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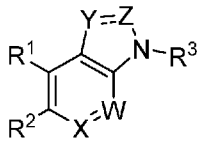
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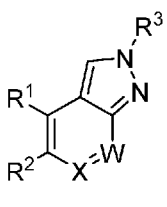
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(54) Title: PYRROLO[2,3-C]PYRIDINES AND RELATED ANALOGS AS LSD-1 INHIBITORS



I

or



II

(57) Abstract: The present disclosure provides compounds represented by Formula I and II: and the pharmaceutically acceptable salts and solvates thereof, wherein R^1, R^2, R^3, X, W, Y, and Z are as defined as set forth in the specification. The present disclosure also provides compounds of Formula I and II for use to treat a condition or disorder responsive to LSD1 inhibition such as cancer.

PYRROLO[2,3-C]PYRIDINES AND RELATED ANALOGS AS LSD-1 INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides lysine specific demethylase-1 inhibitors and therapeutic methods of treating conditions and diseases, e.g., cancer, wherein inhibition of lysine specific demethylase-1 provides a benefit.

Background

[0002] Overexpression of lysine specific demethylase-1 (LSD1 or LSD-1) is observed bladder cancer, non-small cell lung cancer (NSCLC), breast cancer, ovary cancer, glioma, colorectal cancer, sarcoma, neuroblastoma, prostate cancer, esophageal squamous cell carcinoma, papillary thyroid carcinoma, and other cancers. Overexpression of LSD1 is also associated with clinically aggressive cancers such as recurrent prostate cancer, NSCLC, glioma, breast, colon cancer, ovary cancer, esophageal squamous cell carcinoma, and neuroblastoma. Knockdown of LSD1 expression or treatment with small molecular LSD1 inhibitors results in decreased cancer cell proliferation and/or induction of apoptosis. *See, e.g.,* Hayami *et al., Int J Cancer 128*:574-86 (2011); Lv *et al., PLoS One 7*:e35065 (2012); Serce *et al., BMC Clin Pathol 12*:13 (2012); Lim *et al., Carcinogenesis 31*:512-20 (2010); Konovalov and Garcia-Bassets, *J Ovarian Res 6*:75 (2013); Sareddy *et al., Oncotarget 4*:18-28 (2013); Ding *et al., Br J Cancer 109*:994-1003 (2013); Bennani-Baiti *et al., Hum Pathol 43*:1300-7 (2012); Schulte *et al., Cancer Res 69*:2065-71 (2009); Crea *et al., Mol Cancer 11*:52 (2012); Suikki *et al., Prostate 70*:889-98 (2010); Yu *et al., Biochem Biophys Res Commun,. 437*:192-8 (2013); and Kong *et al., Rom J Morphol Embryol,. 54*:499-503 (2013).

[0003] LSD1 inhibitors are being developed for the treatment of cancer and other diseases. For example, small molecule inhibitors of LSD1 are disclosed in US Patent Appl. Publication Nos. 2015/0225394, 2015/0225375, 2015/0225401, 2015/0225379, 2016/0009720, 2016/0009711, 2016/0009712, and 2016/0009721. There is a need in the art for new LSD1-inhibiting molecules.

BRIEF SUMMARY OF THE INVENTION

[0004] In one aspect, the present disclosure provides compounds represented by any one of Formulae **I-VII** or **VIII**, below, and the pharmaceutically acceptable salts and solvates, e.g., hydrates, thereof, collectively referred to as "Compounds of the Disclosure." Compounds of the Disclosure are LSD1 inhibitors or synthetic intermediates used to make LSD1 inhibitors. LSD1 inhibitors are useful in treating or preventing diseases or conditions such as cancer wherein LSD1 inhibition provides a benefit.

[0005] In another aspect, the present disclosure provides methods of treating or preventing a condition or disease by administering a therapeutically effective amount of a Compound of the Disclosure to a subject, e.g., a human patient, in need thereof. The disease or condition of interest treatable or preventable by inhibition of LSD1 is, for example, a cancer, 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 in 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 may reduce the proliferation of unwanted cells by inducing apoptosis in those cells.

[0006] In another aspect, the present disclosure provides a method of inhibiting LSD1 in a subject, comprising administering to the subject a therapeutically effective amount of at least one Compound of the Disclosure.

[0007] In another aspect, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier.

[0008] 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 or preventing diseases or conditions wherein inhibition of LSD1 provides a benefit, e.g., cancer.

[0009] 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.

[0010] In another aspect, the present disclosure provides a Compound of the Disclosure for use in treatment or prevention of a disease or condition of interest, e.g., cancer.

[0011] 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.

[0012] 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.

[0013] In another aspect, the present disclosure provides methods of preparing Compounds of the Disclosure.

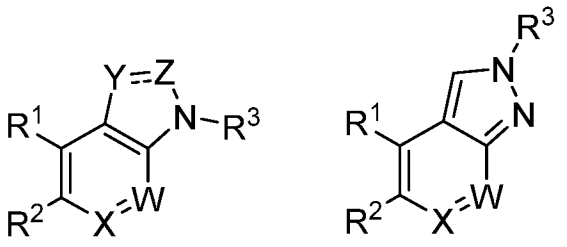
[0014] Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0015] 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

[0016] Compounds of the Disclosure are inhibitors of LSD1.

[0017] In one embodiment, Compounds of the Disclosure are compounds represented by Formulae **I** or **II**:



I or **II** ,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0018] R^1 is selected from the group consisting of halo, optionally substituted C_6-C_{14} aryl, and optionally substituted 5- to 14-membered heteroaryl;

[0019] R^2 is selected from the group consisting of hydrogen, halo, optionally substituted C_6-C_{14} aryl, and optionally substituted 5- to 14-membered heteroaryl;

[0020] R^3 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted 4- to 8-membered heterocyclo, (amino)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl;

[0021] X is selected from the group consisting of $=C(R^{6a})-$ and $=N-$;

[0022] W is selected from the group consisting of $=C(R^{6b})-$ and $=N-$;

[0023] ⎓ is a single or double bond;

[0024] Y is selected from the group consisting of $=C(R^{4a})-$ and $=N-$ when ⎓ is a double bond;

[0025] Y is $-C(H)R^{4b}-$ when ⎓ is a single bond;

[0026] Z is selected from the group consisting of $=C(R^5)-$ and $=N-$ when ⎓ is a double bond;

[0027] Z is $-C(=O)-$ when ⎓ is a single bond;

[0028] R^{4a} is selected from the group consisting of hydrogen, halo, and C_{1-6} alkyl;

[0029] R^{4b} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

[0030] R^5 is selected from the group consisting of hydrogen and C_{1-6} alkyl;

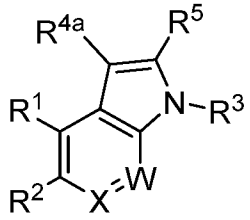
[0031] R^{6a} is selected from the group consisting of hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy; and

[0032] R^{6b} is selected from the group consisting of hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

[0033] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **I**, or a pharmaceutically acceptable salt or solvate thereof.

[0034] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **II**, or a pharmaceutically acceptable salt or solvate thereof.

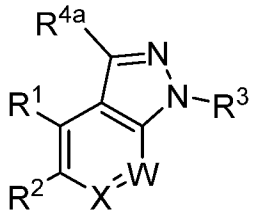
[0035] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **III**:



III,

or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2, R^3, R^{4a}, R^5, X, and W are as defined in connection with Formulae **I** or **II**.

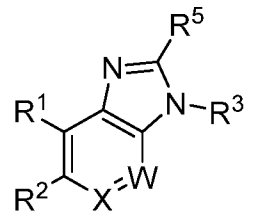
[0036] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **IV**:



IV,

or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2, R^3, R^{4a}, X, and W are as defined in connection with Formulae **I** or **II**.

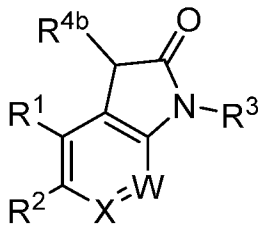
[0037] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **V**:



V,

or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2, R^3, R^5, X, and W are as defined in connection with Formulae **I** or **II**.

[0038] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **VI**:



VI,

or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2, R^3, R^{4b}, X, and W are as defined in connection with Formulae **I** or **II**.

[0039] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, or a pharmaceutically acceptable salt or solvate thereof, wherein X is =N- and W is =C(H)-.

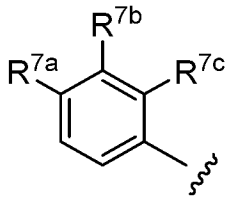
[0040] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, or a pharmaceutically acceptable salt or solvate thereof, wherein X is =C(H)- and W is =N-.

[0041] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halo.

[0042] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is halo.

[0043] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halo, R^2 is halo, and R^3 is selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted 4- to 8-membered heterocyclo, (amino)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In another embodiment, R^3 is selected from the group consisting of (amino)alkyl and (heterocyclo)alkyl.

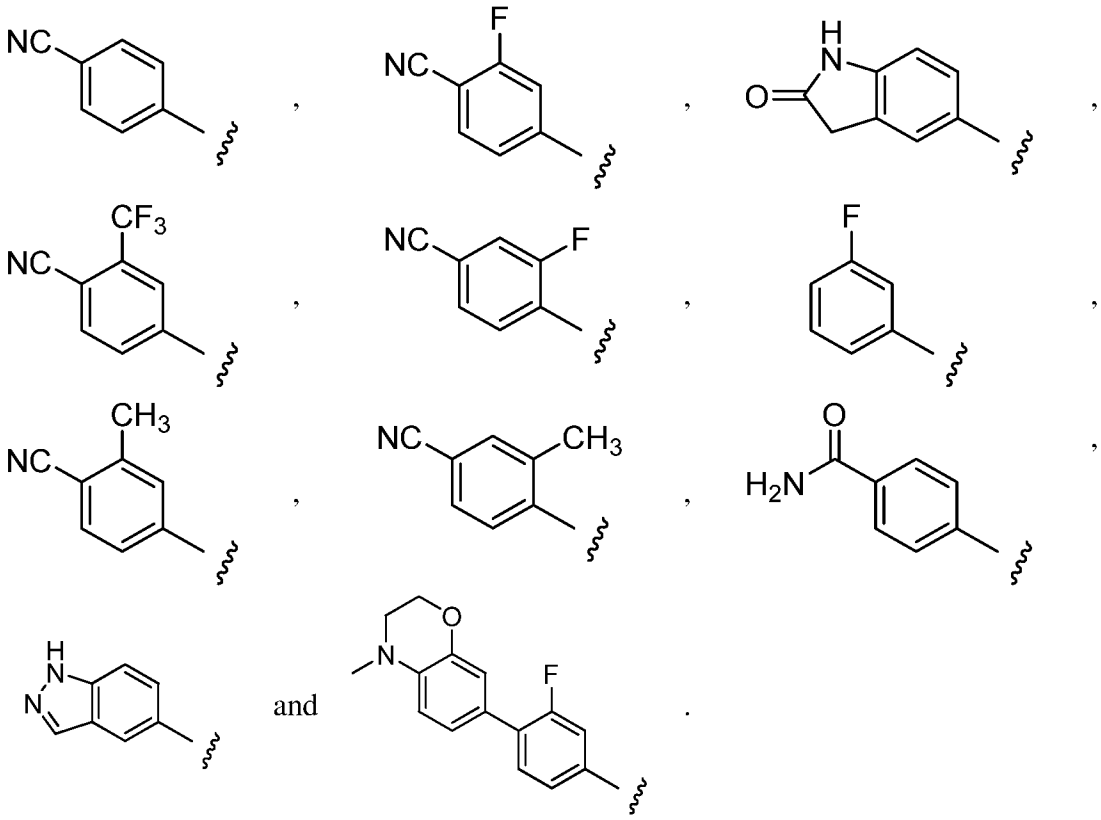
[0044] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted phenyl or optionally substituted 9- to 14-membered heteroaryl. In another embodiment, R^1 is optionally substituted phenyl having Formula **VII**:



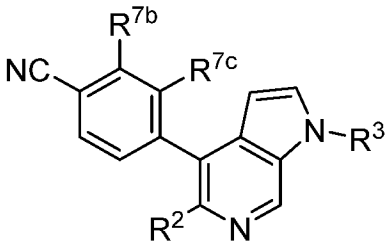
VII,

wherein R^{7a}, R^{7b}, and R^{7c} are each independently selected from the group consisting of hydrogen, halo, cyano, amino hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, optionally substituted phenyl, and carboxamido, or R^{7a} and R^{7b} taken together with the carbon atoms to which they are attached form a 5-, 6-, or 7-membered optionally substituted heterocyclo. In another embodiment, R^{7a} is cyano.

[0045] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted phenyl or optionally substituted 9- to 14-membered heteroaryl selected from the group consisting of:



[0046] In another embodiment, Compounds of the Disclosure are compounds represented by Formula **VIII**:



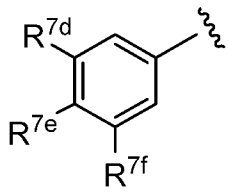
VIII,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0047] R^{7b} and R^{7c} are independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and C_{1-4} haloalkyl; and

[0048] R^2 and R^3 are as defined in connection with Formula **I** and **II**.

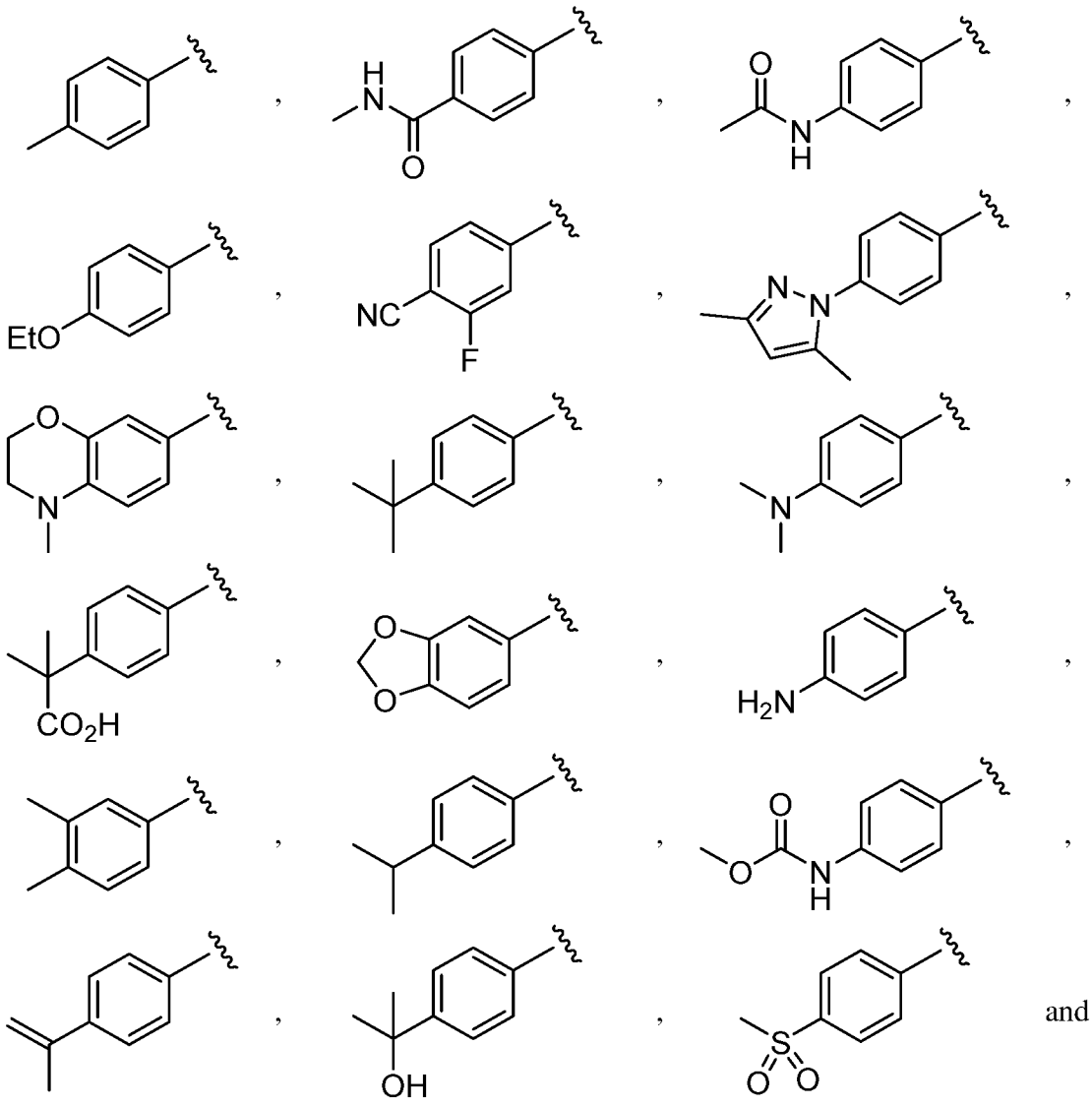
[0049] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted phenyl. In another embodiment, R^2 is optionally substituted phenyl having Formula **IX**:



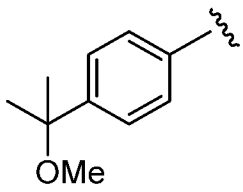
IX,

wherein R^{7d}, R^{7e}, and R^{7f} are each independently selected from the group consisting of hydrogen, halo, cyano, amino, hydroxy, optionally substituted C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, carboxamido, amido, optionally substituted C_{3-6} cycloalkyl, optionally substituted phenyl, and optionally substituted 5- to 9-membered heteroaryl; or R^{7d} and R^{7e} taken together with the carbon atoms to which they are attached form a 5-, 6-, or 7-membered optionally substituted heterocyclo.

