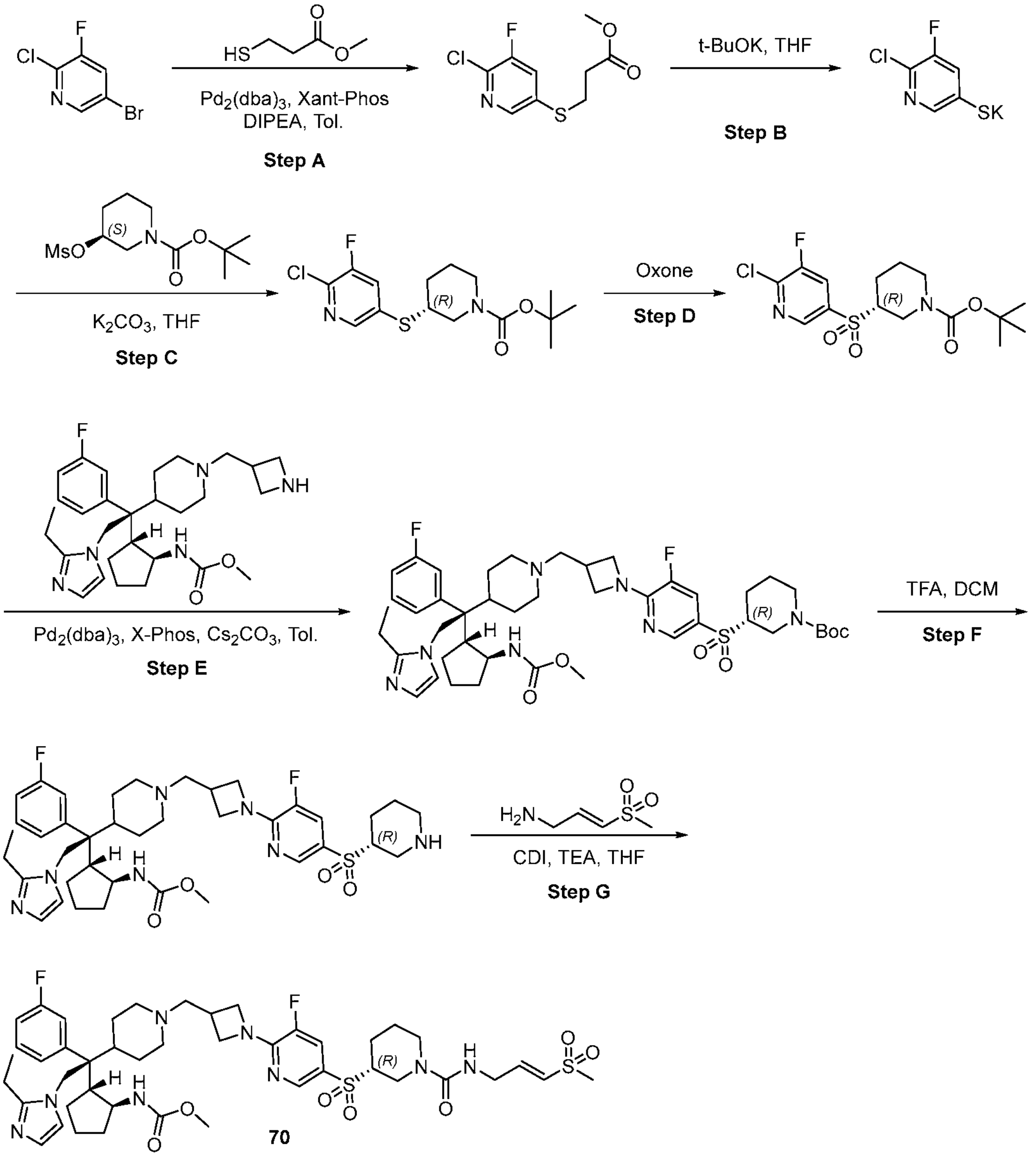


A12 **S19-14**

[000369] (1S,4S)-2-Boc-2,5-diazabicyclo[2.2.1]heptane **A12** (1.0 g, 5.05 mmol) was added to a cold solution, 0°C, of **A13** (1.08 g, 5.55 mmol) and trimethylamine (2.1 mL, 15.2 mmol) dissolved in 40 mL of DCM. After 5h, water was added and the reaction was extracted three times with DCM, concentrated and purified by column to give 1.61 g of **S19-14**.

[000370] Example 4

[000371] Preparation of methyl ((1S,2R)-2-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(1-((1-(3-fluoro-5-(((R)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)piperidin-3-yl)sulfonyl)pyridin-2-yl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate (**Cpd 70**)



70

[000372] **Step A: methyl 3-((6-chloro-5-fluoropyridin-3-yl)thio)propanoate**

[000373] A mixture of 5-bromo-2-chloro-3-fluoropyridine (5.0 g, 23.761 mmol, 1.0 eq.), methyl 3-mercaptopropanoate (2.86 g, 23.761 mmol, 1.0 eq.), $Pd_2(dba)_3$ (1.09 g, 1.188 mmol, 0.05 eq.), XantPhos (0.69 g, 1.19 mmol, 0.05 eq.) and DIPEA (9.20 g, 71.283 mmol, 3.0 eq.) in toluene (25 mL) was at 100°C under N_2 atmosphere for 16h. Then the reaction solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give methyl 3-((6-chloro-5-fluoropyridin-3-yl)thio)propanoate (2.3 g, yield 39%) as a yellow oil. LC-MS: 250 $(M+H)^+$.

[000374] Step B & C: tert-butyl (R)-3-((6-chloro-5-fluoropyridin-3-yl)thio)piperidine-1-carboxylate

[000375] To a solution of methyl 3-((6-chloro-5-fluoropyridin-3-yl)thio)propanoate (1.6 g, 6.408 mmol, 1.0 eq.) in THF (20 mL) was added t-BuOK (1.08 g, 9.612 mmol, 1.5 eq., in 5 mL THF) at -65°C under N_2 atmosphere. Then the reaction mixture was stirred at this temperature for 30 min. Then the reaction mixture was used directly in next step without any further purification. LC-MS: 164 $(M+H)^+$.

[000376] To the above mixture was added tert-butyl (S)-3-((methylsulfonyl)oxy)piperidine-1-carboxylate (2.15 g, 7.690 mmol, 1.2 eq.) and K_2CO_3 (1.77 g, 12.816 mmol, 2.0 eq.). Then the mixture was heated to 80°C for 16 hours under N_2 atmosphere. The reaction mixture was dilute with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give tert-butyl (R)-3-((6-chloro-5-fluoropyridin-3-yl)thio)piperidine-1-carboxylate (1.0 g, yield 45%) as a white solid. LC-MS: 347 $(M+H)^+$.

[000377] Step D: tert-butyl (R)-3-((6-chloro-5-fluoropyridin-3-yl)sulfonyl)piperidine-1-carboxylate

[000378] To a mixture of tert-butyl (R)-3-((6-chloro-5-fluoropyridin-3-yl)thio)piperidine-1-carboxylate (620 mg, 1.787 mmol, 1.0 eq.) in acetone (15 mL) and water (5 mL) was added Oxone (2.74 g, 4.469 mmol, 2.5 eq.) in portions. The mixture was stirred at 25°C for 16h. The reaction mixture was dilute with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give tert-butyl (R)-3-((6-chloro-5-fluoropyridin-3-yl)sulfonyl)piperidine-1-carboxylate (370 mg, yield 55%) as a white solid. LC-MS: 379 $(M+H)^+$.

[000379] Step E: tert-butyl (R)-3-((6-(3-((4-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)ethyl)piperidin-1-yl)methyl)azetidin-1-yl)-5-fluoropyridin-3-yl)sulfonyl)piperidine-1-carboxylate

[000380] A mixture of methyl ((1S,2R)-2-((S)-1-(1-(azetidin-3-ylmethyl)piperidin-4-yl)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)ethyl)

cyclopentyl)carbamate (284 mg, 0.55 mmol, 1.0 eq.), tert-butyl (R)-3-((6-chloro-5-fluoropyridin-3-yl)sulfonyl)piperidine-1-carboxylate (270 mg, 0.72 mmol, 1.3 eq.), $Pd_2(dba)_3$ (10 mg, 0.011 mmol, 0.02 eq.), Xant-Phos (10 mg, 0.021 mmol, 0.04 eq.) and Cs_2CO_3 (538 mg, 1.65 mmol, 3.0 eq.) in toluene (10 mL) was stirred at 100°C under N_2 atmosphere for 16h. The reaction mixture was dilute with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give tert-butyl (R)-3-((6-(3-((4-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)ethyl)piperidin-1-yl)methyl)azetidin-1-yl)-5-fluoropyridin-3-yl)sulfonyl)piperidine-1-carboxylate (150 mg, yield 28%) as a yellow solid. LC-MS: 854 $(M+H)^+$.