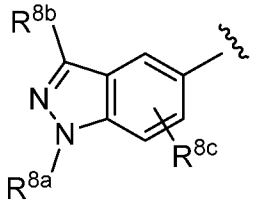
[0050] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted phenyl selected from the group consisting of:



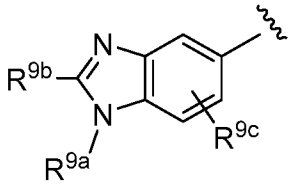
and



[0051] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted 5- to 14-membered heteroaryl. In another embodiment, R^2 is optionally substituted 5- to 14-membered heteroaryl having Formulae **X**, **XI**, or **XII**:

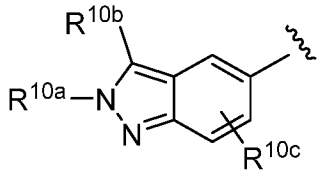


X



XI

or



XII

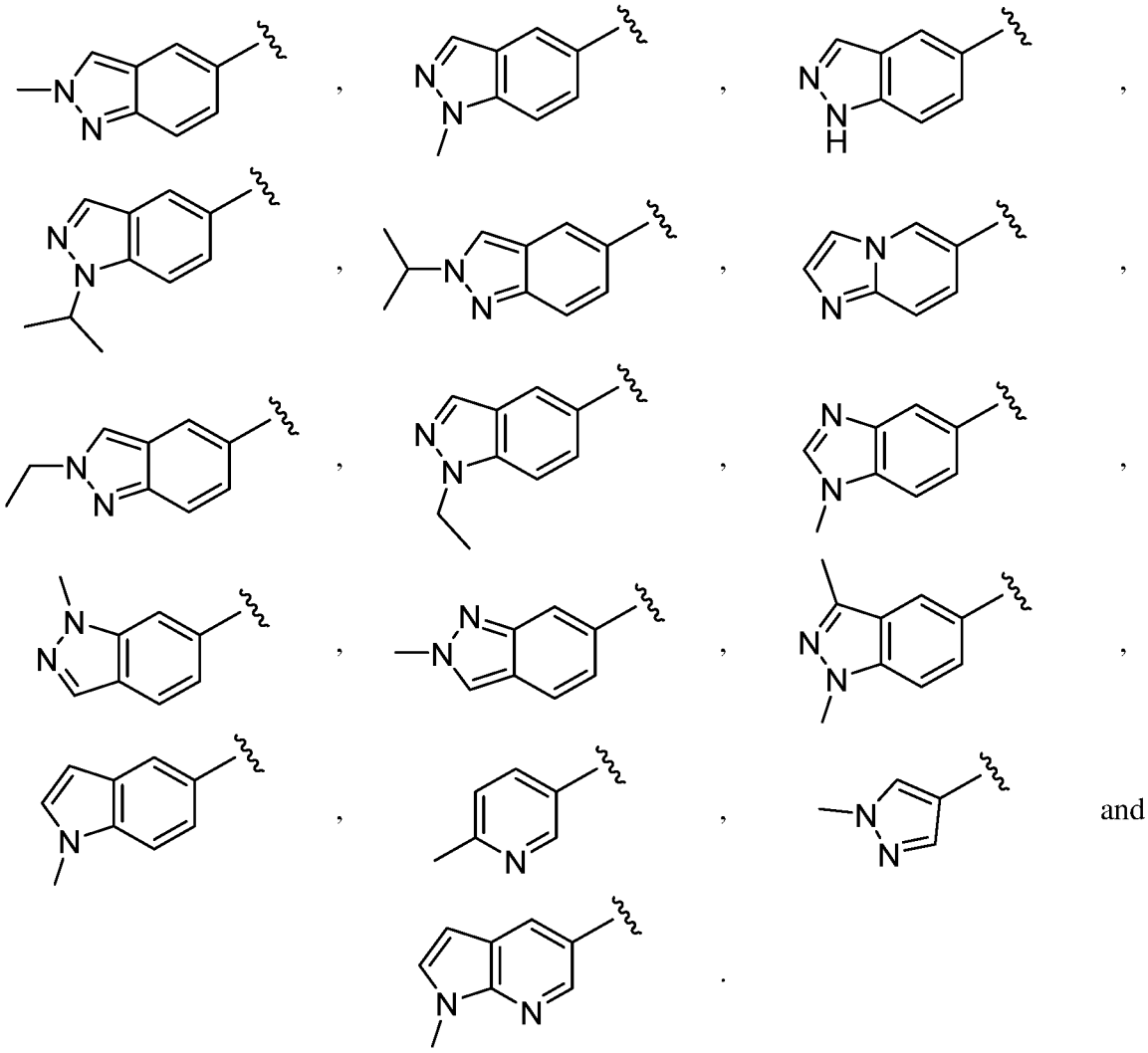
wherein: R^{8a} is selected from the group consisting of hydrogen and C_{1-6} alkyl; R^{8b} is selected from the group consisting of hydrogen and C_{1-6} alkyl; R^{8c} is selected from the group consisting of hydrogen, halo, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy; R^{9a} is selected from the group consisting of hydrogen and C_{1-6} alkyl; R^{9b} is selected from the group consisting of hydrogen and C_{1-6} alkyl; R^{9c} is selected from the group consisting of hydrogen, halo, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy; R^{10a} is selected from the group consisting of hydrogen and C_{1-6} alkyl; R^{10b} is selected from the group consisting of hydrogen and C_{1-6} alkyl; R^{10c} is selected from the group consisting of hydrogen, halo, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

[0052] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted 5- to 14-membered heteroaryl having Formula **X**.

[0053] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted 5- to 14-membered heteroaryl having Formula **XI**.

[0054] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted 5- to 14-membered heteroaryl having Formula **XII**.

[0055] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted 5- to 14-membered heteroaryl selected from the group consisting of:

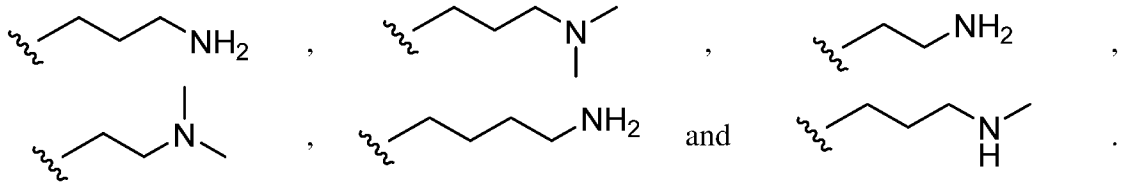


[0056] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from the group consisting of optionally substituted C_{3-8} cycloalkyl, (amino)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In another

embodiment, R^3 is selected from the group consisting of (amino)alkyl and (heterocyclo)alkyl.

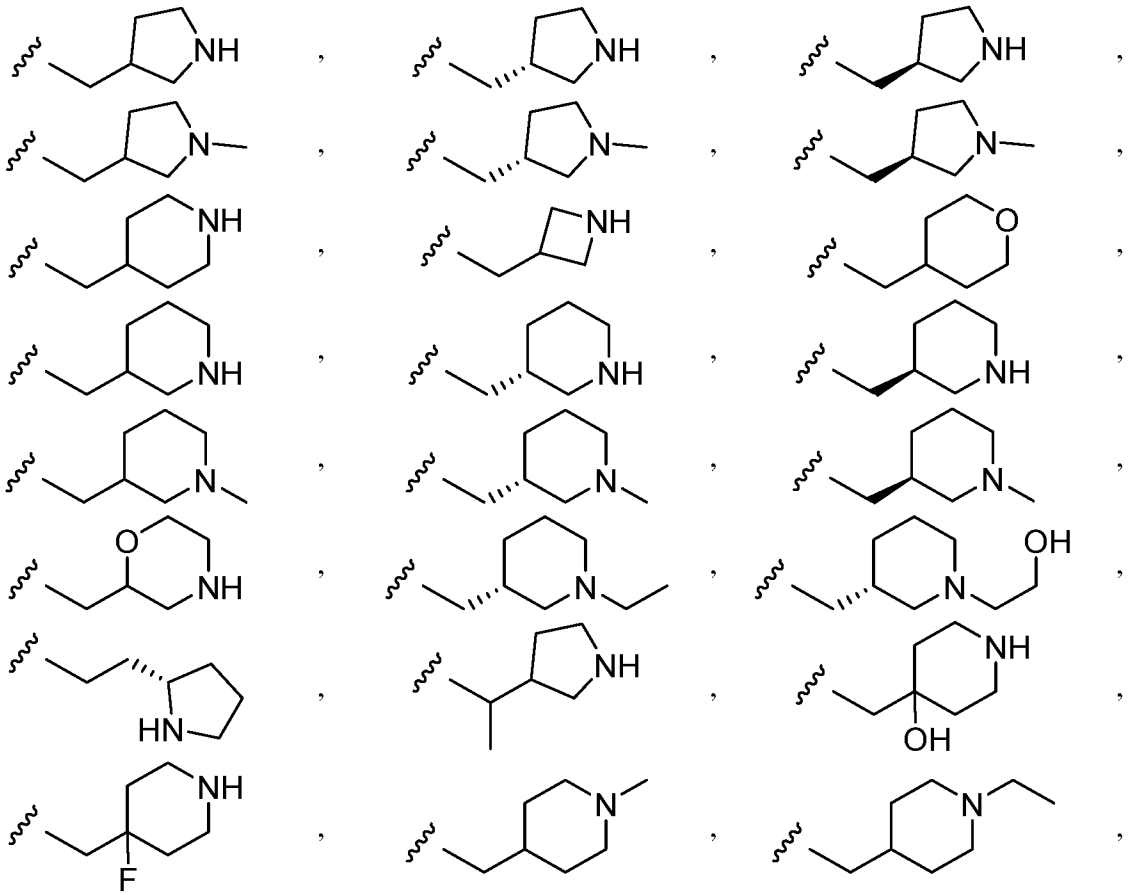
[0057] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is (amino)alkyl.

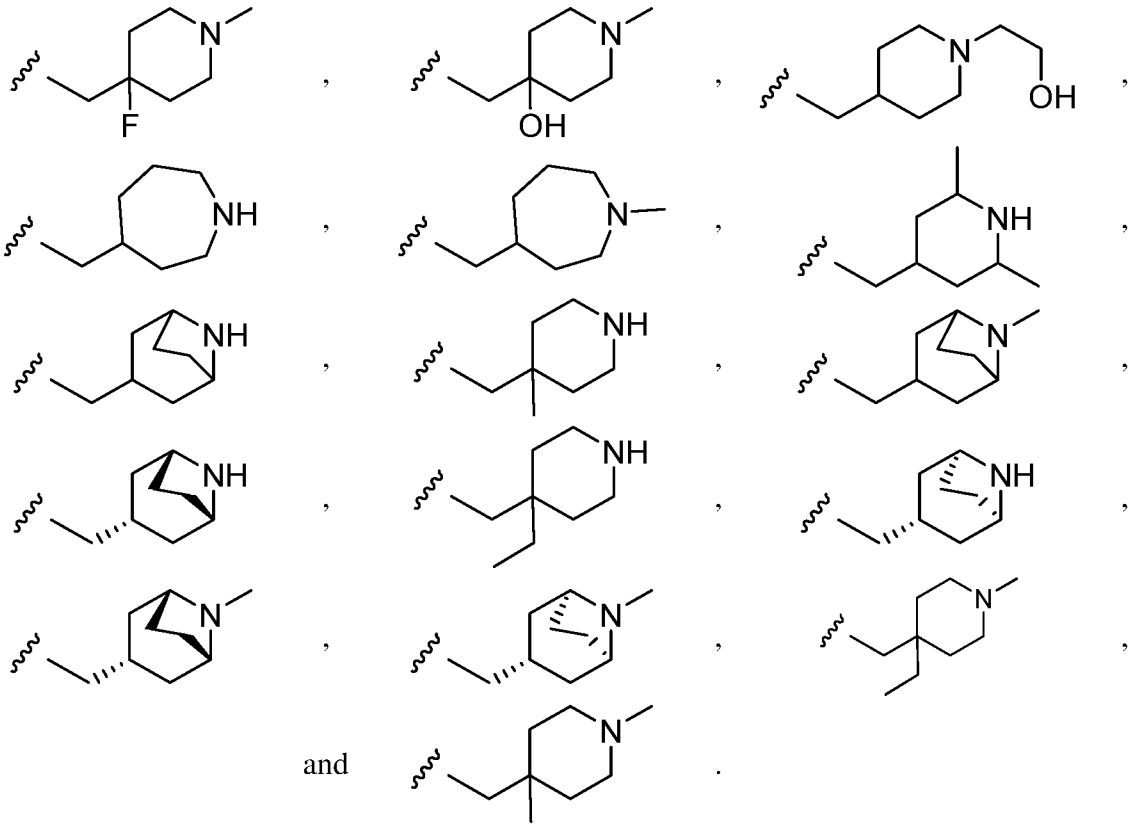
[0058] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is (amino)alkyl selected from the group consisting of:



[0059] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is (heterocyclo)alkyl.

[0060] In another embodiment, Compounds of the Disclosure are compounds represented by any one of Formulae **I-VI** or **VIII**, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is (heterocyclo)alkyl selected from the group consisting of:

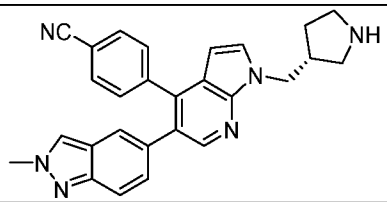
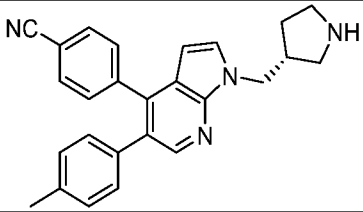
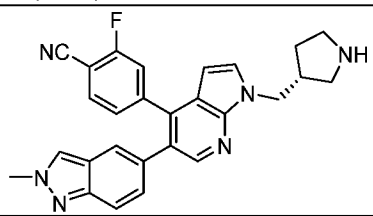


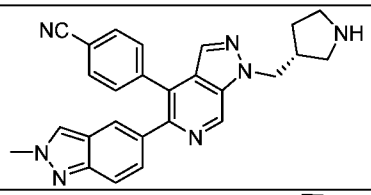
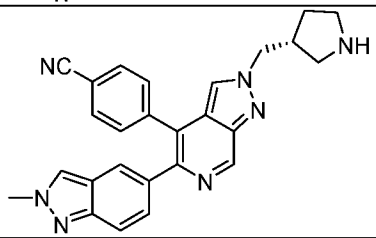
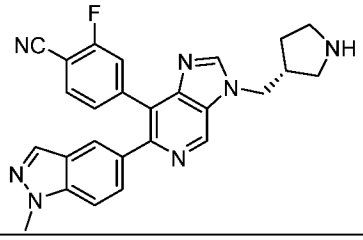
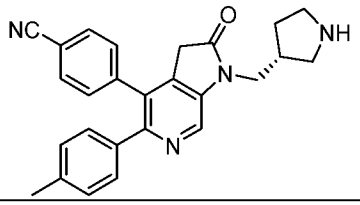
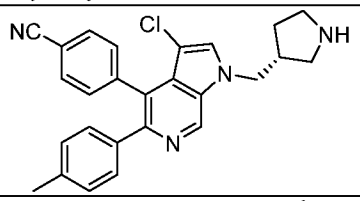
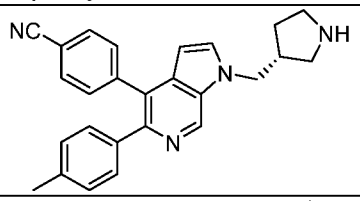
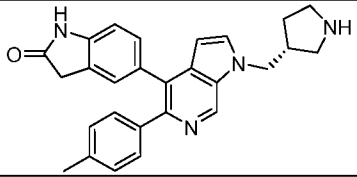
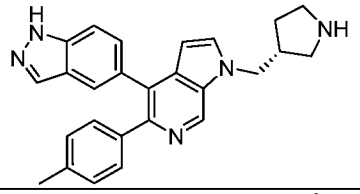
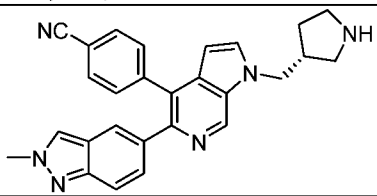


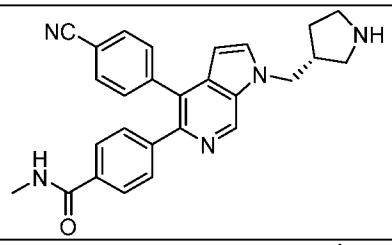
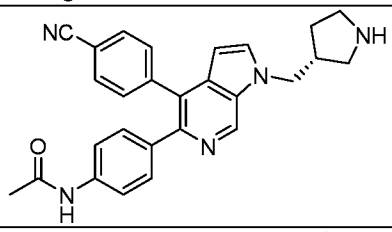
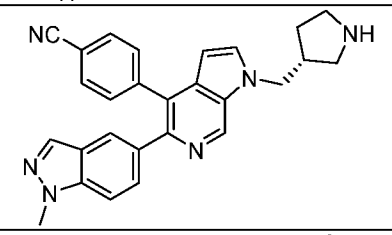
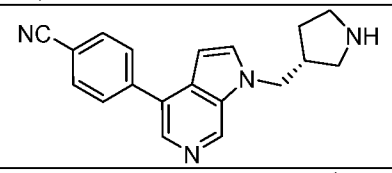
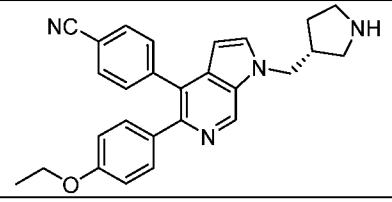
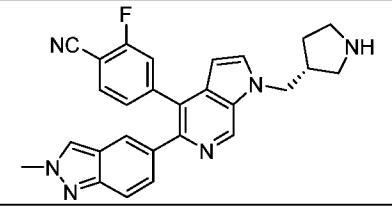
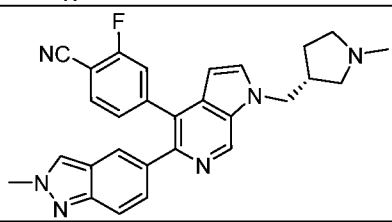
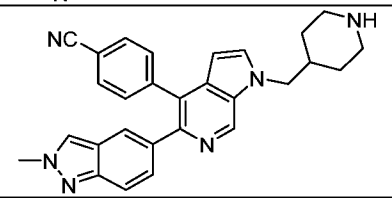
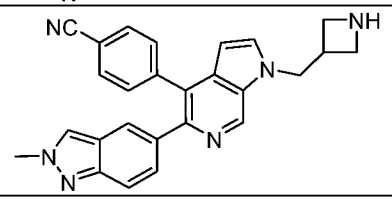
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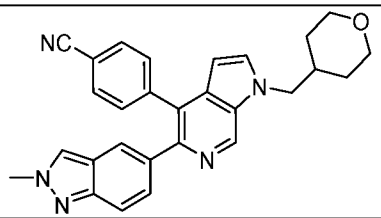
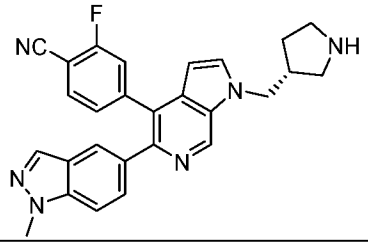
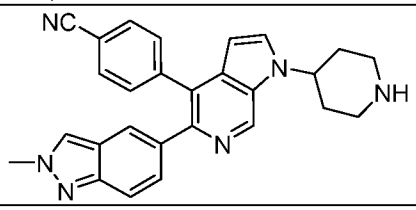
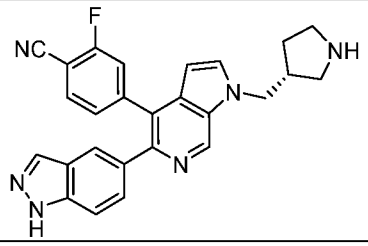
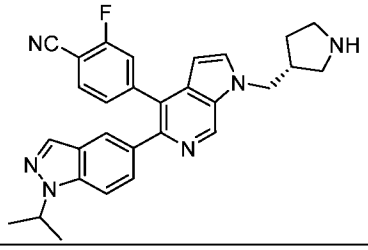
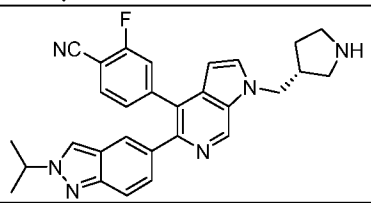
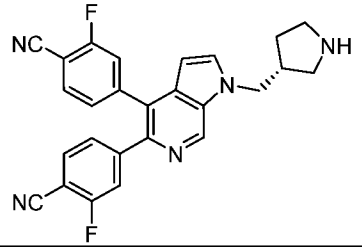
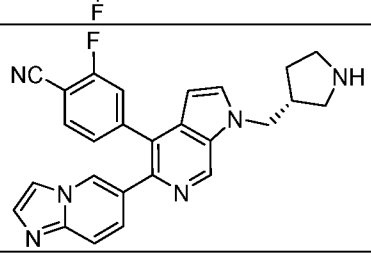
[0061] In another embodiment, Compounds of the Disclosure are any one or more of the compounds of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, Compounds of the Disclosure are 2,2,2-trifluoroacetate (TFA) salts. In another embodiment, Compounds of the Disclosure are hydrochloric acid (HCl) salts.