[000381] Step F: methyl ((1S,2R)-2-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(1-((1-(3-fluoro-5-(((R)-piperidin-3-yl)sulfonyl)pyridin-2-yl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate

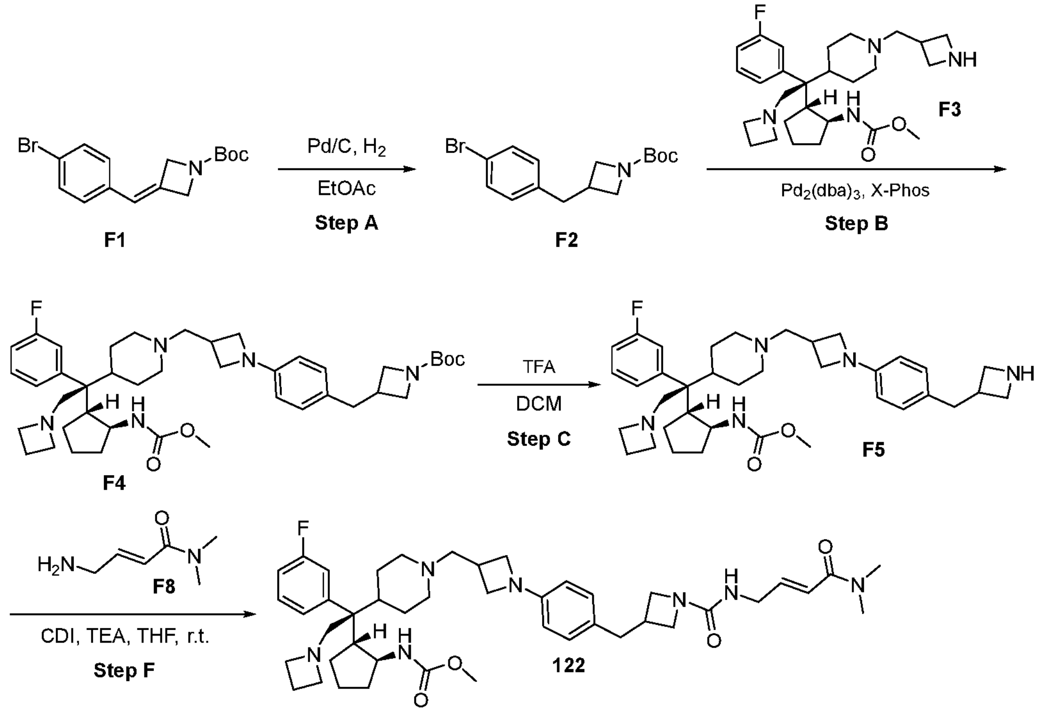
[000382] A solution of tert-butyl (R)-3-((6-(3-((4-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)ethyl) piperidin-1-yl)methyl)azetidin-1-yl)-5-fluoropyridin-3-yl)sulfonyl)piperidine-1-carboxylate (150 mg, 0.176 mmol) and TFA (2 ml) in DCM (6 mL) was stirred at room temperature for 1h. Then the reaction mixture was concentrated under reduced pressure to give methyl ((1S,2R)-2-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(1-((1-(3-fluoro-5-(((R)-piperidin-3-yl)sulfonyl)pyridin-2-yl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate (130 mg, TFA salt) as a yellow oil. LC-MS: 754 $(M+H)^+$.

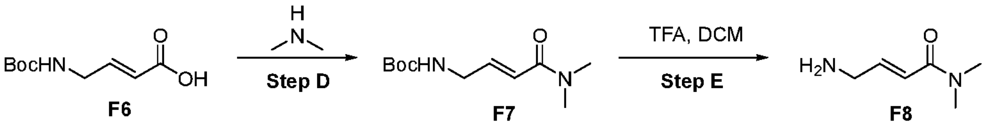
[000383] Step G: methyl ((1S,2R)-2-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(1-((1-(3-fluoro-5-(((R)-1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)piperidin-3-yl)sulfonyl)pyridin-2-yl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate (Cpd 70)

[000384] To a solution (E)-3-(methylsulfonyl)prop-2-en-1-amine (47 mg, 0.345 mmol, 2.0 eq.) in THF (15 mL) was added TEA (0.12 mL, 0.862 mmol, 5.0 eq.) and CDI (67 mg, 0.414 mmol, 2.4 eq.). After stirred at room temperature for 1h, methyl ((1S,2R)-2-((S)-2-(2-ethyl-1H-imidazol-1-yl)-1-(1-((1-(3-fluoro-5-(((R)-piperidin-3-yl)sulfonyl)pyridin-2-yl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl) cyclopentyl)carbamate (130 mg, 0.172 mmol) was added into the above mixture. Then the mixture was stirred at this temperature for 16h. The reaction mixture was dilute with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel and RP-prep-HPLC to give **Cpd 70** (33 mg, yield 21%) as a white solid. LC-MS: 915 $(M+H)^+$. ^1H NMR (400 MHz, MeOD-*d4*) δ 8.28 (d, 1H), 7.67 (dd, 1H), 7.56 - 7.52 (m, 1H), 7.49 - 7.44 (m, 2H), 7.36 (d, 1H), 7.23 - 7.19 (m, 1H), 6.99 (s, 1H), 6.85 (dt, 1H), 6.61 (d, 1H), 4.62 (d, 1H), 4.50 - 4.45 (m, 2H), 4.15 - 4.05 (m, 3H), 4.01 - 3.94 (m, 2H), 3.74 - 3.65 (m, 2H), 3.64 (s, 3H), 3.50 - 3.45 (m, 3H), 3.20 - 3.05 (m, 6H), 2.95 (s, 3H), 2.90 - 2.83 (m, 1H), 2.70 - 2.63 (m, 2H), 2.32 - 2.27 (m, 1H), 2.17 - 2.11 (m, 1H), 2.06 - 2.04 (m, 1H), 1.98 - 1.78 (m, 4H), 1.59 - 1.53 (m, 4H), 1.45 - 1.41 (m, 3H), 1.40 - 1.37 (m, 2H), 1.29 - 1.12 (m, 3H), 1.06 - 0.94 (m, 1H).

[000385] Example 5

[000381] Preparation of methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-((1-(((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamoyl)azetidin-3-yl)methyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate (Cpd 122)





[000382] **Step A: tert-butyl 3-(4-bromobenzyl)azetidine-1-carboxylate**

[000383] A mixture of tert-butyl 3-(4-bromobenzylidene)azetidine-1-carboxylate (F1) (600 mg, 1.851 mmol, 1.0 eq.; Ref : WO2016/30310, 2016, A1 Page 43) and 10% Pd/C (60 mg) in EtOAc (15 mL) was stirred for 2h under H_2 atmosphere (1 atm). The reaction mixture was filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give tert-butyl 3-(4-bromobenzyl)azetidine-1-carboxylate (F2)(500 mg, yield 83%) as a white solid. LC-MS: 326, 328 $(M+H)^+$.

[000384] **Step B: tert-butyl 3-(4-(3-((4-((S)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)ethyl)piperidin-1-yl)methyl)azetidin-1-yl)benzyl)azetidine-1-carboxylate**

[000385] A mixture of methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-(azetidin-3-ylmethyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate (300 mg, 0.635 mmol, 1.0 eq.), tert-butyl 3-(4-bromobenzyl)azetidine-1-carboxylate (412 mg, 1.269 mmol, 2.0 eq.), $Pd_2(dba)_3$ (116 mg, 0.127 mmol, 0.2 eq.), X-Phos (60.54 mg, 0.127 mmol, 0.2 eq.) and Cs_2CO_3 (621 mg, 1.905 mmol, 3.0 eq.) in toluene (15 mL) was stirred at 100 °C under N_2 atmosphere for 16h. Then the reaction mixture was dilute with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel to give tert-butyl 3-(4-(3-((4-((S)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)ethyl)piperidin-1-yl)methyl)azetidin-1-yl)benzyl)azetidine-1-carboxylate (255 mg, yield 56%) as a white oil. LC-MS: 718 $(M+H)^+$.

[000386] **Step C: methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(azetidin-3-ylmethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl) ethyl)cyclopentyl)carbamate**

[000387] To a stirring solution of tert-butyl 3-(4-(3-((4-((S)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-((1R,2S)-2-((methoxycarbonyl)amino)cyclopentyl)ethyl)piperidin-1-yl)methyl)azetidin-1-yl)benzyl)azetidine-1-carboxylate (255 mg, 0.355 mmol) in DCM (10 mL) was added TFA (1 mL). Then the reaction solution was stirred at room temperature for 16h. Then the reaction mixture was dilute with sat. $NaHCO_3$ aq. (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(azetidin-3-ylmethyl)phenyl) azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl) cyclopentyl)carbamate (210 mg, yield 96%) as a yellow oil. LC-MS: 618 $(M+H)^+$.

[000388] **Step D: tert-butyl (E)-(4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate**

[000389] To a mixture of (E)-4-((tert-butoxycarbonyl)amino)but-2-enoic acid (350 mg, 1.739 mmol, 1.0 eq.; Ref: Angewandte Chemie - International Edition; vol. 57; nb. 35; (2018); p. 11193 - 11197), HATU (992 mg, 2.6 mmol, 1.5 eq.), dimethylamine (2.0 M in THF, 1.1 mL, 2.2 mmol, 1.27 eq.) in DCM (15 mL) was added TEA (0.5 mL, 3.479 mmol, 2.0 eq.). The mixture was stirred at 25°C for 16 h. Then the reaction mixture was dilute with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel to give tert-butyl (E)-(4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (100 mg, yield 25%). LC-MS: 229 $(M+H)^+$.

[000390] **Step E: (E)-4-amino-N,N-dimethylbut-2-enamide**

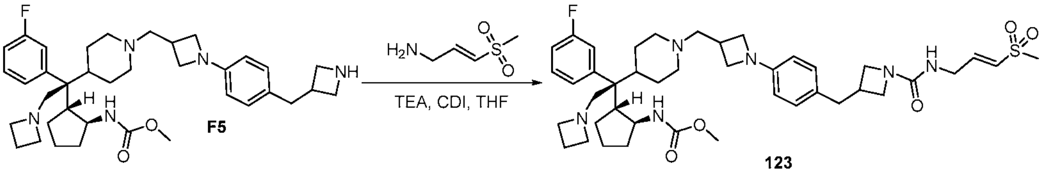
[000391] A mixture of tert-butyl (E)-(4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamate (100 mg, 0.44 mmol) and TFA (0.2 mL) in DCM (5 mL) was stirred at room temperature for 2 h. Then the reaction mixture was concentrated under reduced pressure to give (E)-4-amino-N,N-dimethylbut-2-enamide (130 mg, TFA salt) as a yellow oil. LC-MS: 129 $(M+H)^+$.

[000392] **Step F: methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-((1-(((E)-4-(dimethylamino)-4-oxobut-2-en-1-yl)carbamoyl)azetidin-3-yl)methyl)phenyl) azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl) carbamate (Cpd 122)**

[000393] A solution of (E)-4-amino-N,N-dimethylbut-2-enamide (50 mg, 0.388 mmol, 2.4 eq.), TEA (0.09 mL, 0.648 mmol, 4.0 eq.) and CDI (63 mg, 0.388 mmol, 2.4 eq.) in THF (15 mL) was stirred at room temperature for 1h. Then methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(azetidin-3-ylmethyl)phenyl)azetidin-3-yl)methyl) piperidin-4-yl)-1-(3-fluorophenyl)ethyl)cyclopentyl)carbamate (100 mg, 0.162 mmol, 1.0 eq.) was added to the reaction. After 16h, the reaction mixture was dilute with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel and RP-prep-HPLC to give Cpd 122 (3 mg, yield 2%) as a white solid. LC-MS: 772 $(M+H)^+$. ^1H NMR (400 MHz, MeOD-d_4) δ 7.31 - 7.26 (m, 1H), 7.26 - 7.22 (m, 1H), 7.16 (d, 1H), 7.01 (d, 2H), 6.91 (td, 1H), 6.67 (dt, 1H), 6.45 (dt, 1H), 6.41 (d, 2H), 3.98 - 3.92 (m, 5H), 3.88 (dd, 2H), 3.62 (dd, 2H), 3.47 (s, 3H), 3.41 (dd, 2H), 3.38 - 3.36 (m, 1H), 3.11 (s, 3H), 3.08 - 3.06 (m, 1H), 3.02 - 2.99 (m, 1H), 2.98 (s, 3H), 2.97 - 2.87 (m, 3H), 2.85 - 2.75 (m, 3H), 2.67 - 2.60 (m, 2H), 2.52 (dd, 1H), 2.18 (t, 1H), 2.06 - 1.89 (m, 8H), 1.84 - 1.78 (m, 1H), 1.67 - 1.51 (m, 6H), 0.93 -0.87 (m, 2H).

[000394] Example 6

[000395] **Preparation of methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(3-fluorophenyl)-1-(1-((1-(4-((1-(((E)-3-(methylsulfonyl)allyl)carbamoyl)azetidin-3-yl)methyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)ethyl)cyclopentyl)carbamate (Cpd 123)**



[000396] To a solution of (E)-3-(methylsulfonyl)prop-2-en-1-amine (44 mg, 0.324 mmol, 0.2 eq.) in THF (5 mL) was added TEA (0.1 mL, 0.81 mmol, 5.0 eq.) and CDI (52 mg, 0.32 mmol, 0.2 eq.) at 0°C. The mixture was stirred at room temperature for 1h under N_2 atmosphere. Then methyl ((1S,2R)-2-((S)-2-(azetidin-1-yl)-1-(1-((1-(4-(azetidin-3-ylmethyl)phenyl)azetidin-3-yl)methyl)piperidin-4-yl)-1-(3-fluorophenyl) ethyl)cyclopentyl)carbamate (F5) (100 mg, 0.16 mmol, 1.0 eq.) in THF (5 mL) was added drop-wisely to the above mixture. The mixture was stirred at room temperature for 3h. The reaction mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC and RP-prep-HPLC to give Cpd 123 (2 mg, yield 2%) as a white solid. LC-MS: 779 $(M+H)^+$. ^1H NMR (400 MHz, MeOD-*d4*) δ 7.50 - 7.44 (m, 1H), 7.18 - 7.12 (m, 2H), 7.07 - 7.03 (m, 3H), 6.84 (dt, 1H), 6.58 (dt, 1H), 6.43 (d, 2H), 4.59 - 4.29 (m, 5H), 4.15 (d, 1H), 4.03 - 3.92 (m, 6H), 3.83 - 3.71 (m, 2H), 3.63 (dd, 2H), 3.56 - 3.47 (m, 5H), 3.36 (d, 2H), 3.15 - 3.03 (m, 2H), 3.02 - 2.90 (m, 4H), 2.88 - 2.72 (m, 3H), 2.64 - 2.37 (m, 3H), 2.13 - 1.96 (m, 5H), 1.83 - 1.53 (m, 6H), 1.50 - 1.42 (m, 1H).

[000397] Example 7

[000398] Synthesis and Characterization of Compounds of the Disclosure

[000399] Other Compounds of the Disclosure can be prepared using methods described in preceding Schemes and in the preceding Examples and related methods, *see, e.g.*, WO 2017/192543, WO 2018/183857, WO 2019/191526, WO 2020/072391. The LCMS (ESI) data for representative Compounds of the Disclosure prepared by these methods are provided in Tables 1 and 1A.

[000400] ^1H NMR for additional Compounds of the Disclosure is provided in Table 4.

[000401] Table 4

Cpd No.	**NMR**
58	^{1}H NMR (400 MHz, MeOD-d_4) δ 8.38 (t, 1H), 8.14 - 8.06 (m, 2H), 7.69 (t, 1H), 7.50 - 7.33 (m, 5H), 7.12 (d, 1H), 6.94 (dt, 1H), 6.80 (s, 1H), 6.72 (dd, 2H), 4.61 (d, 2H), 4.45 - 4.33 (m, 3H), 4.24 (dd, 2H), 4.00 - 3.97 (m, 2H), 3.61 (s, 3H), 3.14 - 3.08 (m, 1H), 3.01 - 2.92 (m, 2H), 2.98 (s, 3H), 2.87 - 2.77 (m, 4H), 2.64 - 2.55 (m, 1H), 2.36 - 2.16 (m, 3H), 2.05 (d, 1H), 1.93 - 1.83 (m, 1H), 1.71 (d, 1H), 1.56 - 1.45 (m, 1H), 1.36 - 1.17 (m, 8H), 0.80 - 0.60 (m, 1H)
59	^{1}H NMR (400 MHz, MeOD-d_4) δ 7.59 - 7.41 (m, 4H), 7.38 - 7.28 (m, 2H), 7.24 - 7.16 (m, 1H), 6.95 (d, 1H), 6.85 (dt, 1H), 6.67 - 6.56 (m, 1H), 4.61 - 4.48 (m, 2H), 4.17 - 4.07 (m, 2H), 3.99 - 3.96 (m, 2H), 3.87 - 3.59 (m, 7H), 3.50 - 3.38 (m, 2H), 3.23 - 3.10 (m, 5H), 3.08 - 3.00 (m, 2H), 2.96 (s, 3H), 2.81 - 2.58 (m, 3H), 2.38 -2.30 (m, 1H), 2.17 - 1.79 (m, 6H), 1.79 - 1.48 (m, 4H), 1.47 - 1.27 (m, 7H), 1.25 - 1.14 (m, 2H)
60	^{1}H NMR (400 MHz, MeOD-d_4) δ 7.53 - 7.44 (m, 4H), 7.38 - 7.35 (m, 1H), 7.26 - 7.17 (m, 2H), 7.15 - 6.95 (m, 1H), 6.84 (dt, 1H), 6.65 - 6.57 (m, 2H), 4.80 (d, 1H), 4.62 (d, 1H), 4.32 (t, 2H), 4.15 (d, 1H), 3.98 - 3.87 (m, 5H), 3.75 - 3.66 (m, 2H), 3.64 (s, 3H), 3.49 - 3.42 (m, 3H), 3.14 - 3.06 (m, 4H), 2.97 - 2.95 (m, 4H), 2.70 - 2.63 (m, 2H), 2.32 - 2.26 (m, 1H), 2.14 - 2.01 (m, 3H), 1.91 - 1.72 (m, 4H), 1.59 - 1.50 (m, 3H), 1.44 - 1.28 (m, 9H)
64	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.58 – 7.42 (m, 3H), 7.20 – 7.10 (m, 2H), 7.06 (d, 1H), 6.75 – 6.65 (m, 2H), 6.02 (dt, 1H), 4.58 – 4.46 (m, 2H), 4.42 – 4.18 (m, 9H), 4.14 (d, 1H), 4.04 (t, 1H), 3.98 (t, 1H), 3.89 (dt, 1H), 3.83 – 3.73 (m, 4H), 3.59 (t, 2H), 3.52 – 3.40 (m, 1H), 3.37 (s, 1H), 3.24 – 3.07 (m, 4H), 3.05 – 2.72 (m, 4H), 2.59 – 2.37 (m, 2H), 2.36 – 2.14 (m, 3H), 2.13 – 2.03 (m, 3H), 2.04 – 1.95 (m, 2H), 1.90 – 1.60 (m, 7H), 1.57 – 1.41 (m, 2H), 1.24 – 1.05 (m, 1H)
66	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.58 – 7.43 (m, 3H), 7.20 – 7.10 (m, 2H), 7.05 (d, 1H), 6.79 (dt, 1H), 6.70 (t, 1H), 6.06 (dt, 1H), 4.67 – 4.57 (m, 2H), 4.56 – 4.47 (m, 2H), 4.42 – 4.23 (m, 8H), 4.24 – 4.10 (m, 2H), 3.94 – 3.87 (m, 1H),