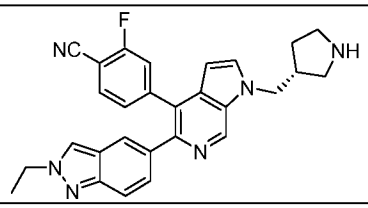
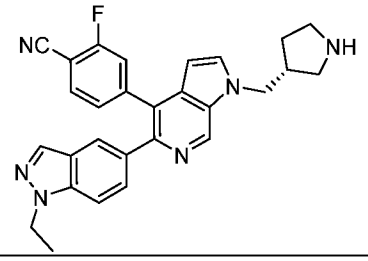
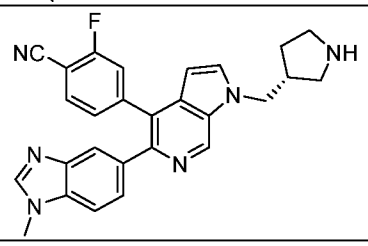
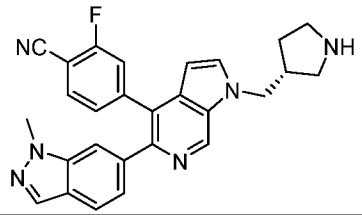
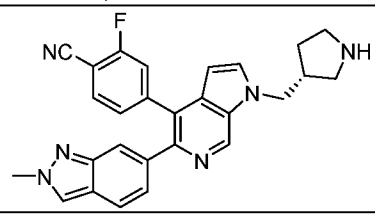
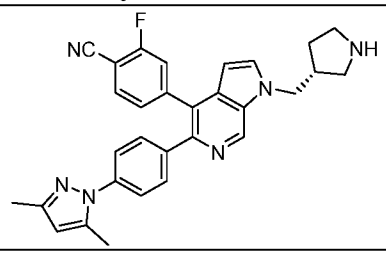
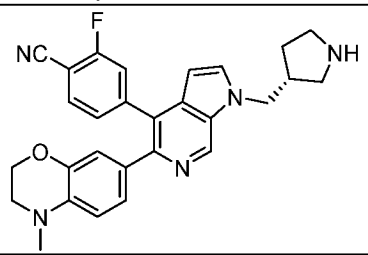
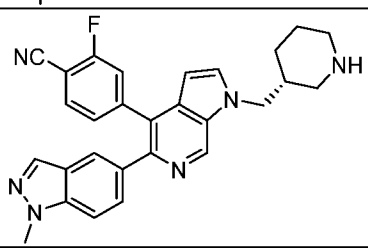
Table 1

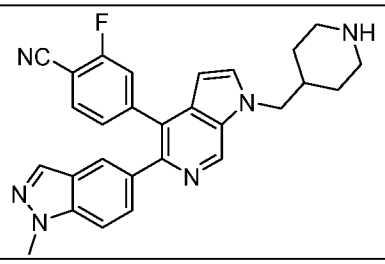
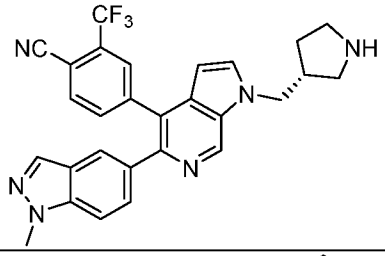
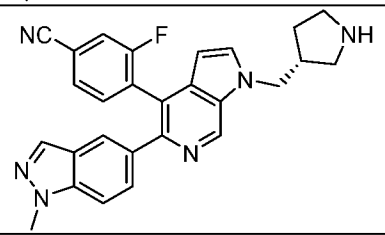
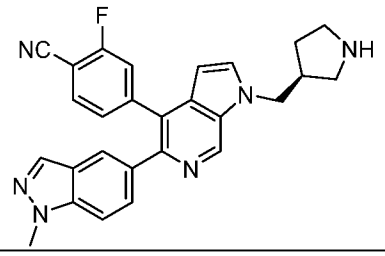
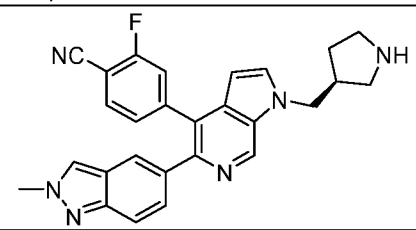
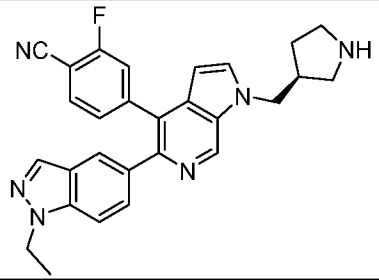
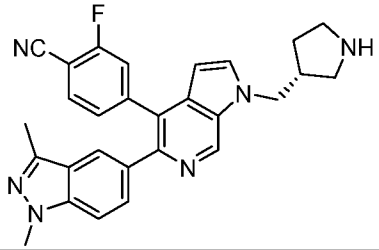
Cpd. No.	Structure	Name
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2		(R)-4-(1-(pyrrolidin-3-ylmethyl)-5-(p-tolyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)benzonitrile
3		(R)-2-fluoro-4-(5-(2-methyl-2H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)benzonitrile

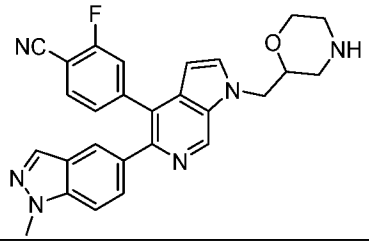
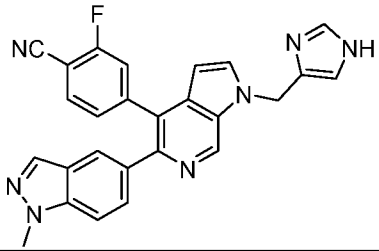
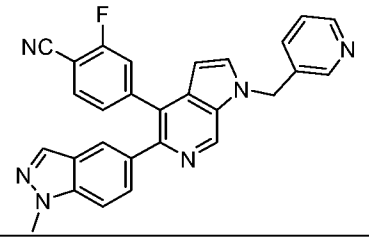
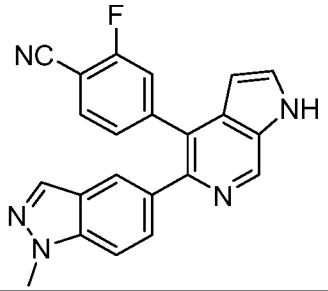
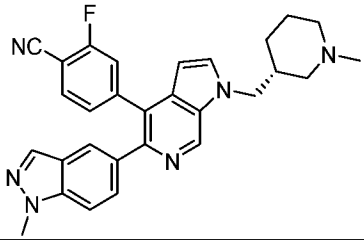
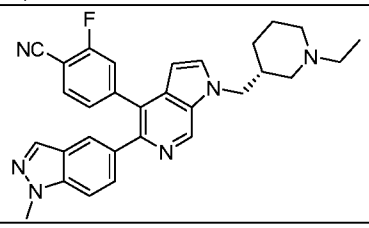
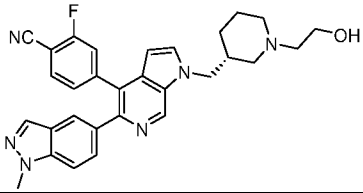
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5		(R)-4-(5-(2-methyl-2H-indazol-5-yl)-2-(pyrrolidin-3-ylmethyl)-2H-pyrazolo[3,4-c]pyridin-4-yl)benzonitrile
6		(R)-2-fluoro-4-(6-(1-methyl-1H-indazol-5-yl)-3-(pyrrolidin-3-ylmethyl)-3H-imidazo[4,5-c]pyridin-7-yl)benzonitrile
7		(R)-4-(2-oxo-1-(pyrrolidin-3-ylmethyl)-5-(p-tolyl)-2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
8		(R)-4-(3-chloro-1-(pyrrolidin-3-ylmethyl)-5-(p-tolyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
9		(R)-4-(1-(pyrrolidin-3-ylmethyl)-5-(p-tolyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
10		(R)-5-(1-(pyrrolidin-3-ylmethyl)-5-(p-tolyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)indolin-2-one
11		(R)-5-(1-(pyrrolidin-3-ylmethyl)-5-(p-tolyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-1H-indazole
12		(R)-4-(5-(2-methyl-2H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

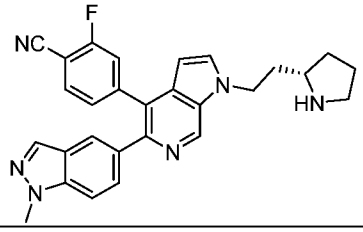
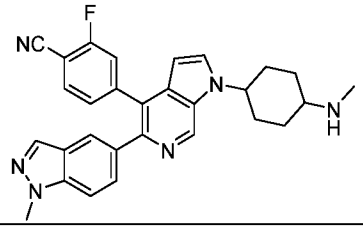
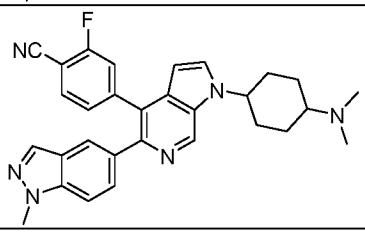
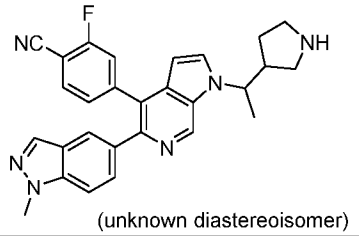
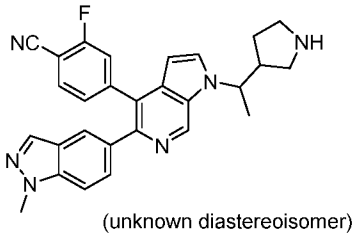
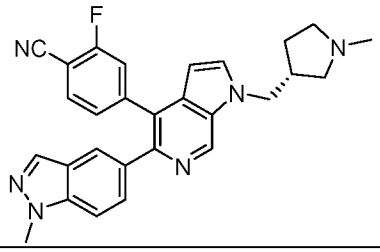
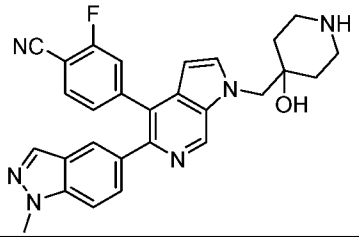
13		(R)-4-(4-(4-cyanophenyl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-5-yl)-N-methylbenzamide
14		(R)-N-(4-(4-(4-cyanophenyl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-5-yl)phenyl)acetamide
15		(R)-4-(5-(1-methyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
16		(R)-4-(1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
17		(R)-4-(5-(4-ethoxyphenyl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
18		(R)-2-fluoro-4-(5-(2-methyl-2H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
19		(R)-2-fluoro-4-(5-(2-methyl-2H-indazol-5-yl)-1-((1-methylpyrrolidin-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
20		4-(5-(2-methyl-2H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
21		4-(1-(azetidin-3-ylmethyl)-5-(2-methyl-2H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

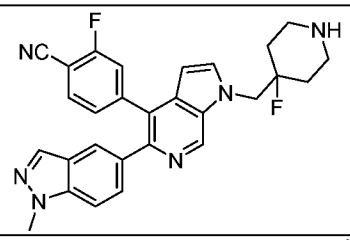
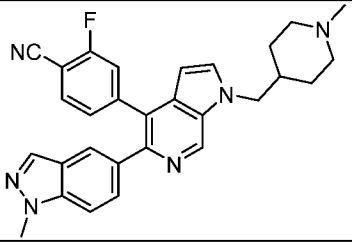
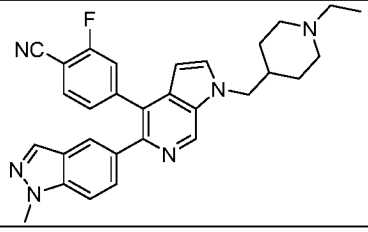
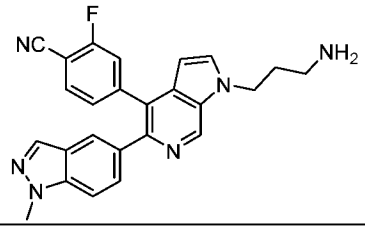
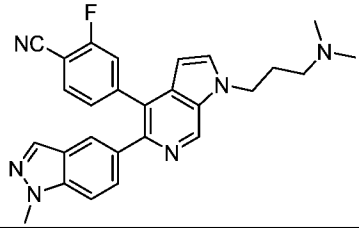
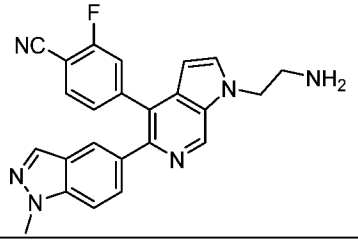
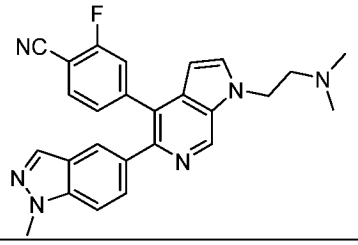
22		4-(5-(2-methyl-2H-indazol-5-yl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
23		(R)-2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
24		4-(5-(2-methyl-2H-indazol-5-yl)-1-(piperidin-4-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
25		(R)-4-(5-(1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
26		(R)-2-fluoro-4-(5-(1-isopropyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
27		(R)-2-fluoro-4-(5-(2-isopropyl-2H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
28		(R)-4,4'-(1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridine-4,5-diyl)bis(2-fluorobenzonitrile)
29		(R)-2-fluoro-4-(5-(imidazo[1,2-a]pyridin-6-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

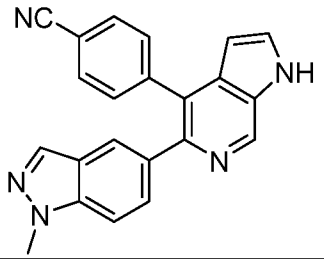
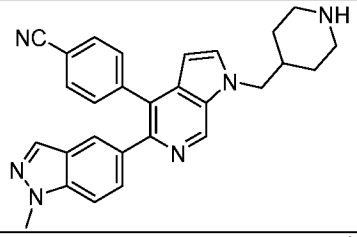
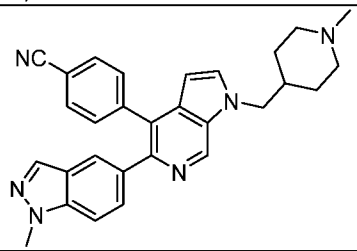
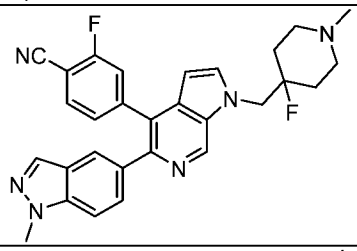
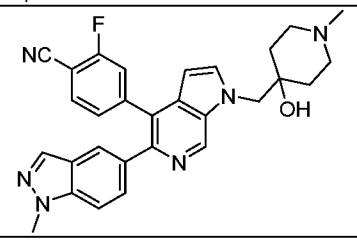
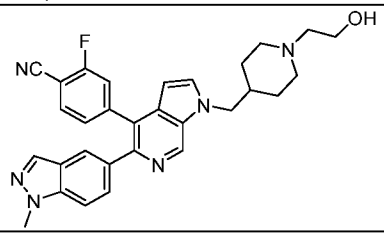
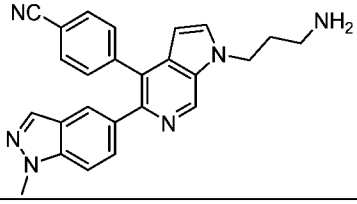
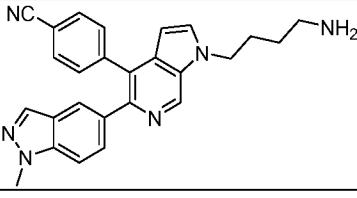
30		(R)-4-(5-(2-ethyl-2H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
31		(R)-4-(5-(1-ethyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
32		(R)-2-fluoro-4-(5-(1-methyl-1H-benzo[d]imidazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
33		(R)-2-fluoro-4-(5-(1-methyl-1H-indazol-6-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
34		(R)-2-fluoro-4-(5-(2-methyl-2H-indazol-6-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
35		(R)-4-(5-(4-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
36		(R)-2-fluoro-4-(5-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
37		(R)-2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(piperidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