	3.82 – 3.68 (m, 5H), 3.59 (t, 2H), 3.52 – 3.40 (m, 1H), 3.37 (s, 1H), 3.23 – 3.04 (m, 4H), 3.01 – 2.73 (m, 3H), 2.60 – 2.27 (m, 3H), 2.12 – 2.03 (m, 3H), 2.04 – 1.95 (m, 2H), 1.93 – 1.72 (m, 4H), 1.72 – 1.60 (m, 3H), 1.56 – 1.43 (m, 2H), 1.22 – 1.05 (m, 1H)
67	^{1}H NMR (400 MHz, MeOD-d_4) δ 7.50 (dd, 1H), 7.43 (dd, 1H), 7.36 (dd, 1H), 7.22 - 7.16 (m, 2H), 7.00 (td, 1H), 6.71 (dt, 1H), 6.61 (t, 1H), 6.46 (d, 1H), 4.31 - 4.27 (m, 2H), 4.20 - 4.13 (m, 1H), 3.94 - 3.82 (m, 5H), 3.71 - 3.61 (m, 8H), 3.49 (s, 3H), 3.27 - 3.22 (m, 4H), 3.15 - 3.08 (m, 6H), 3.00 - 2.94 (m, 1H), 2.59 - 2.41 (m, 3H), 2.14 - 2.04 (m, 6H), 1.87 - 1.74 (m, 5H), 1.67 - 1.42 (m, 8H), 1.35 - 1.25 (m, 2H)
76	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (d, 2H), 7.49 (q, 1H), 7.17 (t, 2H), 7.07 (d, 1H), 6.64 (d, 2H), 6.54 (dd, 1H), 6.18 (dd, 1H), 5.70 (dd, 1H), 4.69 (d, 2H), 4.60 – 4.46 (m, 2H), 4.44 – 4.34 (m, 2H), 4.31 (d, 2H), 4.17 (d, 1H), 4.03 – 3.92 (m, 2H), 3.80 (d, 1H), 3.67 – 3.53 (m, 9H), 3.52 (s, 3H), 3.20 – 3.01 (m, 2H), 2.90 – 2.75 (m, 1H), 2.63 – 2.52 (m, 1H), 2.47 (s, 1H), 2.13 – 1.98 (m, 5H), 1.93 (t, 2H), 1.90 – 1.74 (m, 5H), 1.74 – 1.61 (m, 4H), 1.62 – 1.47 (m, 1H), 1.24 – 1.05 (m, 1H)
80	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.77 – 7.65 (m, 2H), 7.53 – 7.44 (m, 1H), 7.23 – 7.12 (m, 2H), 7.12 – 7.01 (m, 1H), 6.72 – 6.58 (m, 2H), 6.33 – 6.10 (m, 2H), 5.76 – 5.58 (m, 1H), 4.52 (d, 3H), 4.43 – 4.24 (m, 4H), 4.21 – 4.10 (m, 2H), 4.06 (t, 2H), 4.02 – 3.91 (m, 2H), 3.84 – 3.73 (m, 3H), 3.58 (s, 4H), 3.52 (s, 4H), 3.20 – 3.00 (m, 2H), 2.88 – 2.74 (m, 1H), 2.64 – 2.51 (m, 1H), 2.51 – 2.41 (m, 1H), 2.40 – 2.33 (m, 2H), 2.16 – 1.94 (m, 4H), 1.94 – 1.76 (m, 2H), 1.75 – 1.59 (m, 3H), 1.58 – 1.47 (m, 1H), 1.27 – 1.04 (m, 1H)
94	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.70 – 7.63 (m, 2H), 7.50 (q, 1H), 7.22 – 7.13 (m, 2H), 7.08 (d, 1H), 6.65 – 6.57 (m, 2H), 6.38 (dd, 0.5H), 6.30 – 6.22 (m, 1H), 5.82 – 5.74 (m, 1H), 4.97 (dd, 0.5H), 4.77 (dd, 0.5H), 4.62 – 4.44 (m, 2H), 4.42 – 4.32 (m, 3H), 4.29 (d, 2H), 4.17 (d, 1H), 4.08 (dd, 0.5H), 3.94 (t, 3H), 3.89 – 3.70 (m, 3H), 3.66 – 3.55 (m, 5H), 3.55 – 3.43 (m, 4H), 3.23 – 3.01 (m, 3H), 2.90 – 2.68 (m, 4H), 2.61 (dd, 1H), 2.57 – 2.40 (m, 2H), 2.15 – 1.95 (m, 5H), 1.95 – 1.76 (m, 2H), 1.76 – 1.61 (m, 3H), 1.61 – 1.47 (m, 1H), 1.24 – 1.06 (m, 1H)

98	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.70 – 7.64 (m, 2H), 7.54 – 7.45 (m, 1H), 7.22 – 7.13 (m, 2H), 7.08 (d, 1H), 6.65 – 6.57 (m, 2H), 6.38 (dd, 0.5H), 6.30 – 6.25 (m, 1H), 5.81 – 5.74 (m, 1H), 4.97 (dd, 0.5H), 4.77 (dd, 0.5H), 4.62 – 4.47 (m, 2H), 4.44 – 4.32 (m, 3H), 4.31 – 4.25 (m, 2H), 4.17 (d, 1H), 4.08 (dd, 0.5H), 4.00 – 3.90 (m, 3H), 3.89 – 3.71 (m, 3H), 3.65 – 3.55 (m, 5H), 3.52 (d, 4H), 3.21 – 3.01 (m, 3H), 2.90 – 2.68 (m, 3H), 2.61 (dd, 1H), 2.57 – 2.40 (m, 2H), 2.16 – 1.95 (m, 5H), 1.95 – 1.77 (m, 2H), 1.77 – 1.61 (m, 3H), 1.55 (d, 1H), 1.27 – 1.04 (m, 1H)
111	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.73 – 7.68 (m, 2H), 7.50 (q, 1H), 7.18 (t, 2H), 7.08 (d, 1H), 6.67 (dd, 0.5H), 6.63 – 6.57 (m, 2H), 6.42 (dd, 0.5H), 6.22 (ddd, 1H), 5.74 (ddd, 1H), 4.55 (s, 2H), 4.38 (s, 3H), 4.34 – 4.24 (m, 2H), 4.24 – 4.09 (m, 2H), 4.02 – 3.90 (m, 2H), 3.80 (d, 1H), 3.67 – 3.55 (m, 5H), 3.55 – 3.40 (m, 7H), 3.21 – 3.02 (m, 2H), 2.82 (d, 1H), 2.63 – 2.39 (m, 2H), 2.16 – 1.97 (m, 5H), 1.96 – 1.62 (m, 9H), 1.62 – 1.47 (m, 2H), 1.26 – 1.03 (m, 2H)
112	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.74 – 7.68 (m, 2H), 7.50 (q, 1H), 7.23 – 7.13 (m, 2H), 7.11 – 7.04 (m, 1H), 6.67 (dd, 0.5H), 6.63 – 6.57 (m, 1H), 6.42 (dd, 0.5H), 6.22 (ddd, 1H), 5.74 (ddd, 1H), 4.55 (s, 2H), 4.38 (s, 3H), 4.29 (dd, 2H), 4.24 – 4.09 (m, 2H), 4.01 – 3.89 (m, 2H), 3.80 (d, 1H), 3.68 – 3.55 (m, 5H), 3.55 – 3.41 (m, 7H), 3.20 – 3.00 (m, 2H), 2.89 – 2.76 (m, 1H), 2.63 – 2.38 (m, 2H), 2.17 – 1.98 (m, 5H), 1.98 – 1.61 (m, 9H), 1.62 – 1.44 (m, 2H), 1.26 – 1.00 (m, 2H)
114	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.69 (d, 2H), 7.47 (q, 1H), 7.20 – 7.10 (m, 2H), 7.05 (d, 1H), 6.61 (d, 2H), 6.29 – 6.15 (m, 2H), 5.70 (dd, 1H), 4.58 – 4.45 (m, 2H), 4.42 – 4.25 (m, 4H), 4.19 – 4.01 (m, 3H), 3.99 – 3.91 (m, 1H), 3.82 – 3.73 (m, 2H), 3.73 – 3.60 (m, 2H), 3.59 – 3.39 (m, 7H), 3.15 – 2.95 (m, 3H), 2.84 – 2.70 (m, 2H), 2.60 – 2.32 (m, 3H), 2.12 – 1.91 (m, 5H), 1.93 – 1.73 (m, 3H), 1.73 – 1.42 (m, 6H), 1.21 – 1.03 (m, 1H).
116	^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (d, 2H), 7.47 (q, 1H), 7.21 – 7.10 (m, 2H), 7.04 (d, 1H), 6.60 (d, 2H), 6.27 – 6.09 (m, 2H), 5.69 (dd, 1H), 4.66 – 4.58 (m, 1H), 4.58 – 4.46 (m, 2H), 4.41 – 4.31 (m, 2H), 4.29 (d, 1H), 4.27 – 4.18 (m, 1H), 4.18 – 4.10 (m, 2H), 4.00 – 3.88 (m, 3H), 3.81 – 3.73 (m, 2H), 3.65 – 3.58 (m, 1H), 3.56 – 3.51 (m, 2H), 3.50 – 3.49 (m, 2H), 3.47 – 3.40 (m, 2H), 3.12 –

	2.90 (m, 3H), 2.85 – 2.72 (m, 1H), 2.58 – 2.39 (m, 3H), 2.35 – 2.23 (m, 1H), 2.10 – 1.91 (m, 5H), 1.86 – 1.75 (m, 2H), 1.72 – 1.58 (m, 4H), 1.56 – 1.45 (m, 1H), 1.35 – 1.26 (m, 2H), 1.15 – 1.00 (m, 1H)

[000402] Example 8

[000403] **Menin Binding Affinity**

[000404] **Binding Assay 1**

[000405] A fluorescence polarization (FP) competitive binding assay was used to determine the binding affinities of representative menin inhibitors. A FAM labeled fluorescent probe was designed and synthesized based on a MLL1 peptide (FAM-MM2). Equilibrium dissociation constant (K_d) value of FAM-MM2 to menin protein was determined from protein saturation experiments by monitoring the total fluorescence polarization of mixtures composed with the fluorescent probe at a fixed concentration and the protein with increasing concentrations up to full saturation. Serial dilutions of the protein were mixed with FAM-MM2 to a final volume of 200 μl in the assay buffer (PBS with 0.02% Bovine γ-Globulin and 4% DMSO. 0.01% Triton X-100 was added right before assays). Final FAM-MM2 concentration was 2 nM. Plates were incubated at room temperature for 30 minutes with gentle shaking to assure equilibrium. FP values in millipolarization units (mP) were measured using the Infinite M-1000 plate reader (Tecan U.S., Research Triangle Park, NC) in Microfluor 1 96-well, black, v-bottom plates (Thermo Scientific, Waltham, MA) at an excitation wavelength of 485 nm and an emission wavelength of 530 nm. K_d value of FAM-MM2, which was calculated by fitting the sigmoidal dose-dependent FP increases as a function of protein concentrations using Graphpad Prism 6.0 software (Graphpad Software, San Diego, CA), was determined as 1.4 nM.

[000406] The IC_{50} of representative Compounds of the Disclosure were determined in a competitive binding experiment. Mixtures of 5 μl of the tested compounds in DMSO and 195 μl of preincubated protein/probe complex solution in the assay buffer were added into assay plates which were incubated at room temperature for 30 minutes with gentle shaking. Final concentration of the menin protein was 4 nM, and final probe concentration is 2 nM. Negative controls containing protein/probe complex only (equivalent to 0% inhibition), and positive controls containing only free probes (equivalent to 100% inhibition), were included in each assay plate. FP values were measured as described above. IC_{50} values were determined by nonlinear regression fitting of the competition curves.