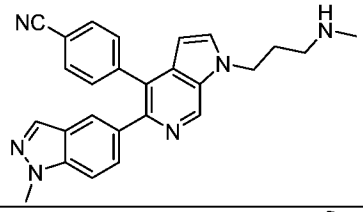
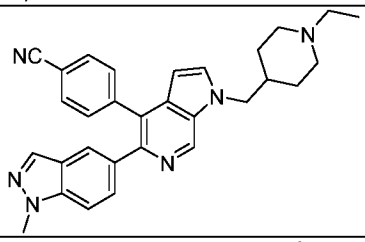
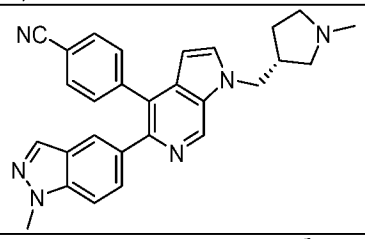
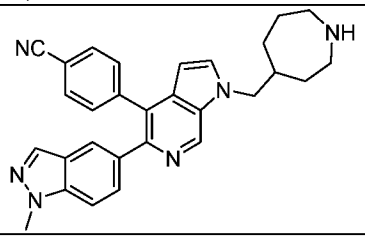
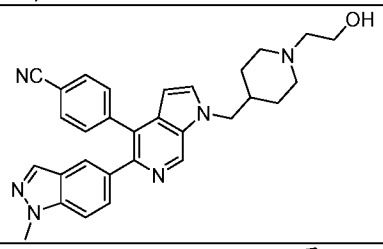
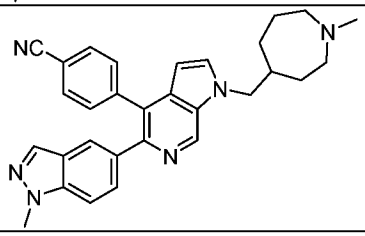
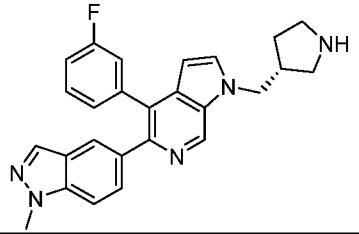
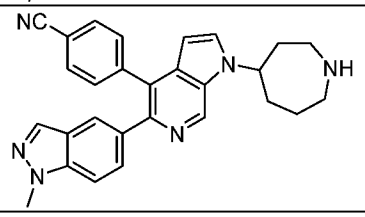
38		2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
39		(R)-4-(5-(1-methyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-(trifluoromethyl)benzonitrile
40		3-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(((R)-pyrrolidin-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
41		(S)-2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
42		(S)-2-fluoro-4-(5-(2-methyl-2H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
43		(S)-4-(5-(1-ethyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
44		(R)-4-(5-(1,3-dimethyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile

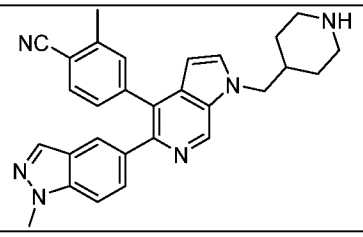
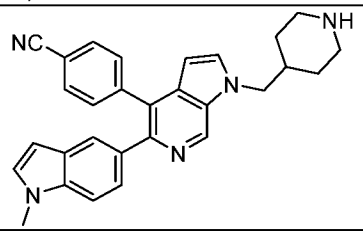
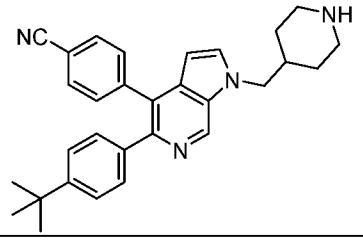
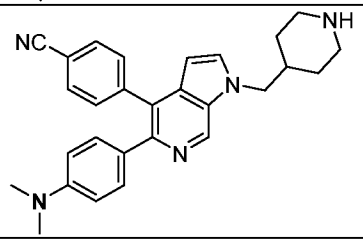
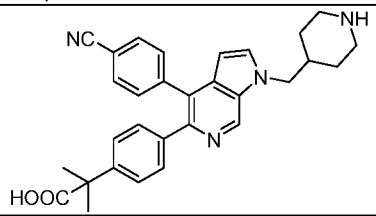
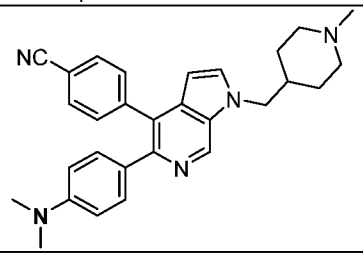
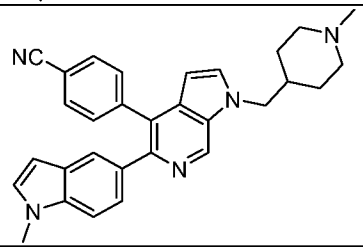
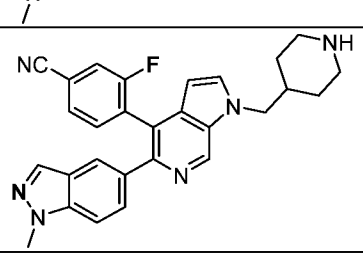
45		2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(morpholin-2-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
46		4-(1-((1H-imidazol-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
47		2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(pyridin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
48		2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
49		(R)-2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylpiperidin-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
50		(R)-4-(1-((1-ethylpiperidin-3-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
51		(R)-2-fluoro-4-(1-((1-(2-hydroxyethyl)piperidin-3-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

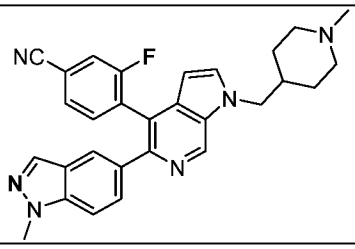
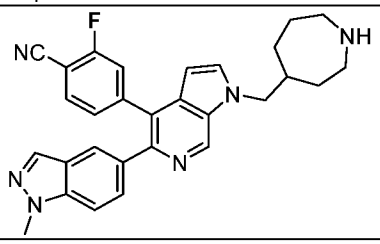
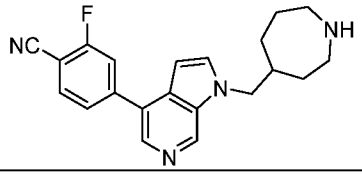
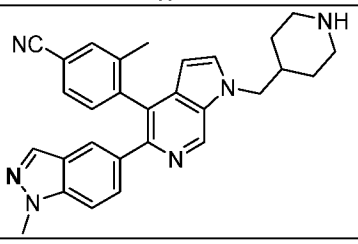
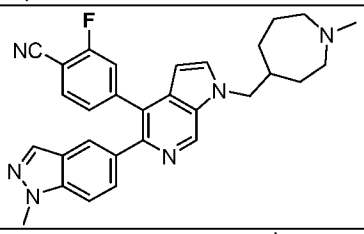
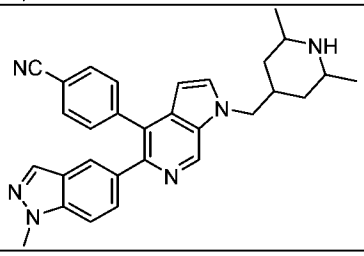
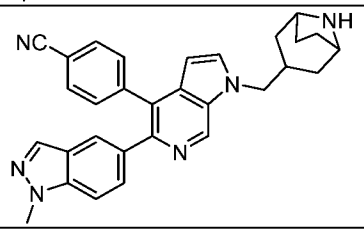
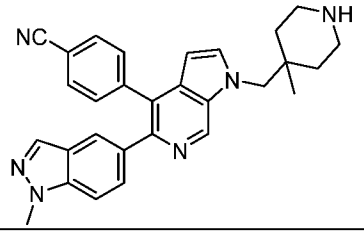
52		(S)-2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(2-(pyrrolidin-2-yl)ethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
53		2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(4-(methylamino)cyclohexyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
54		4-(1-(4-(dimethylamino)cyclohexyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
55	 (unknown diastereoisomer)	2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(1-(pyrrolidin-3-yl)ethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
56	 (unknown diastereoisomer)	2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(1-(pyrrolidin-3-yl)ethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
57		(R)-2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylpyrrolidin-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
58		2-fluoro-4-(1-((4-hydroxypiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

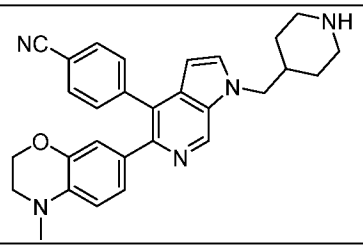
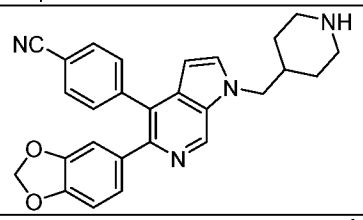
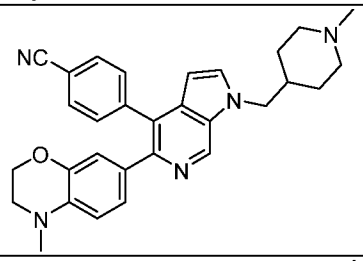
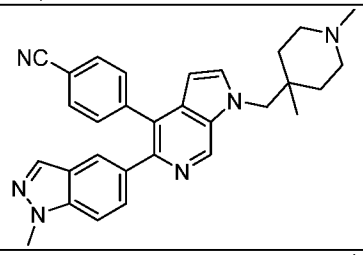
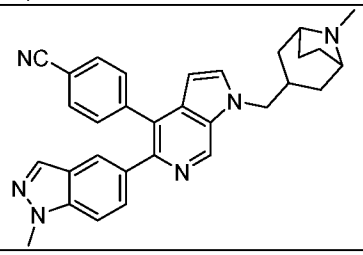
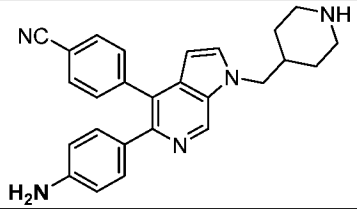
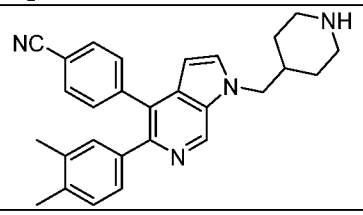
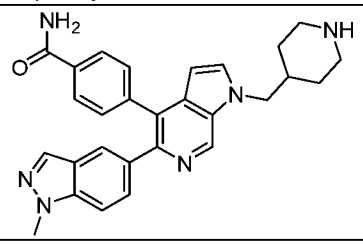
59		2-fluoro-4-(1-((4-fluoropiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
60		2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
61		4-(1-((1-ethylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
62		4-(1-(3-aminopropyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
63		4-(1-(3-(dimethylamino)propyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
64		4-(1-(2-aminoethyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
65		4-(1-(2-(dimethylamino)ethyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile

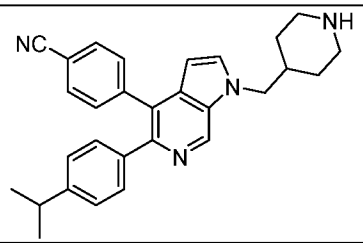
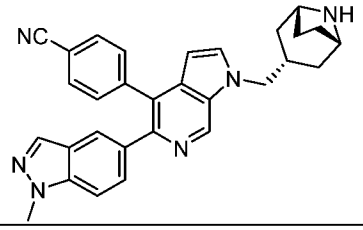
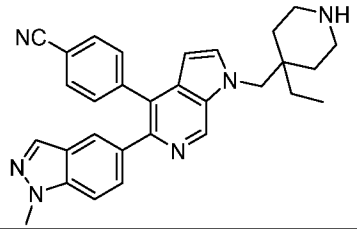
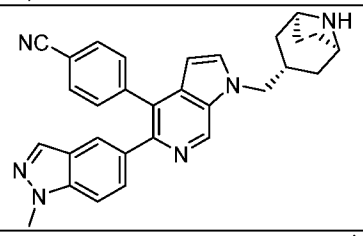
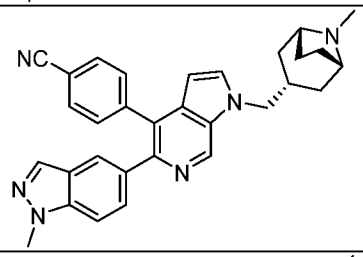
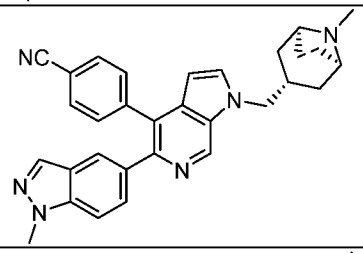
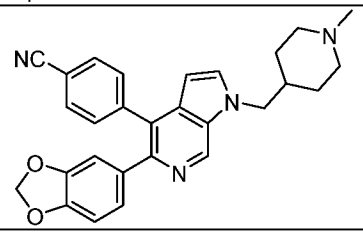
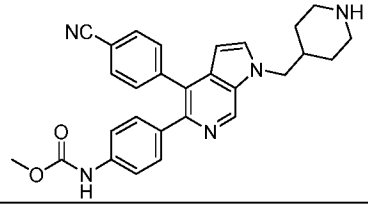
66		4-(5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
67		4-(5-(1-methyl-1H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
68		4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
69		2-fluoro-4-(1-((4-fluoro-1-methylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
70		2-fluoro-4-(1-((4-hydroxy-1-methylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
71		2-fluoro-4-(1-((1-(2-hydroxyethyl)piperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
72		4-(1-(3-aminopropyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
73		4-(1-(4-aminobutyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

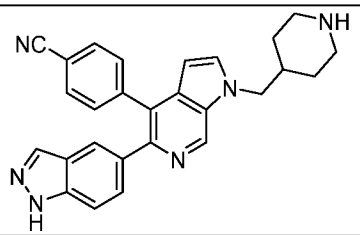
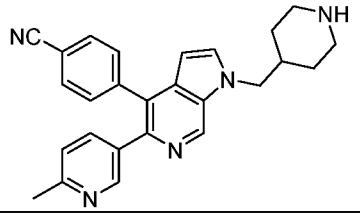
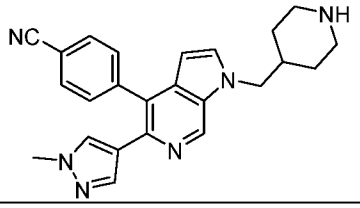
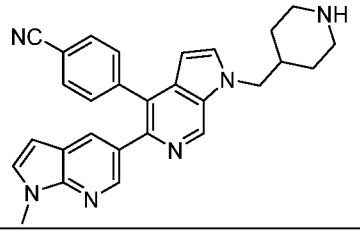
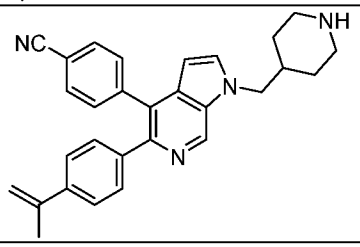
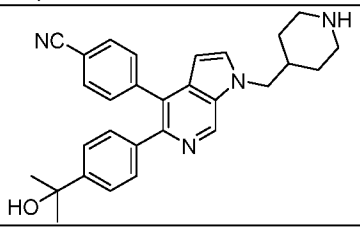
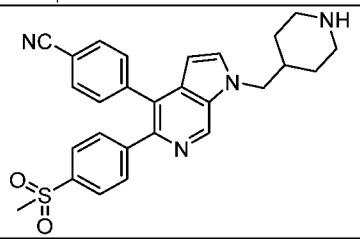
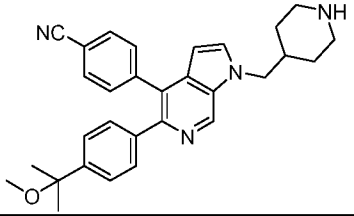
74		4-(5-(1-methyl-1H-indazol-5-yl)-1-(3-(methylamino)propyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
75		4-(1-((1-ethylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
76		(R)-4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylpyrrolidin-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
77		4-(1-(azepan-4-ylmethyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
78		4-(1-((1-(2-hydroxyethyl)piperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
79		4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylazepan-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
80		(R)-5-(4-(3-fluorophenyl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-5-yl)-1-methyl-1H-indazole
81		4-(1-(azepan-4-yl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

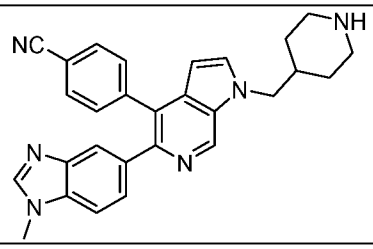
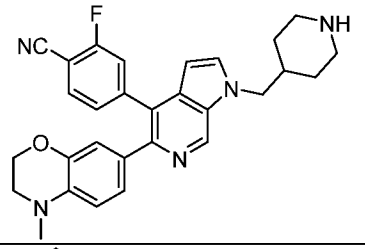
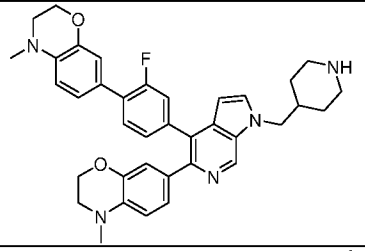
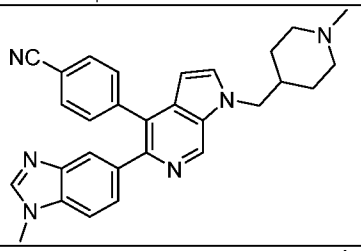
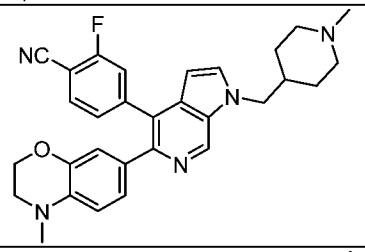
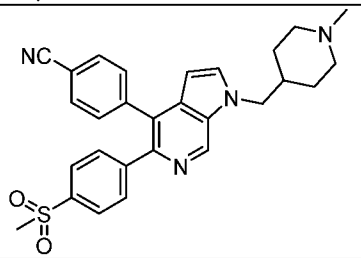
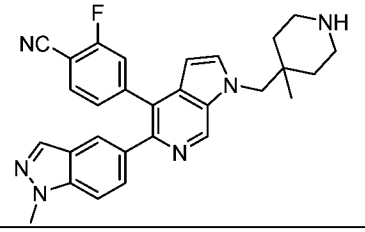
82		2-methyl-4-(5-(1-methyl-1H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
83		4-(5-(1-methyl-1H-indol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
84		4-(5-(4-(tert-butyl)phenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
85		4-(5-(4-(dimethylamino)phenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
86		2-(4-(4-(4-cyanophenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-5-yl)phenyl)-2-methylpropanoic acid
87		4-(5-(4-(dimethylamino)phenyl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
88		4-(5-(1-methyl-1H-indol-5-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
89		3-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