[000407] **Binding Assay 2**

[000408] Compound binding potency was also measured by fluorescence-based polarization ligand displacement assay using one probe, 36, against recombinant menin protein, as described in Zhou (2013) with the following adaptations. *See* Zhou, et al., Structure-Based Design of High-Affinity Macrocyclic Peptidomimetics to Block the Menin-Mixed Lineage Leukemia 1 (MLL1) Protein–Protein Interaction. J. Med. Chem., 2013; 56(3):1113-23. All compounds were prepared as 10 mM stock solutions in DMSO.

[000409] For assay of compounds using probe 36, binding studies were conducted in buffer containing 100 mM potassium phosphate, pH 7.5; 100 ug/ml bovine gamma globulin, 0.02% sodium azide, 0.005% Triton X-100, and 2% DMSO. A 10-point dose response curve of compound was first added to the wells, followed by buffer solution containing 90 nM recombinant menin protein and 6 nM probe 36. The system was allowed to equilibrate for 60 minutes in the dark at room temperature, and then the FP signal was read at Ex480/Em530. The FP signal data was fit to four-parameter dose equation to allow the extraction of IC50 data.

[000410] Specific compounds disclosed herein were tested in the foregoing binding assays, and they were determined have an IC50 as set forth in Table 5. The abbreviation (NT) represents not tested.

[000411] Table 5

Cpd No.	Binding Assay 1 IC_{50} (μM)	Binding Assay 2 IC_{50} (μM)
1	0.0035	NT
2	0.0032	NT
3	0.0031	NT
4	0.0038	NT
5	0.0029	0.031
6	0.0028	0.035
7	0.0050	0.047
8	0.0023	0.044
9	0.0036	0.045
10	0.006	0.046
11	0.024	0.082

Cpd No.	Binding Assay 1 IC$_{50}$ (µM)	Binding Assay 2 IC$_{50}$ (µM)
12	0.005	0.023 0.045 0.087 0.041 0.057
13	0.004	0.043
14	0.003	0.029
15	0.004	0.044
16	0.005	0.039
17	0.004	0.044
18	0.005	NT
19	0.007	NT
20	0.0024	0.068
21	0.0023	NT
22	0.0025	NT
23	0.002	0.033
24	0.002	0.043
25	0.002	0.035
26	0.002	0.038
27	0.003	0.026
28	0.004	0.015 0.041 0.042
29	0.004	0.043
30	0.004	0.043
31	0.002	NT
32	0.004	NT
33	0.004	NT
34	0.003	NT
35	0.001	NT
36	0.002	NT
37	0.003	0.047
38	0.003	0.034
39	0.002	0.034
40	0.006	0.027
41	0.005	0.040
42	0.003	NT
43	0.004	0.019
44	0.001	NT
45	0.005	NT
46	0.003	NT
47	0.004	NT
48	0.002	NT
49	0.004	NT
50	0.004	NT
51	0.004	NT

Cpd No.	Binding Assay 1 IC$_{50}$ (µM)	Binding Assay 2 IC$_{50}$ (µM)
52	0.003	NT
53	0.004	NT
54	0.004	NT
55	0.003	NT
56	0.002	NT
57	0.001	NT
58	NT	0.034
59	NT	0.038
60	NT	0.034
61	0.003	NT
62	0.001	NT
64	0.003	0.038
65	0.003	0.023
66	0.003	0.021
67	NT	0.050
70	NT	0.029
71	0.007	NT
72	0.033	NT
73	0.032	NT
74	0.001	NT
75	0.001	NT
76	0.004	NT
77	0.005	NT
78	0.004	NT
79	0.003	NT
80	0.003	NT
81	0.003	0.023 0.047 0.045 0.045 0.030
82	0.005	0.030
83	0.003	0.026
84	0.004	NT
85	0.012	NT
86	0.004	NT
87	0.005	NT
88	0.006	NT
89	0.005	NT
90	0.005	NT
91	0.004	NT
92	0.004	NT
93	0.004	NT
94	0.004	NT
95	0.005	NT

Cpd No.	Binding Assay 1 IC_{50} (μM)	Binding Assay 2 IC_{50} (μM)
96	0.004	NT
97	0.006	NT
98	0.005	0.060
99	0.001	NT
100	0.020	NT
101	0.01	0.044
102	0.006	0.045
103	0.005	NT
104	0.005	0.042 0.030 0.039 0.053
105	0.005	NT
106	0.015	NT
107	0.093	NT
108	0.006	0.036
109	0.032	NT
110	0.009	NT
111	0.005	NT
112	0.003	0.023
113	0.003	NT
114	0.006	NT
115	0.005	NT
116	0.001	NT
117	0.003	NT
118	0.007	NT
119	0.006	NT
120	0.006	NT
121	0.003	NT
122	NT	0.147
123	NT	NT

[000412] Example 9

[000413] **Cell Growth Inhibition**

[000414] **Procedure 1**

[000415] The effect of representative Compounds of the Disclosure on cell viability was determined in a 4-day or 7-day proliferation assay. Cells were maintained in the appropriate culture medium with 10% FBS at 37°C and an atmosphere of 5% CO_2.

[000416] Cells were seeded in 96-well flat bottom (Corning COSTAR, Corning, NY, cat# 3595) at a density of 2,000-3,000 cells/well in 100 μl of culture medium.

Compounds were serially diluted in the appropriate medium, and 100 μl of the diluted compounds were added to the appropriate wells of the cell plate. After the addition of compounds, the cells were incubated at 37°C in an atmosphere of 5% CO_2 for 4 or 7 days. In the 7-day assays, cell viability was determined using the WST (2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt) Cell Counting-8 Kit (Dojindo Molecular Technologies, Inc., Rockville, MD) according to the manufacturers' instructions. In the 4-day assays, cell viability was determined using the CellTiter-Glo® Luminescent Cell Viability reagent according to the manufacturers' instructions.

[000417] The cell viability reagent was added to each well at a final concentration of 10% (v/v), and then the plates were incubated at 37°C for 1-2 hours for color development. The absorbance was measured at 450 nm using a SPECTRAmax PLUS plate reader (Molecular Devices, Sunnyvale, CA). The readings were normalized to the DMSO-treated cells and the half maximal inhibitory concentration (IC_{50}) was calculated by nonlinear regression (four parameters sigmoid fitted with variable slope, least squares fit, and no constraint) analysis using the GraphPad Prism 5 software (GraphPad Software, La Jolla, CA).

[000418] **Procedure 2**

[000419] The effect of representative Compounds of the Disclosure on cell viability was determined in a 4-day or 7-day proliferation assay. Cells were maintained in the appropriate culture medium with 10% FBS at 37°C and an atmosphere of 5% CO2.

[000420] Cells were seeded in 96-well flat bottom (Corning COSTAR, Corning, NY, cat# 3903) at a density of 4,000-7,500 cells/well in 50 μl of culture medium. Compounds were serially diluted in the appropriate medium, and 50 μl of the diluted compounds were added to the appropriate wells of the cell plate. After the addition of compounds, the cells were incubated at 37°C in an atmosphere of 5% CO2 for 4 or 7 days. Cell viability was determined using the CellTiter-Glo® Luminescent Cell Viability reagent according to the manufacturers' instructions.

[000421] CellTiter-Glo® Luminescent Cell Viability reagent was added to each well and incubated for 10 minutes on an orbital shaker at room temperature. The luminescence signal was measured using EnSpire® plate reader (PerkinElmer, Waltham, MA) The readings were normalized to the DMSO-treated cells and the half maximal inhibitory concentration (IC50) was calculated by nonlinear regression (four parameters sigmoid fitted with variable slope, least squares fit, and no constraint) analysis using the GraphPad Prism 5 software (GraphPad Software, La Jolla, CA).

[000422] Specific compounds disclosed herein were tested in the foregoing assays and they were determined to inhibit cellular proliferation with an IC50 as set forth in Table 6. The abbreviation (NT) represents not tested.

[000423] Table 6

Cpd No.	**Procedure 1 IC_{50} in cell growth inhibition (nM)**		**Procedure 2 IC_{50} in cell growth inhibition (nM)**	
	MV4-11	**MOLM13**	**MV4-11**	**MOLM13**
1	<100	<500	NT	NT
2	<100	<500	NT	NT
3	<50	<100	NT	NT
4	<100	<500	NT	NT
5	<10	<10	<50	<100
6	<10	<10	<50	<100
7	<10	<50	<100	<500
8	<10	<10	<50	<500
9	<10	<10	<50	<500
10	<50	<500	NT	NT
11	<1000	<1000	NT	NT
12	<10	<10	<50	<500
13	<10	<10	<50	<100
14	<10	<10	NT	NT
15	<10	<10	<50	<100
16	<10	<10	NT	NT
17	<10	<10	<50	<500
18	<10	<10	NT	NT
19	<50	<100	NT	NT
20	<50	<500	<50	<500 No fit
21	<10	<50	<50	<500
22	<100	<500	NT	NT
23	<100	<500	<500	No fit
24	<50	<500	<500	>1000
25	<50	<100	<100	No fit
26	<50	<500	<500	No fit
27	<50	<50	<500	<1000
28	<50	<50	<50	<50
29	<50	<50	<50	<500

Cpd No.	**Procedure 1 IC$_{50}$ in cell growth inhibition (nM)**		**Procedure 2 IC$_{50}$ in cell growth inhibition (nM)**	
30	<50	<50	<50	<100
31	<50	<50	NT	NT
32	<50	<50	NT	NT
33	<50	<50	NT	NT
34	<50	<50	NT	NT
35	<50	<50	NT	NT
36	<50	<50	NT	NT
37	<50	<50	NT	NT
38	<10	<50	<50	<50
39	<10	<10	<50	<50
40	<50	<100	NT	NT
41	<50	<100	<100	<500
42	<10	<10	NT	NT
43	<10	<10	<50	<500
44	<10	<10	NT	NT
45	<10	<50	NT	NT
46	<50	<100	NT	NT
47	<100	<100	NT	NT
48	<10	<10	NT	NT
49	<50	<500	NT	NT
50	<100	<500	NT	NT
51	<100	<1000	NT	NT
52	<50	<50	NT	NT
53	<500	<500	NT	NT
54	<50	<500	NT	NT
55	<100	<500	NT	NT
56	<10	<50	NT	NT
57	<50	<100	NT	NT
58	NT	NT	<50	<500
59	NT	NT	<100	>1000
60	NT	NT	<100	<1000
61	<50 (7d)	<100 (7d)	NT	NT
62	<10	<50	NT	NT
64	<500	<500	NT	NT
65	<500	<1000	NT	NT
66	<100	<500	NT	NT
67	NT	NT	<500	>1000
70	NT	NT	<100	<1000
71	<100 (7d)	<500 (7d)	NT	NT
72	NT	NT	NT	NT
73	NT	NT	NT	NT

Cpd No.	**Procedure 1 IC$_{50}$ in cell growth inhibition (nM)**		**Procedure 2 IC$_{50}$ in cell growth inhibition (nM)**	
74	<50 (7d)	<100 (7d)	NT	NT
75	<50 (7d)	<500 (7d)	NT	NT
76	<100 (7d)	<500 (7d)	NT	NT
77	<500 (7d)	<500 (7d)	NT	NT
78	<100 (7d)	<500 (7d)	NT	NT
79	<100 (7d)	<100 (7d)	NT	NT
80	<50 (7d)	<50 (7d)	NT	NT
81	<50 (7d)	<50 (7d)	<100	<500
82	<50 (7d)	<50 (7d)	NT	NT
83	<50 (7d)	<100 (7d)	NT	NT
84	<50 (7d)	<100 (7d)	NT	NT
85	<50 (7d)	<50 (7d)	NT	NT
86	<10 (7d)	<50 (7d)	NT	NT
87	<50 (7d)	<50 (7d)	NT	NT
88	<100 (7d)	<500 (7d)	NT	NT
89	<100 (7d)	<100 (7d)	NT	NT
90	<50 (7d)	<100 (7d)	NT	NT
91	<100 (7d)	<500 (7d)	NT	NT
92	<500 (7d)	<500 (7d)	NT	NT
93	<100 (7d)	<500 (7d)	NT	NT
94	<500 (7d)	<500 (7d)	NT	NT
95	<100 (7d)	<500 (7d)	NT	NT

Cpd No.	**Procedure 1 IC$_{50}$ in cell growth inhibition (nM)**		**Procedure 2 IC$_{50}$ in cell growth inhibition (nM)**	
96	<10 (7d)	<50 (7d)	NT	NT
97	<10 (7d)	<10 (7d)	NT	NT
98	<10 (7d)	<50 (7d)	<100	<500
99	<10 (7d)	<10 (7d)	NT	NT
100	NT	NT	NT	NT
101	NT	NT	NT	NT
102	<500 (7d)	<1000 (7d)	NT	NT
103	<50 (7d)	<50 (7d)	NT	NT
104	<50 (7d)	<50 (7d)	NT	NT
105	<500 (7d)	<500 (7d)	NT	NT
106	<50 (7d)	<500 (7d)	NT	NT
107	<500 (7d)	<1000 (7d)	NT	NT
108	<50 (7d)	<100 (7d)	NT	NT
109	NT	NT	NT	NT
110	<50	<10	NT	NT
111	<50 (7d)	<50 (7d)	NT	NT
112	<50 (7d)	<100 (7d)	NT	NT
113	<100 (7d)	<500 (7d)	NT	NT
114	<10 (7d)	<50 (7d)	NT	NT
115	<50 (7d)	<500 (7d)	NT	NT
116	<10 (7d)	<50 (7d)	NT	NT
117	<50 (7d)	<500 (7d)	NT	NT
118	<50 (7d)	<500 (7d)	NT	NT
119	<50 (7d)	<500 (7d)	NT	NT
120	<500	>1000	NT	NT

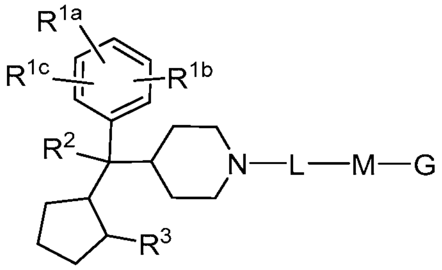
Cpd No.	**Procedure 1 IC_{50} in cell growth inhibition (nM)**		**Procedure 2 IC_{50} in cell growth inhibition (nM)**	
121	<500	>1000	NT	NT
122	NT	NT	>1000	>1000
123	NT	NT	<100	<1000

[000424] Having now fully described the methods, compounds, and compositions of matter provided herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof.

[000425] All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

What is Claimed Is:

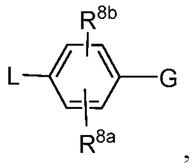
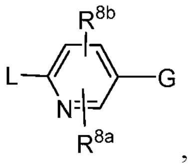
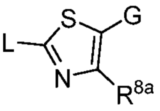
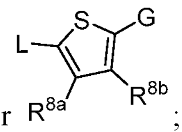
1. A compound having Formula **Ia**,



Ia

or a pharmaceutically acceptable salt thereof, wherein

L-M-G is

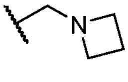
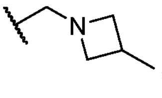
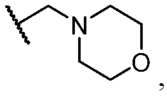
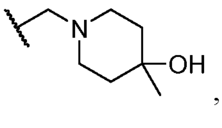
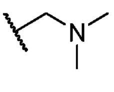
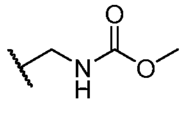
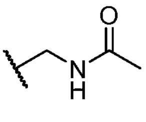
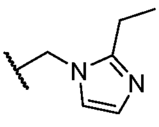
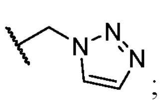
,
,
, or
;

M-1 M-2 M-3 M-4

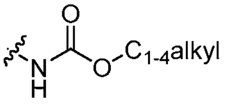
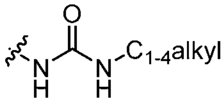
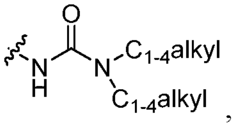
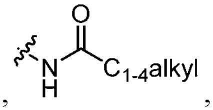
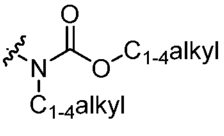
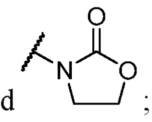
R^{1a}, R^{1b}, and R^{1c} are each independently selected from the group consisting of hydrogen and halo;

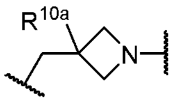
G is $-SO_2-X-Z^2$ or $-CH_2-X-Z^2$;

R^2 is selected from the group consisting of:

,
,
,
,
,
,
,
, and
;

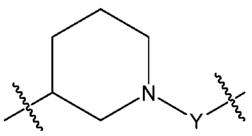
R^3 is selected from the group consisting of:

,
,
,
,
, and
;

L is , wherein the nitrogen atom of L is attached to the M;

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

X is selected from the group consisting of:



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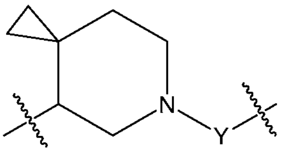

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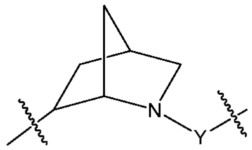

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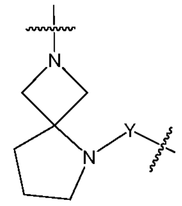

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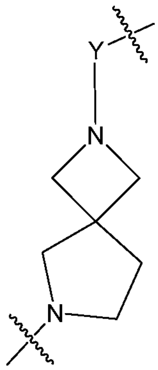

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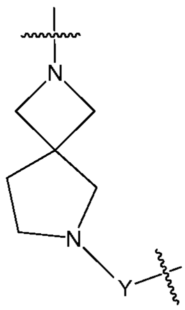

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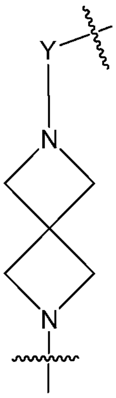
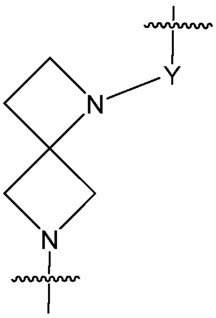
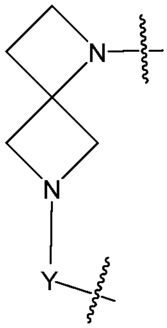


X-26 ,



X-27 ,



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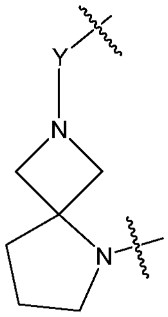

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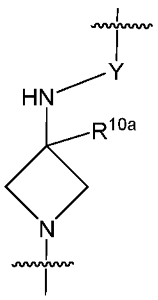

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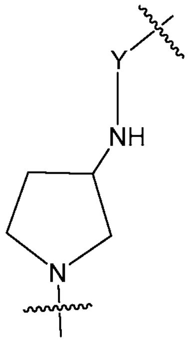

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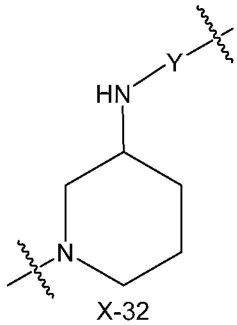

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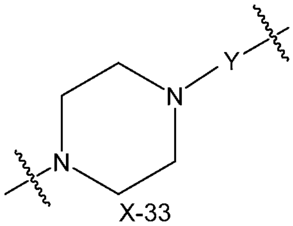