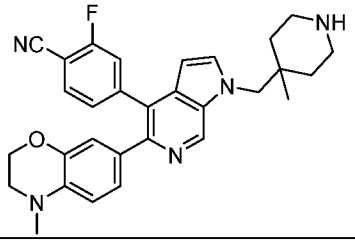
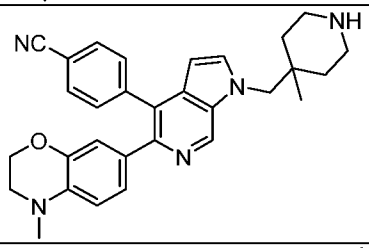
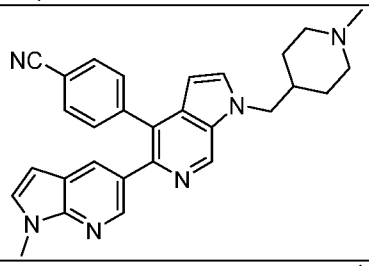
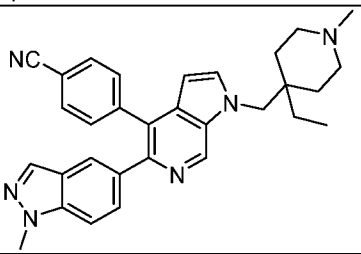
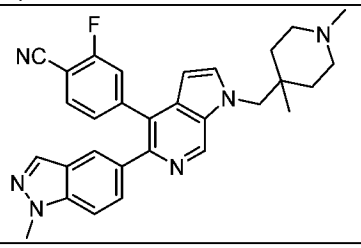
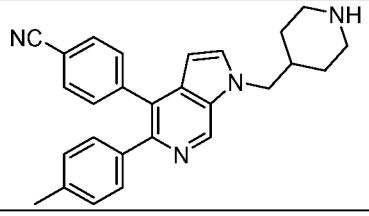
90		3-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
91		4-(1-(azepan-4-ylmethyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
92		4-(1-(azepan-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
93		3-methyl-4-(5-(1-methyl-1H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
94		2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylazepan-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
95		4-(1-((2,6-dimethylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
96		4-(1-((8-azabicyclo[3.2.1]octan-3-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
97		4-(5-(1-methyl-1H-indazol-5-yl)-1-((4-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

98		4-(5-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
99		4-(5-(benzo[d][1,3]dioxol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
100		4-(5-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
101		4-(1-((1,4-dimethylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
102		4-(5-(1-methyl-1H-indazol-5-yl)-1-((8-methyl-8-azabicyclo[3.2.1]octan-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
103		4-(5-(4-aminophenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
104		4-(5-(3,4-dimethylphenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
105		4-(5-(1-methyl-1H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzamide

106		4-(5-(4-isopropylphenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
107		4-(1-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
108		4-(1-((4-ethylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
109		4-(1-(((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
110		4-(5-(1-methyl-1H-indazol-5-yl)-1-(((1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
111		4-(5-(1-methyl-1H-indazol-5-yl)-1-(((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
112		4-(5-(benzo[d][1,3]dioxol-5-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
113		methyl (4-(4-(4-cyanophenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-5-yl)phenyl)carbamate

114		4-(5-(1H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
115		4-(5-(6-methylpyridin-3-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
116		4-(5-(1-methyl-1H-pyrazol-4-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
117		4-(5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
118		4-(1-(piperidin-4-ylmethyl)-5-(4-(prop-1-en-2-yl)phenyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
119		4-(5-(4-(2-hydroxypropan-2-yl)phenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
120		4-(5-(4-(methylsulfonyl)phenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
121		4-(5-(4-(2-methoxypropan-2-yl)phenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

122		4-(5-(1-methyl-1H-benzo[d]imidazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
123		2-fluoro-4-(5-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
124		7-(4-(3-fluoro-4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)phenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-5-yl)-4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine
125		4-(5-(1-methyl-1H-benzo[d]imidazol-5-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
126		2-fluoro-4-(5-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
127		4-(1-((1-methylpiperidin-4-yl)methyl)-5-(4-(methylsulfonyl)phenyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
128		2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-((4-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

129		2-fluoro-4-(5-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1-((4-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
130		4-(5-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)-1-((4-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
131		4-(5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
132		4-(1-((4-ethyl-1-methylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile
133		4-(1-((1,4-dimethylpiperidin-4-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)-2-fluorobenzonitrile
134		4-(1-(piperidin-4-ylmethyl)-5-(p-tolyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile

[0062] Compounds of the Disclosure inhibit LSD1 and are useful in the treatment or prevention of a variety of diseases and conditions. In particular, Compounds of the Disclosure are useful in methods of treating or preventing a disease or condition wherein inhibition of LSD1 provides a benefit, for example, cancers and proliferative diseases. The therapeutic methods of this disclosure comprise administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need thereof. The present methods also encompass administering a second therapeutic agent to the

subject 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 subject in need thereof, e.g., a chemotherapeutic agent and/or radiation known as useful in treating a particular cancer.

[0063] Certain of the Compounds of the Disclosure may exist as stereoisomers, *i.e.,* isomers that differ only in the spatial arrangement of atoms, including optical isomers and conformational isomers (or conformers) and tautomers. The disclosure includes all stereoisomers, both as pure individual stereoisomer preparations and enriched preparations of each, and both the racemic mixtures of such stereoisomers as well as the individual diastereomers and enantiomers that may be separated according to methods that are well known to those of skill in the art.

[0064] 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).

[0065] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[0066] 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.

[0067] The term "racemic" or "racemate" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.

[0068] 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.

[0069] 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.

[0070] 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. Certain compounds of the Disclosure can have an ee of about 70% or more, e.g., about 80% or more, about 90% or more, about 91% or more, about 92% or more, about 93% or more, about 94% or more, about 95% or more, about 96% or more, about 97% or more, about 98% or more, or about 99% or more.

[0071] The terms "enantiomerically pure" or "enantiopure" refer to a sample of a chiral substance all of whose molecules (within the limits of detection) have the same chirality sense.

[0072] The terms "enantiomerically enriched" or "enantioenriched" refer to a sample of a chiral substance whose enantiomeric ratio is greater than 50:50. Enantiomerically enriched compounds may be enantiomerically pure. Certain compounds of the Disclosure are enantioenriched.

[0073] Salts and solvates, e.g., hydrates, of the Compounds of the Disclosure can also be used in the methods disclosed herein.

[0074] The present disclosure encompasses the preparation and use of salts of Compounds of the Disclosure. As used herein, a "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. Non-limiting 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, hydrates, or solvates thereof.

[0075] The present disclosure encompasses the preparation and use of solvates of Compounds of the Disclosure. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound of the present disclosure with a solvent molecule such as, e.g., a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to compound of the present disclosure is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. Compounds of the Disclosure can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, and ethanol, and it is intended that the disclosure includes both solvated and unsolvated forms of Compounds of the Disclosure.

[0076] One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate would

involve dissolving a Compound of the Disclosure in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, e.g., filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

[0077] The present disclosure provides Compounds of the Disclosure as inhibitors of LSD1 for the treatment of a variety of diseases and conditions wherein inhibition has a beneficial effect, e.g., cancer. Compounds of the Disclosure typically have a binding affinity (IC_{50}) to LSD1 of less than 100 μM, e.g., less than about 50 μM, less than about 25 μM, and less than about 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, less than about 0.01 μM, less than about 0.005 μM, or less than about 0.001 μM. In one embodiment, the present disclosure relates to a method of treating a subject suffering from a disease or condition wherein inhibition of LSD1 provides a benefit comprising administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need thereof.

[0078] Since Compounds of the Disclosure are LSD1 inhibitors, a number of diseases and conditions mediated by LSD1 can be treated by employing these compounds. The present disclosure is thus directed generally to a method for treating a condition or disorder responsive to inhibition of LSD1, or an isoform or mutant thereof, in a subject, e.g., an animal, e.g., a human patient, suffering from, or at risk of suffering from, the condition or disorder, the method comprising administering to the subject an effective amount of one or more Compounds of the Disclosure. In one embodiment, the subject to be treated by the Compound of the Disclosure is a human cancer patient.

[0079] The present disclosure is also directed to a method of inhibiting LSD1, or an isoform or mutant thereof, in an animal, e.g., a human cancer patient, in need thereof, said method comprising administering to the animal an effective amount of at least one Compound of the Disclosure.

[0080] 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.

[0081] Further provided are kits comprising a Compound of the Disclosure and, optionally, a second therapeutic agent useful in the treatment of diseases and conditions wherein inhibition of LSD1, or an isoform or mutant thereof, provides a benefit, packaged separately or together, and an insert having instructions for using these active agents.

[0082] 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, e.g., a disease or condition wherein inhibition of LSD1 or other therapeutic target 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.

[0083] 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 a subject in need thereof within such established ranges.

[0084] 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.

[0085] 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, Diseases and conditions treatable by the methods of the present disclosure are cancer, a chronic autoimmune disorder, an inflammatory condition, or a proliferative disorder. 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 LSD1 in the patient.

[0086] In one embodiment, the disease to be treated or prevented by the Compound of the Disclosure is cancer. In another embodiment, the present disclosure provides a

method of treating or preventing cancer in a subject in need thereof comprising administering a therapeutically effective amount of a Compound of the Disclosure to the subject. While not being limited to a specific mechanism, in some embodiments, Compounds of the Disclosure can treat or prevent cancer by inhibiting LSD1. Examples of treatable cancers include, but are not limited to, any one or more of the cancers of Table 2.

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	

[0087] In another embodiment, the cancer is a leukemia, for example a leukemia selected from acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia and mixed lineage leukemia (MLL). 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.

[0088] In another embodiment, the cancer is acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer,

esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, or papillary thyroid carcinoma.

[0089] In another embodiment, the cancer is anaplastic large-cell lymphoma, non-small cell lung cancer, diffuse large B-cell lymphoma, inflammatory myofibroblastic tumors, neuroblastoma, anaplastic thyroid cancer, and rhabdomyosarcoma.

[0090] In another embodiment, the cancer is breast cancer, colorectal cancer, esophageal squamous cell cancer, and renal cell carcinoma.

[0091] 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.

[0092] 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, appendictitis, 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] 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.

[0100] 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.

[0101] 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 LSD1 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. 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.

[0102] 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, 0.05, 0.5, 5, 10, 20, 30, 40, 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 milligrams, including all doses between 0.005 and 500 milligrams.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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 compound targeting/decreasing protein or lipid kinase activity, a compound targeting/decreasing protein or lipid phosphatase activity, or any further anti-angiogenic compound.

[0107] Non-limiting 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.

[0108] Non-limiting 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.

[0109] 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.

[0110] 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.

[0111] Exemplary non-limiting alkylating agents include cyclophosphamide, ifosfamide, melphalan, and nitrosoureas, such as carmustine and lomustine.

[0112] Exemplary non-limiting 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.

[0113] Exemplary non-limiting 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.

[0114] Exemplary non-limiting mTOR inhibitors include compounds that inhibit the mammalian target of rapamycin (mTOR) and possess antiproliferative activity such as sirolimus, everolimus, CCI-779, and ABT578.

[0115] Exemplary non-limiting 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.

[0116] Exemplary non-limiting platin compounds include carboplatin, cis-platin, cisplatinum, and oxaliplatin.

[0117] Exemplary non-limiting methionine aminopeptidase inhibitors include bengamide or a derivative thereof and PPI-2458.

[0118] Exemplary non-limiting bisphosphonates include etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, and zoledronic acid.

[0119] Exemplary non-limiting antiproliferative antibodies include trastuzumab, trastuzumab-DMl, cetuximab, bevacizumab, rituximab, PR064553, and 2C4. The term “antibody" includes 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.

[0120] Exemplary non-limiting heparanase inhibitors include compounds that target, decrease, or inhibit heparin sulfate degradation, such as PI-88 and OGT2115.

[0121] 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.

[0122] Exemplary non-limiting telomerase inhibitors include compounds that target, decrease, or inhibit the activity of telomerase, such as compounds that inhibit the telomerase receptor, such as telomestatin.

[0123] Exemplary non-limiting proteasome inhibitors include compounds that target, decrease, or inhibit the activity of the proteasome including, but not limited to, bortezomid.

[0124] 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; and ALK inhibitors, which are compounds which target, decrease, or inhibit anaplastic lymphoma kinase.

[0125] Exemplary non-limiting Flt-3 inhibitors include PKC412, midostaurin, a staurosporine derivative, SU11248, and MLN518.

[0126] Exemplary non-limiting 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.

[0127] 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); 1) 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 El.l, 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.

[0128] 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.

[0129] 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.

[0130] Additional, non-limiting, exemplary chemotherapeutic compounds, one or more of which may be used in combination with a present LSD1 inhibitors 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.

[0131] Other examples of second therapeutic agents, one or more of which a present LSD1 inhibitor 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.

[0132] 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.

[0133] 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. In one embodiment, the disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and a pharmaceutically acceptable excipient.

[0134] 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%, e.g., 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%, e.g., about 1% to about 50%, by weight, of a Compound of the Disclosure.

[0135] 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 composition for intravenous, cutaneous, or subcutaneous injection typically contains an isotonic vehicle.

[0136] Compounds of the Disclosure can be readily combined with pharmaceutically acceptable carriers well-known in the art. In one embodiment, a pharmaceutical composition comprising a Compound of the Disclosure, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier, is provided. 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.

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] The term "a disease or condition wherein inhibition of LSD1 provides a benefit" pertains to a disease or condition in which LSD1, is important or necessary, e.g., for the onset, progress, expression of that disease or condition, or a disease or a condition which is known to be treated by an LSD1 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 a LSD1 inhibitor for any particular cell type, for example, by assays which conveniently can be used to assess the activity of particular compounds.

[0143] The terms "LSD1," "lysine specific demethylase-1," "lysine-specific histone demethylase 1A," "lysine (K)-specific demethylase 1A," or "LSD-1" are synonymous terms that refer to a protein in humans encoded by the KDM1A gene. The term LSD1 includes isoforms and mutants of LSD1. LSD1 is a flavin-dependent monoamine oxidase, which can demethylate mono- and di-methylated lysines, specifically histone 3, lysines 4 and 9 (H3K4 and H3K9).

[0144] 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.

[0145] 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 inhibitors of LSD1 and can be used in treating or preventing diseases and conditions wherein inhibition of LSD1 provides a benefit.

[0146] 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. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need of such treatment. 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.

[0147] As used herein, the terms "prevent," "preventing," and "prevention" refer to a method of preventing the onset of a disease or condition and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent," "preventing," and

"prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease. The terms "prevent," "preventing" and "prevention" 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.

[0148] 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 a subject 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 or stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., retard to some extent or stop) cancer cell infiltration into peripheral organs; inhibit (i.e., retard to some extent or stop) tumor metastasis; inhibit, to some extent, tumor growth; 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.

[0149] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0150] 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.

[0151] "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 a subject 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 a subject 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.

[0152] The use of the terms "a", "an", "the", and similar referents in the context of describing the 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 merely 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.

[0153] In the present disclosure, the term "halo" as used by itself or as part of another group refers to -Cl, -F, -Br, or -I.

[0154] In the present disclosure, the term "nitro" as used by itself or as part of another group refers to $-NO_2$.

[0155] In the present disclosure, the term "cyano" as used by itself or as part of another group refers to -CN.

[0156] In the present disclosure, the term "hydroxy" as used by itself or as part of another group refers to -OH.

[0157] 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 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.

[0158] In the present disclosure, the term "optionally substituted alkyl" as used by itself or as part of another group means that the alkyl as defined above 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 cycloalkyl. In one embodiment, the optionally substituted alkyl is substituted with two substituents. In another embodiment, the optionally substituted alkyl is substituted with one substituent. Non-limiting exemplary optionally substituted alkyl groups include $-CH_2CH_2NO_2$, $-CH_2SO_2CH_3$ $CH_2CH_2CO_2H$, $-CH_2CH_2SO_2CH_3$, $-CH_2CH_2COPh$, and $-CH_2C_6H_{11}$.

[0159] In the present disclosure, the term "cycloalkyl" as used by itself or as part of another group refers to saturated and partially unsaturated (containing one or two double

bonds) cyclic aliphatic hydrocarbons containing one, two, or 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 group has two rings. In one embodiment, the cycloalkyl group has one ring. In another embodiment, the cycloalkyl group is a C_{3-8} cycloalkyl group. In another embodiment, the cycloalkyl group is a C_{3-6} cycloalkyl group. Non-limiting exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, cyclopentenyl, and cyclohexenyl.

[0160] In the present disclosure, the term "optionally substituted cycloalkyl" as used by itself or as part of another group means that the cycloalkyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently selected from the group consisting of from halo, nitro, cyano, hydroxy, amino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, amido, carboxamido, sulfonamido, alkylcarbonyl, 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, mercaptoalkyl, and (heterocyclo)alkyl. In one embodiment, the optionally substituted cycloalkyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkyl is substituted with one substituent.

[0161] In the present disclosure, the term "alkenyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one, two, or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is a C_{2-6} alkenyl group. In another embodiment, the alkenyl group is a C_{2-4} alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

[0162] In the present disclosure, the term "optionally substituted alkenyl" as used herein by itself or as part of another group means the alkenyl as defined above 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, amido, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocyclo.

[0163] In the present disclosure, the term "alkynyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one, two, or three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-to-carbon triple bond. In one embodiment, the alkynyl group is a C_{2-6} alkynyl group. In another embodiment, the alkynyl group is a C_{2-4} alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

[0164] In the present disclosure, the term "optionally substituted alkynyl" as used herein by itself or as part of another group means the alkynyl as defined above 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, amido, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocyclo.

[0165] In the present disclosure, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl group 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.

[0166] In the present disclosure, the term "hydroxyalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three, hydroxy groups. In one embodiment, the hydroxyalkyl group is a monohydroxyalkyl group, i.e., substituted with one hydroxy group. In another embodiment, the hydroxyalkyl group is a dihydroxyalkyl group, i.e., substituted with two hydroxy groups.

[0167] In another embodiment, the hydroxyalkyl group is a C_{1-4} hydroxyalkyl group. 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.

[0168] 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 group is a C_{1-4} alkoxy group. In another embodiment, the alkoxy group is a C_{1-4} alkyl attached to a terminal oxygen atom, e.g., methoxy, ethoxy, and *tert*-butoxy.

[0169] In the present disclosure, the term "alkylthio" as used by itself or as part of another group refers to a sulfur atom substituted by an optionally substituted alkyl group. In one embodiment, the alkylthio group is a C_{1-4} alkylthio group. Non-limiting exemplary alkylthio groups include $-SCH_3$ and $-SCH_2CH_3$.

[0170] In the present disclosure, the term "alkoxyalkyl" as used by itself or as part of another group refers to an alkyl group 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.

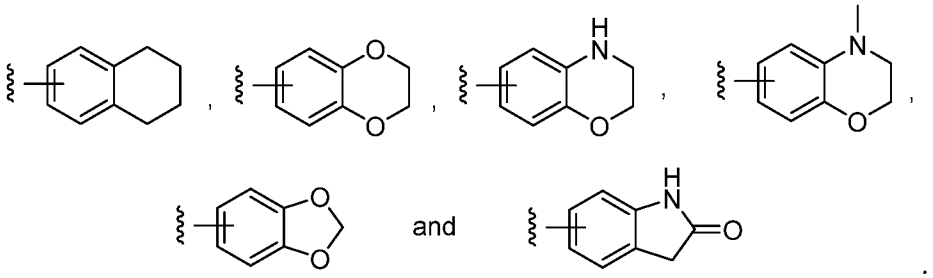
[0171] In the present disclosure, the term "haloalkoxy" as used by itself or as part of another group refers to a haloalkyl attached to a terminal oxygen atom. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

[0172] In the present disclosure, the term "aryl" as used by itself or as part of another group refers to a monocyclic or bicyclic aromatic ring system having from six to fourteen carbon atoms, i.e., C_6-C_{14} aryl, or the number of carbon atoms designated. 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. In another embodiment, the aryl group is phenyl.

[0173] In the present disclosure, the term "optionally substituted aryl" as used herein by itself or as part of another group means that the aryl as defined above is either unsubstituted or substituted with one to five substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, amido, carboxamido, sulfonamido, alkylcarbonyl, 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, mercaptoalkyl, and (heterocyclo)alkyl.

[0174] In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In one 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. 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-di-methoxyphenyl, 3,5-di-fluorophenyl 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, and 3-chloro-4-fluorophenyl. The term optionally substituted aryl is meant to include groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Non-limiting examples include:



[0175] 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-.

[0176] In the present disclosure, the term "aralkyloxy" as used by itself or as part of another group refers to an aralkyl group attached to a terminal oxygen atom. A non-limiting exemplary aralkyloxy group is $PhCH_2O$-.

[0177] In the present disclosure, the term "heteroaryl" or "heteroaromatic" refers to 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. 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 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), or 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. The heteroaryl can be attached to the remained of the molecule through any available carbon or nitrogen atom.

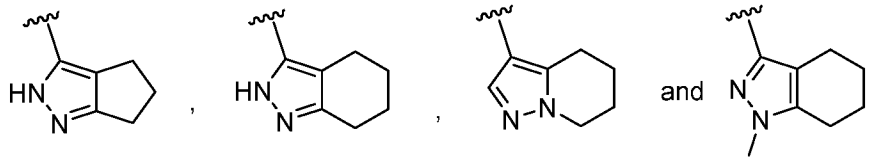
[0178] In one embodiment, the heteroaryl is a 5- or 6-membered heteroaryl. In one embodiment, the heteroaryl is a 5-membered heteroaryl, i.e., the heteroaryl is a monocyclic aromatic ring system having 5 ring atoms wherein at least one carbon atom of the ring is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. Non-limiting exemplary 5-membered heteroaryl groups include thienyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, and isoxazolyl.

[0179] 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.

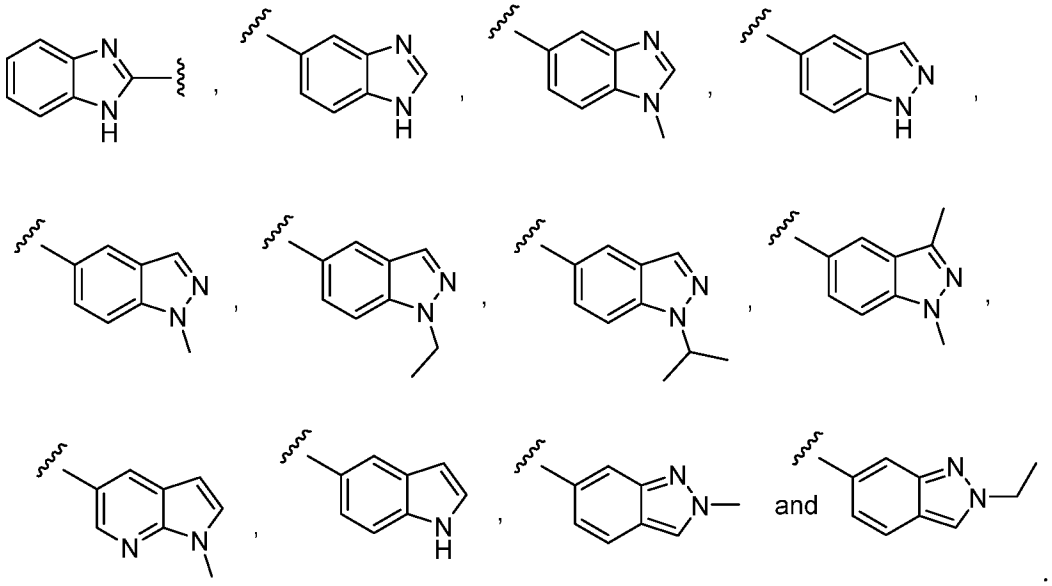
[0180] In the present disclosure, the term "optionally substituted heteroaryl" as used by itself or as part of another group means that the heteroaryl as defined above is either unsubstituted or substituted with one to four substituents, e.g., one or two substituents,

independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, amido, carboxamido, sulfonamido, alkylcarbonyl, 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, mercaptoalkyl, and (heterocyclo)alkyl. In one embodiment, the optionally substituted heteroaryl has one substituent. Any available carbon or nitrogen atom can be substituted.

[0181] The term optionally substituted heteroaryl is also meant to include groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Non-limiting examples include:



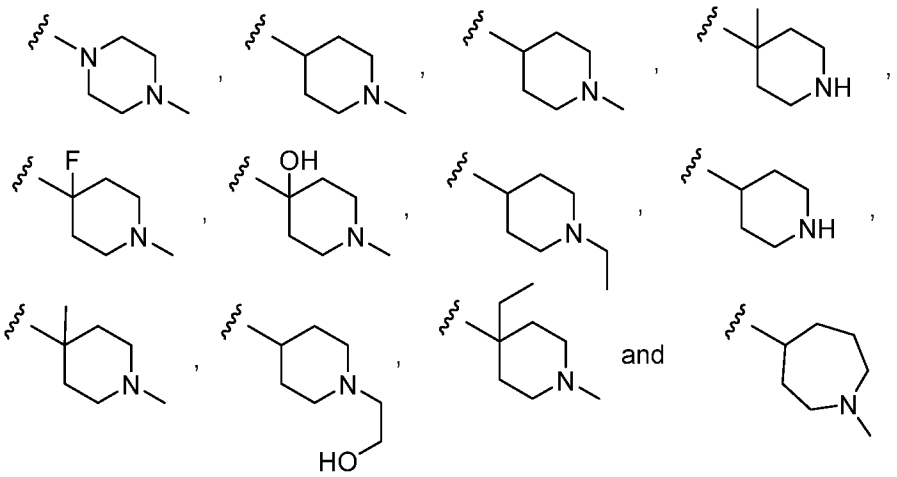
[0182] In another embodiment, the heteroaryl is an optionally substituted 9- to 14-membered bicyclic aromatic ring system, wherein at least one carbon atom of one of the rings is replaced with a heteroatom independently selected from the group consisting of oxygen, nitrogen, and sulfur. Non-limiting exemplary 9- to 14-membered bicyclic aromatic ring systems include:



[0183] In the present disclosure, the term "heterocycle" or "heterocyclo" as used by itself or as part of another group refers to 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. In one embodiment, the heterocyclo is a 4- to 8-membered heterocyclo. 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" is meant to include 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" is also meant to include groups having fused optionally substituted aryl groups, e.g., indolinyl, chroman-4-yl. In one embodiment, the heterocyclo group is a 5- or 6-membered cyclic group containing one ring and one or two oxygen and/or nitrogen atoms. 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 dioxanyl, tetrahydropyranyl, 2-oxopyrrolidin-3-yl, piperazin-2-one, piperazine-2,6-dione, 2-imidazolidinone, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, and indolinyl.

[0184] In the present disclosure, the term "optionally substituted heterocyclo" as used herein by itself or part of another group means the heterocyclo as defined above is either unsubstituted or substituted with one to four substituents independently selected from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, amido, carboxamido, sulfonamido, alkylcarbonyl, 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, mercaptoalkyl, or (heterocyclo)alkyl. Substitution may occur on any available carbon or nitrogen atom, or both. Non-limiting exemplary optionally substituted heterocyclo groups include:



[0185] In the present disclosure, the term "amino" as used by itself or as part of another group refers to a radical of the formula $-NR^{30a}R^{30b}$, wherein R^{30a} and R^{30b} are independently hydrogen, alkyl, hydroxyalkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, or optionally substituted heteroaryl, or R^{30a} and R^{30b} are taken together to form a 3- to 8-membered optionally substituted heterocyclo. In one embodiment, R^{30a} and R^{30b} are independently hydrogen or C_{1-4} alkyl. Non-limiting exemplary amino groups include $-NH_2$ and $-N(H)(CH_3)$.

[0186] In the present disclosure, the term "(amino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an amino group. In one embodiment, the (amino)alkyl is a C_{1-6} alkyl substituted with an amino group, i.e., an (amino)C_{1-6} alkyl. In another embodiment, the (amino)alkyl is an (amino)C_{1-4} alkyl. Non-limiting exemplary (amino)alkyl groups include $-CH_2CH_2NH_2$, $-CH_2CH_2N(H)CH_3$, $-CH_2CH_2N(CH_3)_2$, and $-CH_2N(H)$cyclopropyl.

[0187] In the present disclosure, the term "carboxamido" as used by itself or as part of another group refers to a radical of formula $-C(=O)NR^{31a}R^{31b}$, wherein R^{31a} and R^{31b} are each independently hydrogen, optionally substituted alkyl, hydroxyalkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclo, or optionally substituted heteroaryl, or R^{31a} and R^{31b} taken together with the nitrogen to which they are attached form a 3- to 8-membered optionally substituted heterocyclo group. In one embodiment, R^{31a} and R^{31b} are each independently hydrogen or optionally substituted alkyl. In one embodiment, R^{31a} and R^{31b} 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 $-CONH_2$, $-CON(H)CH_3$, $-CON(CH_3)_2$, and -CON(H)Ph.

[0188] In the present disclosure, the term "amido" as used by itself or as part of another group refers to a radical of formula $-N(R^{32a})C(=O)R^{32b}$, wherein R^{32a} is hydrogen or C_{1-4} alkyl; and R^{32b} is C_{1-6} alkyl, optionally substituted cycloalkyl, optionally substituted aryl, C_{1-4} alkoxy, or amino. In one embodiment, R^{32a} is hydrogen. In another embodiment, R^{32b} is C_{1-4} alkyl, C_{1-4} alkoxy, or amino. Non-limiting exemplary amido groups include $-N(H)C(=O)CH_3$, $-N(H)C(=O)OCH_3$, and $-N(H)C(=O)N(H)CH_3$.

[0189] In the present disclosure, the term "sulfonamido" as used by itself or as part of another group refers to a radical of the formula $-SO_2NR^{8a}R^{8b}$, wherein R^{8a} and R^{8b} are each independently hydrogen, optionally substituted alkyl, or optionally substituted aryl, or R^{8a} and R^{8b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. Non-limiting exemplary sulfonamido groups include $-SO_2NH_2$, $-SO_2N(H)CH_3$, and $-SO_2N(H)Ph$.

[0190] 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 by an alkyl group. A non-limiting exemplary alkylcarbonyl group is $-COCH_3$.

[0191] 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 by an optionally substituted aryl group. A non-limiting exemplary arylcarbonyl group is -COPh.

[0192] 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 by an alkoxy group. Non-limiting exemplary alkoxycarbonyl groups include -C(=O)OMe, -C(=O)OEt, and -C(=O)OtBu.

[0193] In the present disclosure, the term "alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, i.e., $-SO_2-$, substituted by any of the above-mentioned optionally substituted alkyl groups. A non-limiting exemplary alkylsulfonyl group is $-SO_2CH_3$.

[0194] In the present disclosure, the term "arylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, i.e., $-SO_2-$, substituted by any of the above-mentioned optionally substituted aryl groups. A non-limiting exemplary arylsulfonyl group is $-SO_2Ph$.

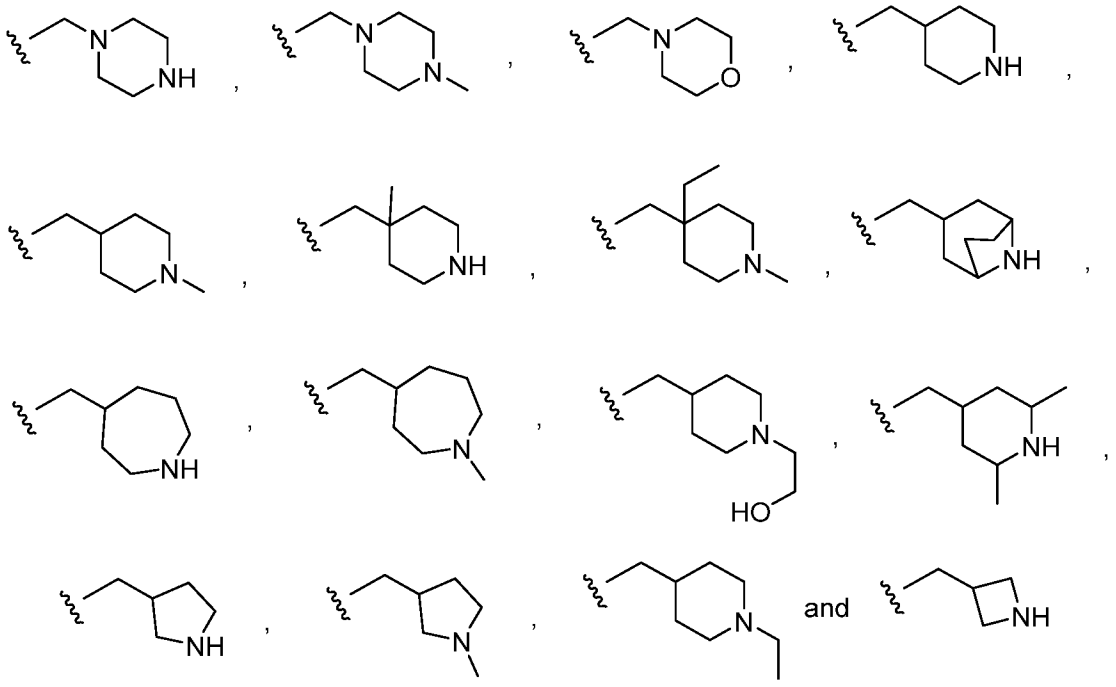
[0195] In the present disclosure, the term "mercaptoalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted by a –SH group.

[0196] In the present disclosure, the term "carboxy" as used by itself or as part of another group refers to a radical of the formula -COOH.

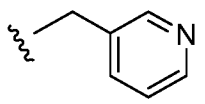
[0197] In the present disclosure, the term "carboxyalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with a -COOH. A non-limiting exemplary carboxyalkyl group is $-CH_2CO_2H$.

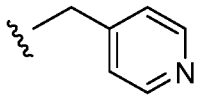
[0198] In the present disclosure, the terms "aralkyl" or "arylalkyl" as used by themselves or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted aryl groups. In one embodiment, the optionally substituted aralkyl group is a C_{1-4} alkyl substituted with one optionally substituted aryl group. In one embodiment, the optionally substituted aralkyl group is a C_1 or C_2 alkyl substituted with one optionally substituted aryl group. In one embodiment, the optionally substituted aralkyl group is a C_1 or C_2 alkyl substituted with one optionally substituted phenyl group. Non-limiting exemplary optionally substituted aralkyl groups include benzyl, phenethyl, $-CHPh_2$, $-CH_2$(4-F-Ph), $-CH_2$(4-Me-Ph), $-CH_2$(4-CF_3-Ph), and $-CH$(4-F-Ph)$_2$.