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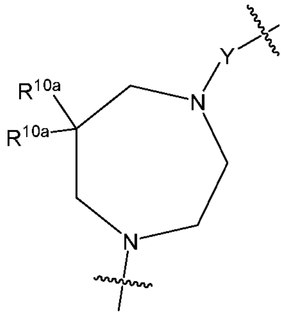

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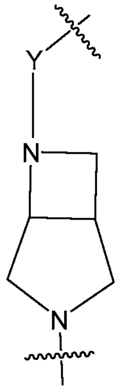

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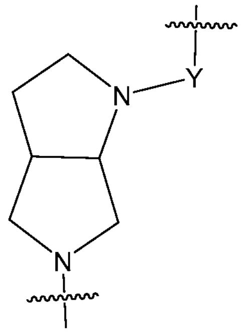
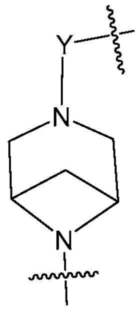
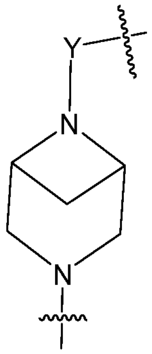


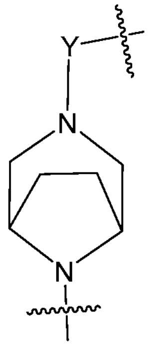
X-36 ,



X-37 ,



X-38 ,



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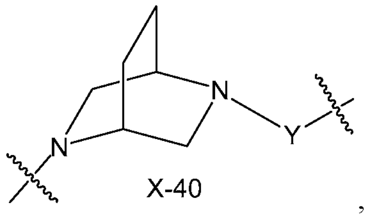
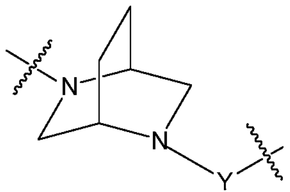


X-40 ,



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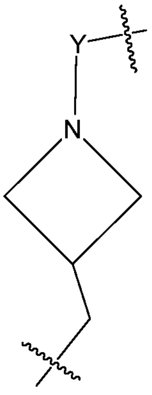
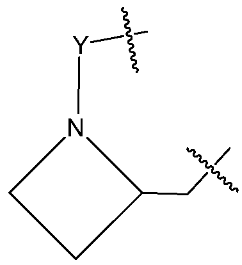
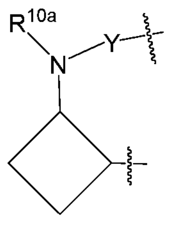


X-42 ,



X-43 ,



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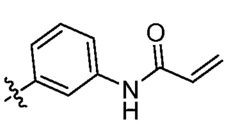
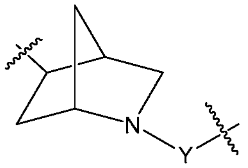
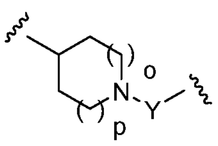


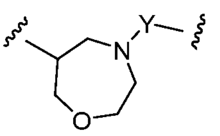
X-45 ,



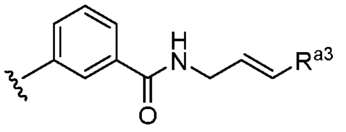
X-46



X-1 ,

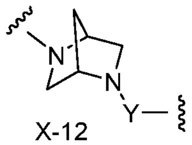


X-9 ,



X-10

, and



X-12 ;

wherein Y is attached to Z^2;

Y is -C(=O)- ;

o and p are each independently 0, 1, 2, or 3;

Z^2 is selected from the group consisting of $-C(R^{13a})=C(R^{13b})(R^{13c})$, $-C \equiv CR^{13d}$, and R^{a4}, Z^2 is absent when X is X-10 or when X is X-45;

R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen, $-SO_2-C_1-C_6$ alkyl and halo;

R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and di-C_1-C_6 alkylaminoC_1-C_4 alkyl;

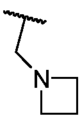
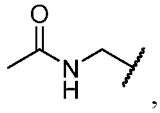
R^{a3} is selected from the group consisting of C_1-C_6 alkoxycarbonyl-, heterocyclyl-carbonyl-, halo-substituted heterocyclyl-carbonyl-, C_1-C_6 alkylamide and C_1-C_6 alkylsulfonyl;

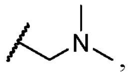
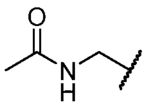
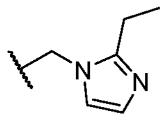
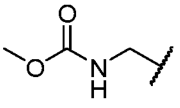
R^{a4} is -N(H)CH_2CH=CH-R^{a5}; and

R^{a5} is selected from the group consisting of C_1-C_6 alkoxycarbonyl-, heterocyclyl-carbonyl-, halo-substituted heterocyclyl-carbonyl-, C_1-C_6 alkylamide and C_1-C_6 alkylsulfonyl;

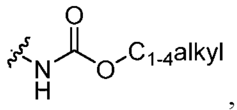
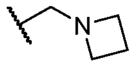
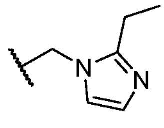
provided:

when X is X-1, o and p are each 0, and Z^2 is $C(R^{13a})=C(R^{13b})(R^{13c})$, then none of R^{13a}, R^{13b} and R^{13c} is dimethylaminomethyl;

when X is X-1 or X-20, R^{10a} is hydrogen, F, OH, methyl or methoxy, Z^2 is $-C\equiv CR^{13d}$, and R^2 is  or , then R^{13d} is not hydrogen or methyl;

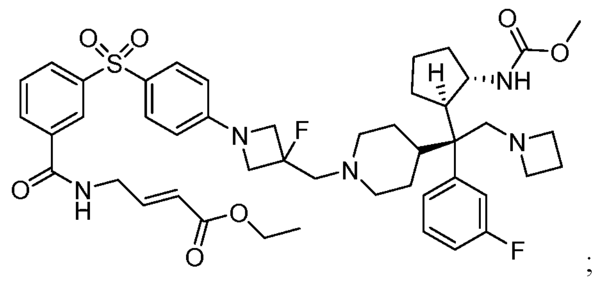
when X is X-1 or X-20, Z^2 is $CH=CH_2$, and R^2 is , , , , or , then R^{10a} is not hydrogen, F, OH, fluoromethyl, methyl or methoxy;

when X is X-9 and Z^2 is $CH=CH_2$, then R^{10a} is not hydrogen, F, or methyl;

when X is X-45 and R^3 is , then R^2 is not  or ;

and

the compound of formula (I) is not



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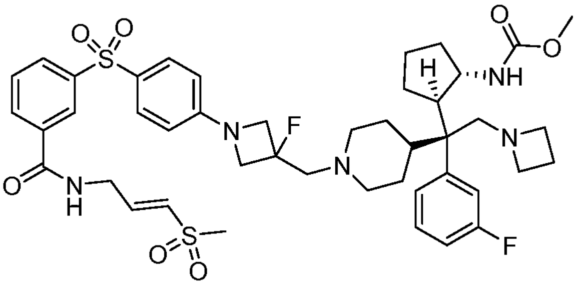

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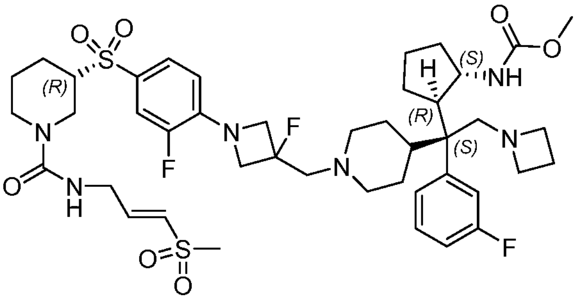

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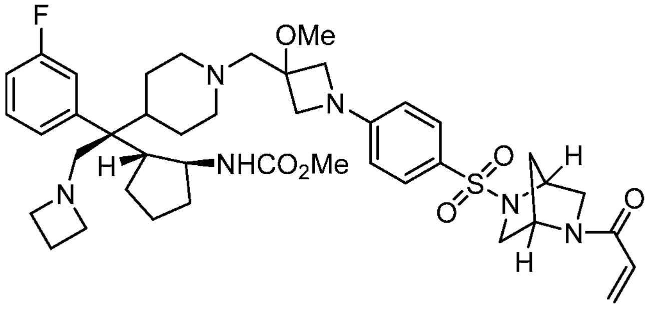
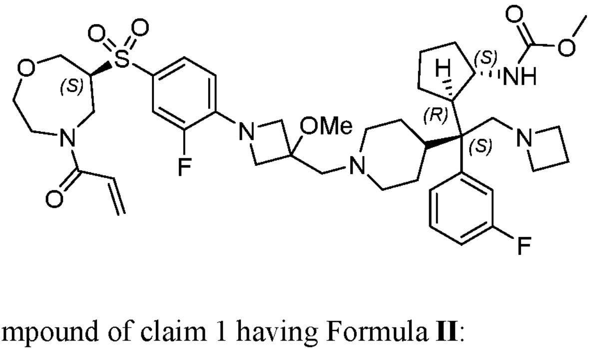
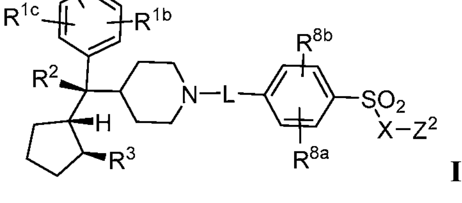


; or



.

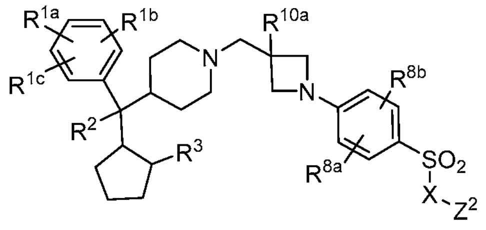
2. The compound of claim 1 having Formula **II**:



II,

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 having Formula **XI**

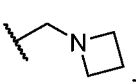
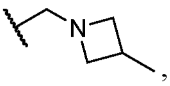
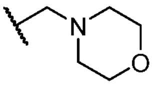
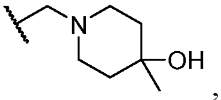
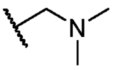
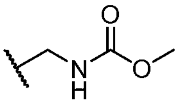


XI.