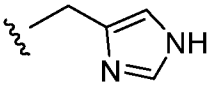
[0199] In the present disclosure, the terms "(heterocyclo)alkyl" as used by itself or part of another group refers to an alkyl group substituted with one or two optionally substituted heterocyclo groups. In one embodiment, the (heterocyclo)alkyl is a C_{1-4} alkyl substituted with one optionally substituted heterocyclo group, i.e., a (heterocyclo)C_{1-4} alkyl. In another embodiment, the (heterocyclo)alkyl is a C_{1-4} alkyl substituted with one optionally substituted 4- to 8-membered heterocyclo group, i.e., a (4- to 8-membered heterocyclo)C_{1-4} alkyl. Non-limiting exemplary (heterocyclo)alkyl groups include:



[0200] In the present disclosure, the terms "(heteroaryl)alkyl" as used by itself or part of another group refers to an alkyl group substituted with one or two optionally substituted heteroaryl groups. In one embodiment, the (heteroaryl)alkyl is a C_{1-4} alkyl substituted with one optionally substituted heteroaryl group, i.e., a (heteroaryl)C_{1-4} alkyl. In another embodiment, the (heteroaryl)alkyl is a C_{1-4} alkyl substituted with one optionally substituted 5- or 6-membered heteroaryl group, i.e., a (5- or 6-membered heteroaryl)C_{1-4} alkyl. Non-limiting exemplary (heteroaryl)alkyl groups include:



,


and


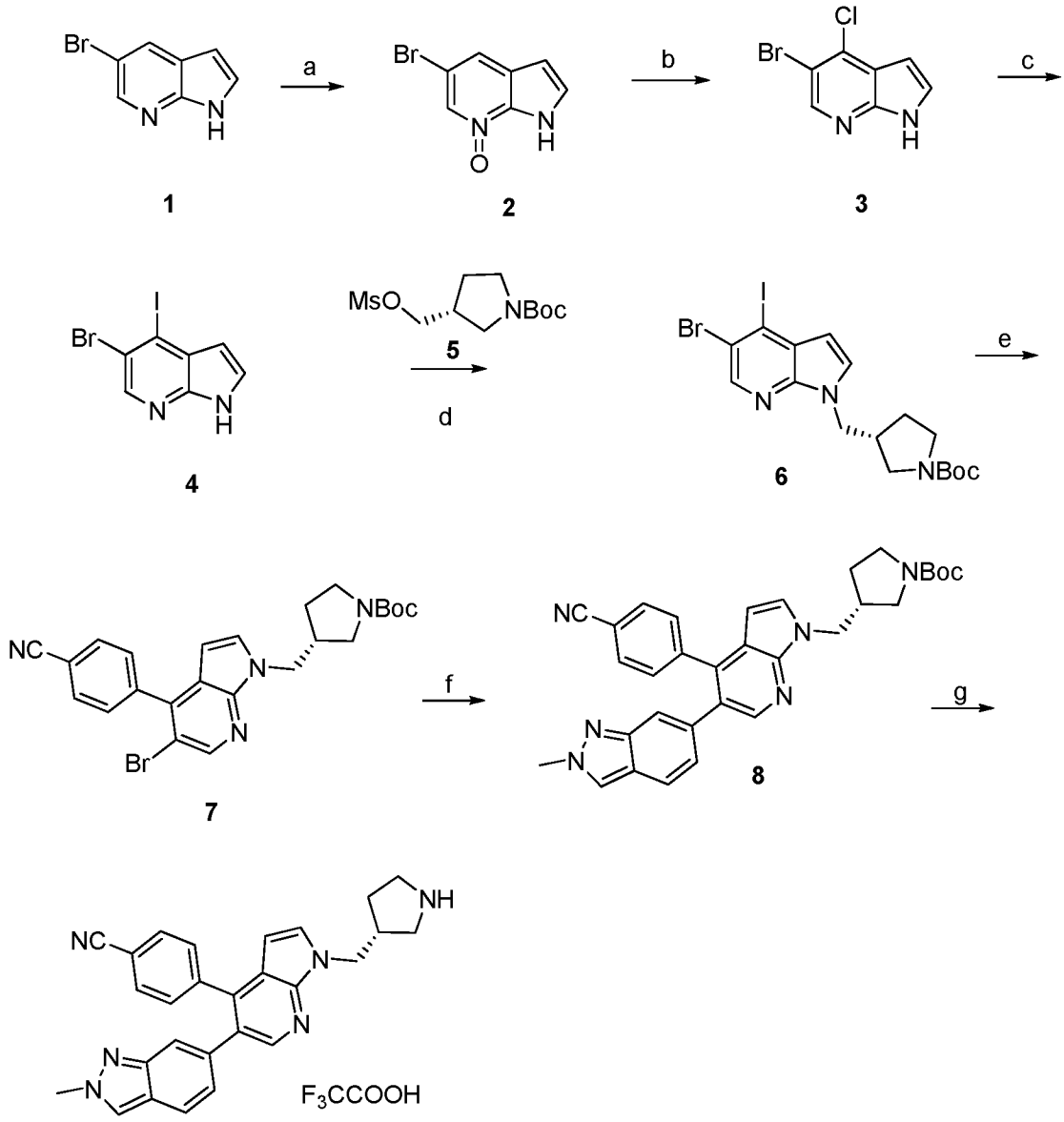
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EXAMPLES

EXAMPLE 1

Synthesis of (R)-4-(5-(2-methyl-2H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)benzonitrile (Cpd. No. 1)

Scheme 1



Cpd. No. 1 (TFA salt)

[0201] Reagents and conditions for Scheme 1: (a) mCPBA, EA, 0 °C – rt, 3 h; (b) $POCl_3$, NMP, -20 °C – rt; (c) NaI, AcCl, CH_3CN, overnight; 1 N NaOH, MeOH; (d) NaH, DMF, 0 – 50 °C, overnight; (e) $Pd(PPh_3)_4$, Na_2CO_3, Aryl boronic acid, toluene/EtOH/H_2O (2/1/1), 80 °C, 8 h, N_2; (f) $Pd(PPh_3)_4$, Na_2CO_3, Aryl boronic acid, toluene/EtOH/H_2O (2/1/1), 110 °C, 50 min; (g) DCM/TFA (4/1), rt.

[0202] Step a:

[0203] To a mixture of **1** (2.5 g, 0.69 mmol) in 50 mL of ethyl acetate was added portionwise mCPBA at 0 °C. The resulting mixture was stirred at room temperature for 3 h. The mixture was neutralized by saturated solution of sodium carbonate and extracted with THF. The organic layer was washed with water, brine and dried over anhydrous

sodium sulfate and concentrated under vacuum. The crude product was recrystallized from ethyl acetate to afford 2.6 g of **2**, which was used in the next step without further purification. $[M+H]^+$: 214.96.

[0204] Step b:

[0205] A suspension of **2** (2.60 g, 12.20 mmol) in 10 mL of NMP was cooled to -20 °C. $POCl_3$ (5.69 mL, 61.02 mmol) was added dropwise. The mixture was gradually warmed to room temperature and then cooled by an ice-bath. The reaction was quenched with water. The resulting mixture was directly purified by reverse flash column to afford 1.5 g of **3**. ^1H NMR (400 MHz, CDCl3) δ 9.93 (br, 1H), 8.42 (s, 1H), 7.41 (s, 1H), 6.65 (s, 1H).

[0206] Step c:

[0207] To a mixture of **3** (1.50 g, 6.48 mmol) in 20 mL of anhydrous acetonitrile was added sodium iodide (4.86 g, 32.40 mmol), followed by addition of acetyl chloride. The resulting mixture was stirred under reflux overnight. After cooled to room temperature, the mixture was filtered. The filtered cake was suspended in 20 mL of methanol. 20 mL of 1 N NaOH was added. Stirring was continued for 1 h. The mixture was filtered. The white solid was collected to give 1.10 g of **4**. ^1H NMR (400 MHz, DMSO) δ 8.28 (s, 1H), 7.62 (d, J = 3.4 Hz, 1H), 6.28 (d, J = 3.2 Hz, 1H).

[0208] Step d:

[0209] To an ice-cooled solution of **4** (200 mg, 0.62 mmol) in 4 mL of anhydrous DMF was added sodium hydride (37 mg, 0.93 mmol, 60% dispersion in mineral oil). The resulting mixture was stirred 15 min, followed by addition of **5** (208 mg, 0.74 mmol). Then the mixture was heated at 50 °C overnight. The reaction was quenched with 0.4 mL of saturated aq. NH_4Cl. The mixture was directly purified by reverse flash column to afford 258 mg of **6**. $[M+H]^+$: 507.02; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.22 (d, *J* = 3.5 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 4.33-4.13 (m, 2H), 3.54-3.34 (m, 2H), 3.34-3.19 (m, 1H), 3.18-3.02 (m, 1H), 2.83-2.66 (m, 1H), 1.92-1.82 (m, 1H), 1.67-1.56 (m, 1H), 1.43 (s, 9H).

[0210] Step e:

[0211] A mixture of **6** (124 mg, 0.24 mmol), 4-Cyanophenylboronic acid (36 mg, 0.24 mmol), $Pd(PPh_3)_4$ (14 mg mg, 12.25 μmol) and Na_2CO_3 (78 mg, 0.73 mmol) in 4 mL of a mixture solvent of toluene/ethanol/H_2O (2/1/1) was evacuated and refilled with nitrogen three times. The resulting mixture was stirred at 80 °C for 8 h and concentrated under vacuum. The residue was purified by flash silica gel column (0-60 % EA in hexane

gradient) to give 54 mg of **7**. $[M+H]^+$: 503.01, 505.00; ^1H NMR (400 MHz, CDCl3) δ 8.49 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 3.5 Hz, 1H), 6.18 (d, J = 3.3 Hz, 1H), 4.42-4.20 (m, 2H), 3.57-3.40 (m, 2H), 3.37-3.25 (m, 1H), 3.15 (dd, J = 10.8, 7.1 Hz, 1H), 2.87-2.74 (m, 1H), 2.00-1.88(m, 1H), 1.74-1.64 (m, 1H), 1.45 (s, 9H).

[0212] Step f:

[0213] A mixture of **7** (27 mg, 56 μmol), (2-methyl-2H-indazol-5-yl)boronic acid (12 mg, 67 μmol), $Pd(PPh_3)_4$ (3.2 mg, 2.80 μmol) and Na_2CO_3 (17.8 mg, 0.17 mmol) in 2 mL of toluene/EtOH/H_2O (2/1/1) was heated at 150 °C for 50 min under microwave irradiation. The resulting mixture was concentrated under vacuum and purified by flash silica gel column (0-100% EA in hexane gradient) to afford 22 mg of **8** $[M+H]^+$: 533.14.

[0214] Step g:

[0215] A solution of **8** (40 mg) was dissolved in 2.5 mL of DCM/TFA. The resulting solution was stirred at room temperature for 2 h and concentrated under vacuum. The residue was purified by reverse phase HPLC to give Cpd. No. 1 as the TFA salt. $[M+H]^+$: 433.25.

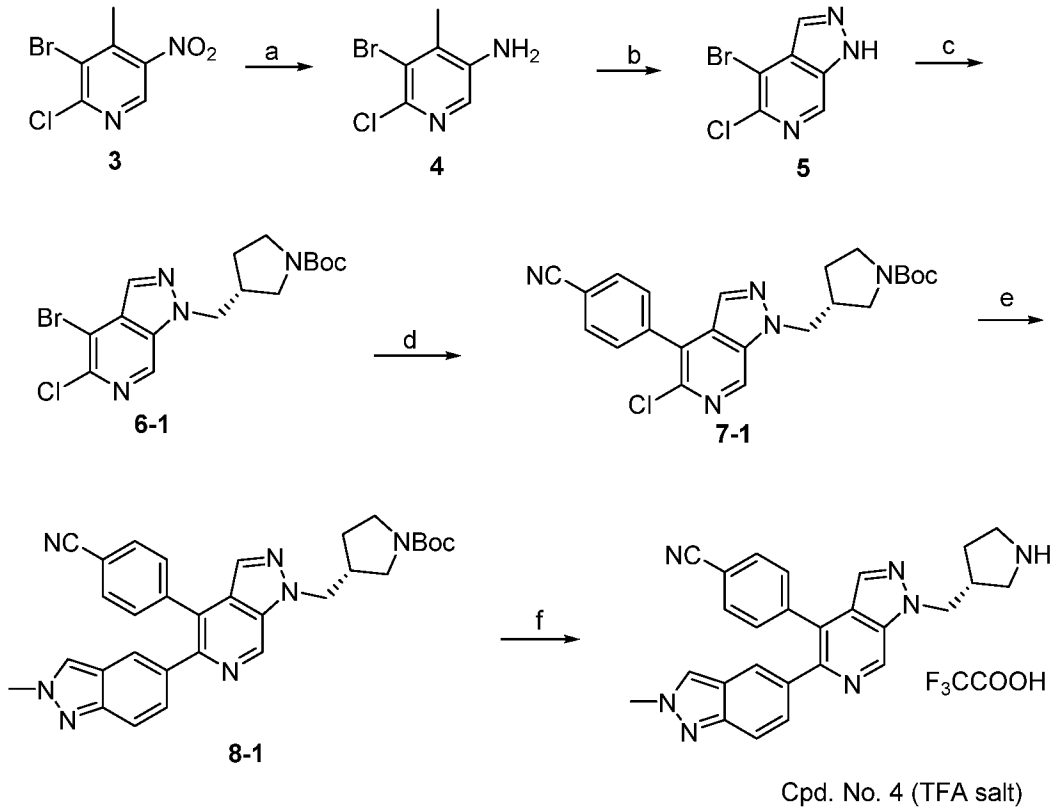
EXAMPLE 2

Synthesis of (R)-4-(5-(2-methyl-2H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrazolo[3,4-c]pyridin-4-yl)benzonitrile (Cpd. No. 4)

and

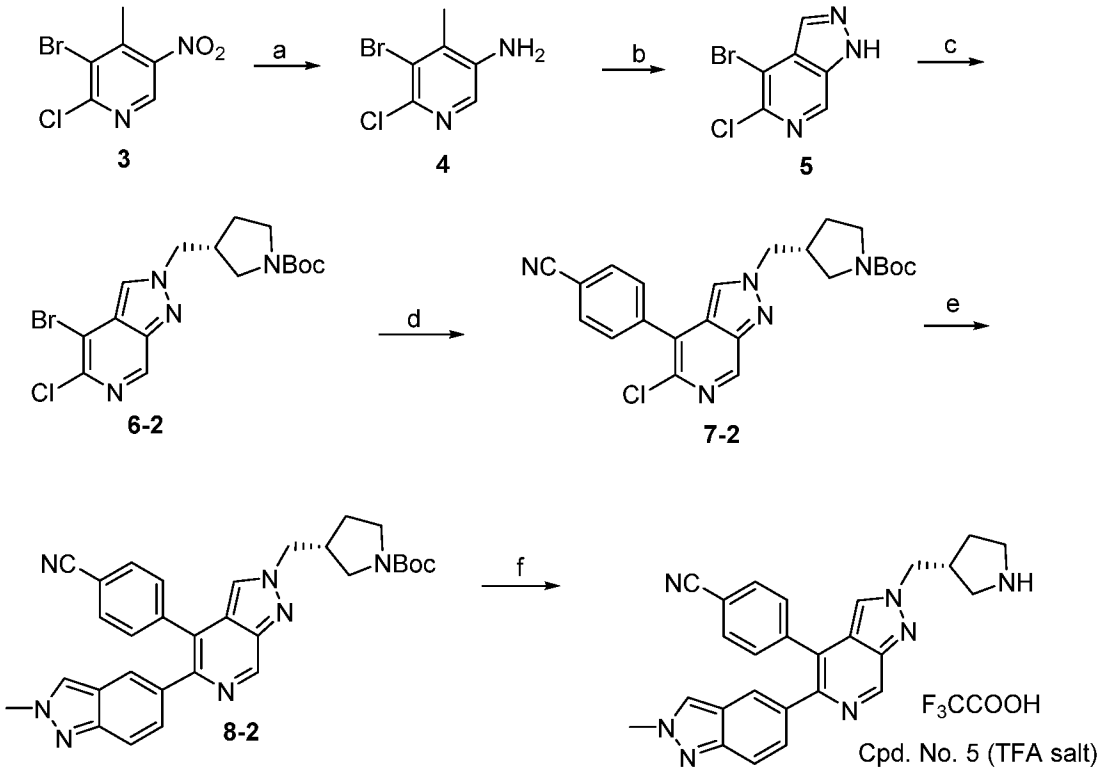
(R)-4-(5-(2-methyl-2H-indazol-5-yl)-2-(pyrrolidin-3-ylmethyl)-2H-pyrazolo[3,4-c]pyridin-4-yl)benzonitrile (Cpd. No. 5)

Scheme 2A



Cpd. No. 4 (TFA salt)

Scheme 2B



Cpd. No. 5 (TFA salt)

[0216] Reagents and conditions for Schemes 2A and 2B: (a) Zn, NH_4Cl, THF/MeOH (10/1), 0 °C–rt, 3 h; (b) AcOH, $NaNO_2$, rt, 2d; (c) **5** in Scheme 1 of EXAMPLE 1, NaH, DMF, 0–50 °C, overnight; (d) $Pd(PPh_3)_4$, Na_2CO_3, 4-Cyanophenylboronic acid, toluene/EtOH/H_2O (2/1/1), 80 °C, 8 h, N_2; (e) $Pd(PPh_3)_4$, Na_2CO_3, (2-methyl-2H-indazol-5-yl)boronic acid, toluene/EtOH/H_2O (2/1/1), 110 °C, 50 min; (f) DCM/TFA (4/1), rt.

[0217] Step a:

[0218] To an ice-bath cooled solution of **3** (300 mg, 1.19 mmol) in 11 mL of THF/MeOH (v/v = 10/1) was added ammonium chloride (638 mg, 11.93 mmol), followed by addition of zinc powder (780 mg, 11.93 mmol). The resulting mixture was gradually warmed to room temperature for 3 h. Then the mixture was filtered. The mother liquid was concentrated under vacuum. The residue was extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound as a brown solid, which was used in the next step without further purification. $[M+H]^+$: 220.87, 222.84, 224.86.

[0219] Step b:

[0220] A solution of sodium nitrite (280 mg, 4.06 mmol) in 1 mL of water was dropwise added to a solution of **4** (900 mg, 4.06 mmol) in 10 mL of AcOH. The resulting solution was stirred at room temperature for 2 days. Then the mixture was directly purified by flash reverse phase column (0-100% acetonitrile in water) to afford 358 mg of the title compound. $[M+H]^+$: 231.92, 233.92.

[0221] Step c: General procedure (example for preparation of Cpd. No. 4 in Scheme 2A)

[0222] Procedure is similar to the one described in step d in Scheme 1 of EXAMPLE 1. $[M+H]^+$: 415.07, 417.06. ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.00 (s, 1H), 4.41 (t, *J* = 10.1 Hz, 2H), 3.62-3.22 (m, 2H), 3.19- 3.05 (m, 1H), 2.93-2.76 (m, 1H), 2.03-1.89 (m, 1H), 1.74-1.59 (m, 1H), 1.42 (s, 9H).

[0223] Step d: General procedure (example for preparation of Cpd. No. 4 in Scheme 2A)

[0224] Procedure is similar to the one described in step e in Scheme 1 of EXAMPLE 1. $[M+Na]^+$: 460.11, 461.97;

[0225] Step e: General procedure (example for preparation of Cpd. No. 4 in Scheme 2A)

[0226] Procedure is similar to the one described in step f in Scheme 1 of EXAMPLE 1. Yield: 60%; ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.94 (s, 1H), 7.85 (s, 1H), 7.65-7.60 (m, 3H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 9.4 Hz, 1H), 4.58 (d, *J* = 7.6 Hz, 2H), 4.21 (s, 3H), 3.57-3.47 (m, 2H), 3.41-3.30 (m, 1H), 3.25-3.19 (m, 1H), 2.99-2.90 (m, 1H), 2.01-1.95 (m, 1H), 1.77 (s, 2H), 1.46 (d, *J* = 1.1 Hz, 9H).