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1 to 3, wherein:

R^2 is selected from the group consisting of:


, 
, 
, 
, 
, 
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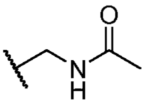
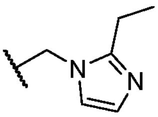
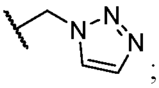
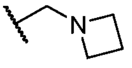

, 
, and 
;

R^{10a} is selected from the group consisting of hydrogen, fluoro, cyano, methyl, methoxy, ethoxy, and hydroxy;

Z^2 is selected from the group consisting of $-C(R^{13a})=C(R^{13b})(R^{13c})$, and $-C\equiv CR^{13d}$;

R^{8a} and R^{8b} are independently selected from the group consisting of hydrogen and fluoro; and

R^{13a}, R^{13b}, R^{13c}, and R^{13d} are each independently selected from the group consisting of hydrogen, methyl, and dimethylaminomethyl.

5. The compound of any one of claims 1-4, wherein R^2 is 
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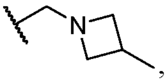
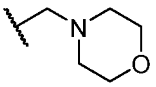
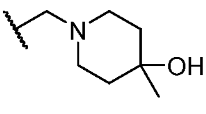
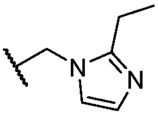
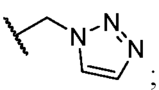
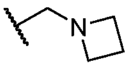

, 
, 
, 
, or 
;

or a pharmaceutically acceptable salt thereof.

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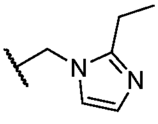
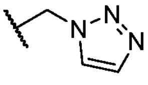
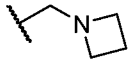

, or

;

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein R^2 is .

8. The compound of any one of claims 1-7, wherein R^{8a} and R^{8b} are hydrogen, or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1-7, wherein R^{8a} is fluoro, or a pharmaceutically acceptable salt thereof.

10. The compound of any one of claims 1-9, wherein at least one of R^{1a}, R^{1b} and R^{1c} is a fluoro, or a pharmaceutically acceptable salt thereof.

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

12. The compound of any one of claims 1-10, wherein R^{10a} is fluoro, or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 1-12, wherein X is X-1, X-9, or X-12, or a pharmaceutically acceptable salt thereof.

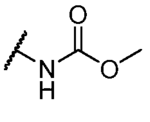
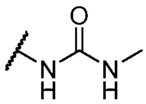
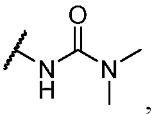
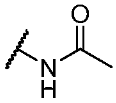
14. The compound of any one of claims 1-13, wherein X is X-1, or a pharmaceutically acceptable salt thereof.

15. The compound of any one of claims 1-13, wherein X is X-9, or a pharmaceutically acceptable salt thereof.

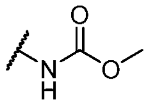
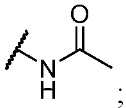
16. The compound of any one of claims 1-12, wherein X is X-10, or a pharmaceutically acceptable salt thereof.

17. The compound of any one of claims 1-13, wherein X is X-12, or a pharmaceutically acceptable salt thereof.

18. The compound of any one of claims 1-10, wherein X is X-21, X-22, X-23, X-24, X-25, X-26, X-27, X-28, X-29, X-30, X-31, X-32, X-33, X-34, X-35, X-36, X-37, X-38, X-39, X-40, X-41, X-42, X-43, X-44, or X-46.

19. The compound of any one of claims 1-18, wherein R^3 is , , , or ;

or a pharmaceutically acceptable salt thereof.

20. The compound of any one of claims 1-19, wherein R^3 is  or ;

or a pharmaceutically acceptable salt thereof.

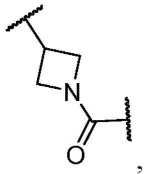
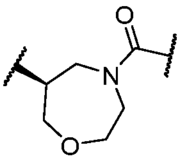
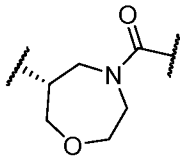
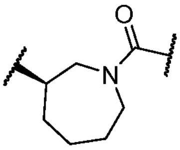
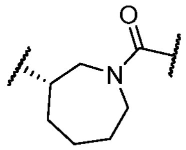
21. The compound of any one of claims 1-20, wherein Z^2 is -C(R^{13a})=C(R^{13b})(R^{13c}), or a pharmaceutically acceptable salt thereof.

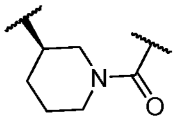
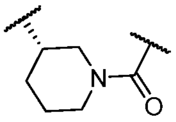
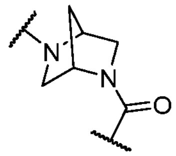
22. The compound of claim 21, wherein R^{13a} and R^{13b} are hydrogen and R^{13c} is dimethylaminomethyl, or a pharmaceutically acceptable salt thereof.

23. The compound of claim 21, wherein R^{13c} is methyl and R^{13a} and R^{13b} are hydrogen, or a pharmaceutically acceptable salt thereof.

24. The compound of claim 21, wherein each of R^{13a}, R^{13b}, and R^{13c} is hydrogen, or a pharmaceutically acceptable salt thereof.

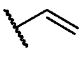
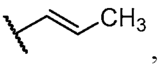
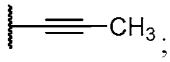
25. The compound of any one of claims 1-12 and 19-24, wherein X is selected from the group consisting of:

,
,
,
,
,

,
,
,

wherein the carbonyl is attached to Z^2, or a pharmaceutically acceptable salt thereof.

26. The compound of any one of claims 1-20, wherein Z^2 is selected from the group consisting of:

, , and ;

or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1, wherein the compound is any one or more of the compounds of Table 1, or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1, wherein the compound is any one or more of the compounds of Table 1A, or a pharmaceutically salt thereof.

29. A pharmaceutical composition comprising the compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30. A method of treating a patient, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein the patient has cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

31. The method of claim 30, wherein the patient has cancer.

32. The method of claim 31, wherein the cancer is any one or more of the cancers of Table 2.

33. The method of claim 32, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.

34. The method of any one of claims 30-32 further comprising administering a therapeutically effective amount of a second therapeutic agent useful in the treatment of the disease or condition.

35. The pharmaceutical composition of claim 29 for use in treating cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

36. The pharmaceutical composition of claim 35 for use in treating cancer.

37. The pharmaceutical composition of claim 36, wherein the cancer is any one or more of the cancers of Table 2.

38. The pharmaceutical composition of claim 36, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.

39. A compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, for use in treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

40. The compound of claim 39 for use in treating cancer.

41. The compound of claim 40, wherein the cancer is any one or more of the cancers of Table 2.

42. The compound of claim 40, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.

43. Use of a compound of any one of claims 1-28, or a pharmaceutically acceptable salt 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.

44. The use of claim 43 for treatment of cancer.

45. The use of claim 44, wherein the cancer is any one or more of the cancers of Table 2.

46. The use of claim 44, wherein the cancer is selected from the group consisting of acute monocytic leukemia, acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, and mixed lineage leukemia.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2020/053186

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 C07D413/14 C07D487/04 C07D487/08 A61P35/00
C07D487/10 A61K31/4427

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/183857 A1 (UNIV MICHIGAN REGENTS [US]) 4 October 2018 (2018-10-04) cited in the application paragraph [0001]; claims 1,34,37 -----	1-46
A	WO 2017/192543 A1 (UNIV MICHIGAN [US]) 9 November 2017 (2017-11-09) cited in the application paragraph [0001]; claim 71 -----	1-46

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 12 November 2020	Date of mailing of the international search report 02/02/2021
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Johnson, Claire

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/053186

Box No. II **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

7(completely); 1-6, 8-46(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 7(completely); 1-6, 8-46(partially)

   Compounds of formula Ia wherein R2 is a methylene group substituted by a substituted N atom, wherein said N atom is not part of a heteroaryl group.

   \-\-\-

2. claims: 1-6, 8-46(all partially)

   Compounds of formula Ia wherein R2 is a methylene group substituted by a 2-ethylimidazole ring.

   \-\-\-

3. claims: 1-6, 8-46(all partially)

   Compounds of formula Ia wherein R2 is a methylene group substituted by a triazole ring.

   \-\-\-

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANGELO AGUILAR ET AL: "Structure-Based Discovery of M-89 as a Highly Potent Inhibitor of the Menin-Mixed Lineage Leukemia (Menin-MLL) Protein-Protein Interaction", JOURNAL OF MEDICINAL CHEMISTRY, vol. 62, no. 13, 11 July 2019 (2019-07-11), pages 6015-6034, XP055644111, ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.9b00021 figure 1; table 3	1-46
X,P	WO 2020/072391 A1 (UNIV MICHIGAN REGENTS [US]; AGIOS PHARMACEUTICALS INC [US]) 9 April 2020 (2020-04-09) cited in the application paragraph [0003]; claim 1; table 1.1	1-46
X,P	WO 2019/191526 A1 (UNIV MICHIGAN REGENTS [US]) 3 October 2019 (2019-10-03) cited in the application paragraph [0001]; claim 1; tables 1A-1C	1-46
X,P	SHILIN XU ET AL: "Discovery of M-808 as a Highly Potent, Covalent, Small-Molecule Inhibitor of the Menin-MLL Interaction with Strong In Vivo Antitumor Activity", JOURNAL OF MEDICINAL CHEMISTRY, vol. 63, no. 9, 27 April 2020 (2020-04-27), pages 4997-5010, XP055749739, ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.0c00547 table 1	1-46

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/053186

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EA 201992320 A1	22-04-2020
		EP 3600313 A1	05-02-2020
		JP 2020515571 A	28-05-2020
		KR 20190133224 A	02-12-2019
		SG 11201909083U A	30-10-2019
		US 2020022953 A1	23-01-2020
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		EP 3774731 A1	17-02-2021
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		WO 2019191526 A1	03-10-2019