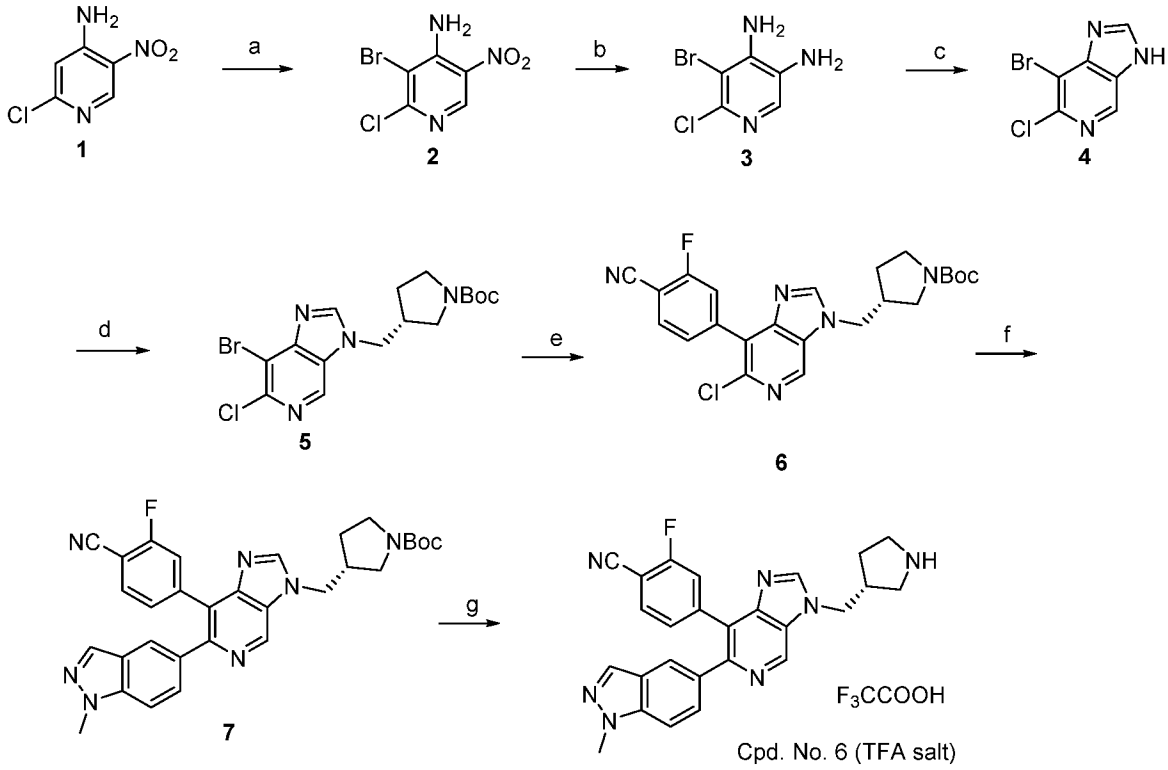
[0227] Step f: General procedure (example for preparation of Cpd. No. 4 in Scheme 2A)

[0228] Procedure is similar to the one described in step g in Scheme 1 of EXAMPLE 1.

EXAMPLE 3

Synthesis of (R)-2-fluoro-4-(6-(1-methyl-1H-indazol-5-yl)-3-(pyrrolidin-3-ylmethyl)-3H-imidazo[4,5-c]pyridin-7-yl)benzonitrile (Cpd. No. 6)

Scheme 3



[0229] Reagents and conditions for Scheme 3: (a) NBS, AcOH, 60 °C, 4 h; (b) Zn, NH_4Cl, THF/MeOH (10/1), 0 °C–rt, 3 h; (c) Formic acid, reflux, 18 h; (d) **5** in Scheme 1 of EXAMPLE 1, NaH, DMF, 0 – 50 °C, overnight; (e) $Pd(PPh_3)_4$, Na_2CO_3, (4-cyano-3-fluorophenyl)boronic acid, toluene/EtOH/H_2O (2/1/1), 80 °C, 8 h, N_2; (f) $Pd(PPh_3)_4$, Na_2CO_3, (1-methyl-1H-indazol-5-yl)boronic acid, toluene/EtOH/H_2O (2/1/1), 110 °C, 50 min; (g) DCM/TFA (4/1), rt.

[0230] Step a:

[0231] NBS (564 mg, 3.17 mmol) was added to a solution of **1** (500 mg, 2.88 mmol) in 8 mL of AcOH. The resulting mixture was stirred at 60 °C for 4 h. After cooled to room temperature, the mixture was diluted with water. The precipitate was collected by filtration to afford 580 mg of 2 as a yellow solid, which was used in the next step without further purification. $[M+H]^+$: 251.91, 253.96.

[0232] Step b:

[0233] Compound **2** (400 mg, 1.58 mmol) was dissolved in 15 mL THF/MeOH (v/v = 2/1). To the solution was added ammonium chloride (848 mg, 15.84 mmol), followed addition of zinc powder at 0 °C. The resulting mixture was gradually warmed to room temperature for 5 h. TLC indicated the starting material was completely converted. The mixture was filtered through a layer of celite. The mother liquid was concentrated. The residue was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the crude diamine intermediate, which was used in the next step without further purification.

[0234] Step c:

[0235] The crude **3** above was dissolved in 10 mL of formic acid. The resulting solution was refluxed for 18 h and then concentrated. The residue was diluted with aq. sodium carbonate and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford **4**. $[M+H]^+$: 231.96, 233.93.

[0236] Step d:

[0237] Procedure is similar to the one described in step d in Scheme 1 of EXAMPLE 1. Yield: 5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.07 (s, 1H), 4.36-4.15 (m, 2H), 3.63-3.27(m, 3H), 3.19-3.05 (m, 1H), 2.83-2.70 (m, 1H), 2.08-1.95 (m, 1H), 1.79-1.63 (m, 1H), 1.44 (s, 9H).

[0238] Step e:

[0239] Procedure is similar to the one described in step e in Scheme 1 of EXAMPLE 1. $[M+H]^+$: 456.17, 458.10; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.02 (s, 1H), 7.80-7.75 (m, 1H), 7.57-7.51 (m, 2H), 4.39-4.25 (m, 2H), 3.59 -3.34 (m, 3H), 3.22-3.11 (m, 1H), 2.88-2.74 (m, 1H), 2.09-1.97 (m, 1H), 1.75-1.63 (m, 2H), 1.45 (s, 9H).

[0240] Step f:

[0241] Procedure is similar to the one described in step f in Scheme 1 of EXAMPLE 1. $[M+H]^+$: 552.19.

[0242] Step g:

[0243] Procedure is similar to the one described in step g in Scheme 1 of EXAMPLE 1.

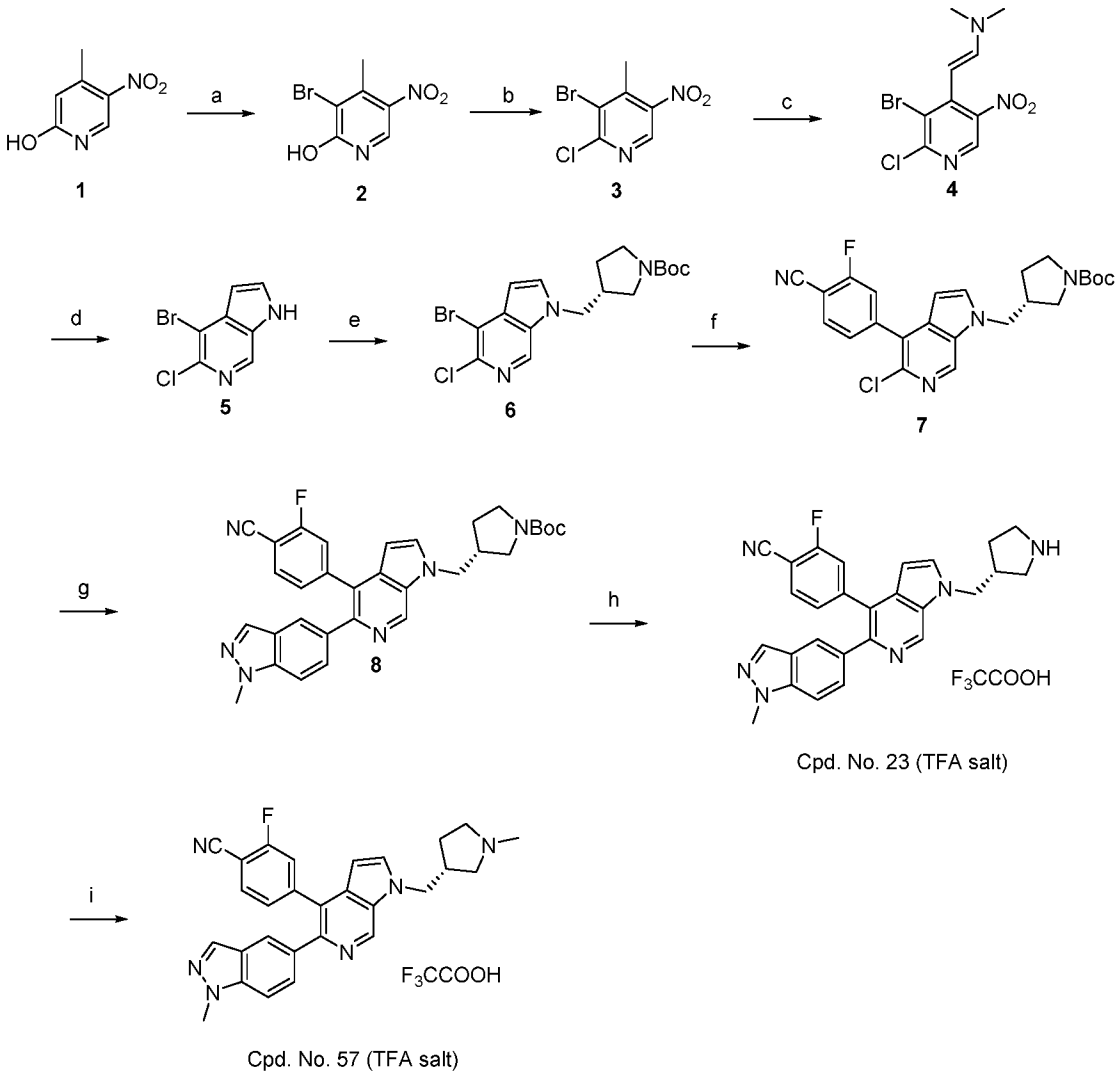
EXAMPLE 4

Synthesis of (R)-2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-(pyrrolidin-3-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile (Cpd. No. 23)

and

(R)-2-fluoro-4-(5-(1-methyl-1H-indazol-5-yl)-1-((1-methylpyrrolidin-3-yl)methyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile (Cpd. No. 57)

Scheme 4



[0244] Reagents and conditions for Scheme 4: (a) Br_2, H_2O, 40 °C, 5 h; (b) $POCl_3$, 110 °C, 5 h; (c) DMF-DMA, toluene, 80 °C, 5 h; (d) Fe, AcOH, 70 °C, 3 h; (e) **5** in Scheme 1 of EXAMPLE 1, NaH, DMF, p-toluenesulfonic acid esters, 0-80 °C, overnight; (f) Aryl boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O (4/2/1), 90 °C, 16 h; (g) Aryl boronic acids or esters, $Pd(OAc)_2$, Xphos, K_3PO_4, 110 °C 16 h; (h) DCM/TFA (4/1), rt; (i) Aldehyde, Et_3N, $NaBH(OAc)_3$, DCM, rt, overnight.

[0245] Step a:

[0246] A suspension of **1** (3.0 g, 19.46 mmol) was heated to 40 °C. Bromine (1.1 mL, 21.41 mmol) was added dropwise. The resulting mixture was stirred at 40 °C for 5 h. The mixture was filtered. The cake was collected to give 3.46 g of the title compound.

$[M+H]^+$: 232.94, 234.96; ^1H NMR (400 MHz, DMSO) δ 13.03 (br, 1H), 8.57 (s, 1H), 2.58 (s, 3H).

[0247] Step b:

[0248] A mixture of 3.45 g of **2** in 20 mL of $POCl_3$ was heated at 110 °C for 5 h. The solution was concentrated under vacuum. The residue was cooled by ice-bath. The cold water was added dropwise to the residue. The precipitate was collected by filtration and dried to afford 3.3 g of the title compound. $[M+H]^+$: 250.92, 252.92; ^1H NMR (400 MHz, DMSO) δ 8.96 (s, 1H), 2.63 (s, 3H).

[0249] Step c:

[0250] A solution of **3** (1.89 g, 7.52 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (3.02 mL, 22.55 mmol) in 20 mL of toluene was heated at 80 °C for 5 h. The resulting burgundy solution was concentrated under vacuum to afford the enamine intermediate 4, which was used in the next step without further purification. $[M+H]^+$: 305.90, 307.90, 309.90.

[0251] Step d:

[0252] The crude intermediate of the last step **4** was dissolved in 30 mL of acetic acid. Iron powder (2.10 g, 37.58 mmol) was added to the solution. The resulting mixture was stirred at 70 °C for 3 h. The mixture was filtered through a layer of celite. The mother liquid was concentrated. The residue was purified by flash reverse phase column with 0-100% gradient of acetonitrile in water to give 550 mg of the title compound. $[M+H]^+$: 230.96, 232.93; ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (br, 1H), 8.59 (s, 1H), 7.52 (t, J = 2.9 Hz, 1H), 6.65 (t, J = 2.3 Hz, 1H).

[0253] Step e:

[0254] To an ice-cooled solution of **5** (310 mg, 1.34 mmol) in 6 mL of anhydrous DMF was added sodium hydride (80 mg, 2.01 mmol, 60% dispersion in mineral oil). The resulting mixture was stirred 15 min, followed by addition of 5 in Scheme 1 of EXAMPLE 1 (393 mg, 1.41 mmol). Then the mixture was heated at 80 °C overnight. The reaction was quenched with 0.5 mL of saturated aq. NH_4Cl. The mixture was directly purified by reverse flash column (0-100% acetonitrile in water) to afford 311 mg of **6**. $[M+H]^+$: 414.10, 416.13; ^1H NMR (400 MHz, CDCl3) δ 8.41 (s, 1H), 7.29 (dd, J = 3.1, 1.1 Hz, 1H), 6.52 (s, 1H), 4.16 (d, J = 7.3 Hz, 2H), 3.54-3.26 (m, 3H), 3.16-3.01 (m, 1H), 2.77-2.63 (m, 1H), 1.96-1.86 (m, 1H), 1.65-1.56 (m, 1H), 1.43 (s, 9H).

[0255] Step f:

[0256] A mixture of **6** (105 mg, 0.25 mmol), (4-cyano-3-fluorophenyl)boronic acid (44 mg, 0.26 mmol), $Pd(PPh_3)_4$ (15 mg, 12.66 μmol) and Na_2CO_3 (80 mg, 0.76 mmol) in 7 mL of a mixture solvent of toluene/ethanol/H_2O (4/2/1) was evacuated and refilled with nitrogen three times. The resulting mixture was stirred at 80 °C overnight and concentrated under vacuum. The residue was purified by flash silica gel column (0-100% EA in hexane gradient) to give 112 mg of **7**. $[M+H]^+$: 455.17.

[0257] Step g:

[0258] To a 50 mL of round bottle was charged with **7** (19 mg, 0.42 mmol), K_3PO_4 (18 mg, 0.84 mmol), $Pd(OAc)_2$ (0.47 mg, 2.09 μmol), Xphos (1.99 mg, 4.18 μmol) and (1-methyl-1H-indazol-5-yl)boronic acid (11 mg, 0.63 mmol). The bottle was evacuated and refilled with nitrogen three times. Then 2 mL of a mixture of solvent of nBuOH/H_2O (v/v = 4:1) was added via syringe. The resulting mixture was evacuated and refilled with nitrogen three times. Then the mixture was heated at 105 °C for 16 h. LC-MS monitored that the starting material was completely converted. The mixture was concentrated and purified by flash silica gel column (0-10% MeOH in EA) to afford **8**. $[M+H]^+$: 550.64; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.87 (s, 1H), 7.68 (d, *J* = 0.7 Hz, 1H), 7.47 (t, *J* = 7.1 Hz, 1H), 7.28 (d, *J* = 2.6 Hz, 1H), 7.25-7.18 (m, 2H), 7.18-7.13 (m, 1H), 7.12-7.08 (m, 1H), 6.36 (s, 1H), 4.31-4.18 (m, 2H), 4.01 (s, 3H), 3.54-3.39 (m, 2H), 3.36-3.25 (m, 1H), 3.17-3.06 (m, 1H), 2.84-2.70 (m, 1H), 1.95- 1.91(m, 1H), 1.71- 1.60(m, 1H), 1.41 (s, 9H).

[0259] Step h:

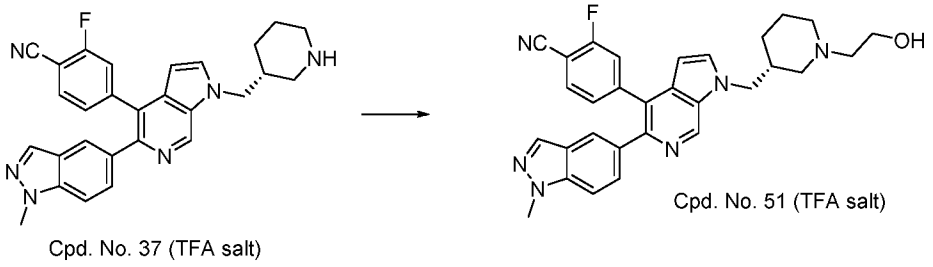
[0260] Procedure is similar to the one described in step g in Scheme 1 of EXAMPLE 1 to give Cpd. No. 23 as the TFA salt.

[0261] Step i:

[0262] Cpd. No. 23 (87 mg, 0.13 mmol) was dissolved in 5 mL of DCM. To the solution was added Et_3N (0.36 mL, 0.26 mmol) and aq. formaldehyde (0.29 mL, 0.38 mmol, 37% Wt in water), followed by addition of sodium triacetoxyborohydride (81 mg, 0.38 mmol). The resulting mixture was stirred at room temperature overnight. LC-MS indicated the starting material was not completely converted. Additional 3 equivalent formaldehyde and sodium triacetoxyborohydride were added. Stirring was continued for 8 h. Then the mixture was concentrated under vacuum. The residue was purified by reverse HPLC (15-75% acetonitrile in water containing 0.1% TFA) to give 80 mg of Cpd. No. 57.

EXAMPLE 5

Synthesis of (R)-2-fluoro-4-(1-((1-(2-hydroxyethyl)piperidin-3-yl)methyl)-5-(1-methyl-1H-indazol-5-yl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile (Cpd. No. 51)

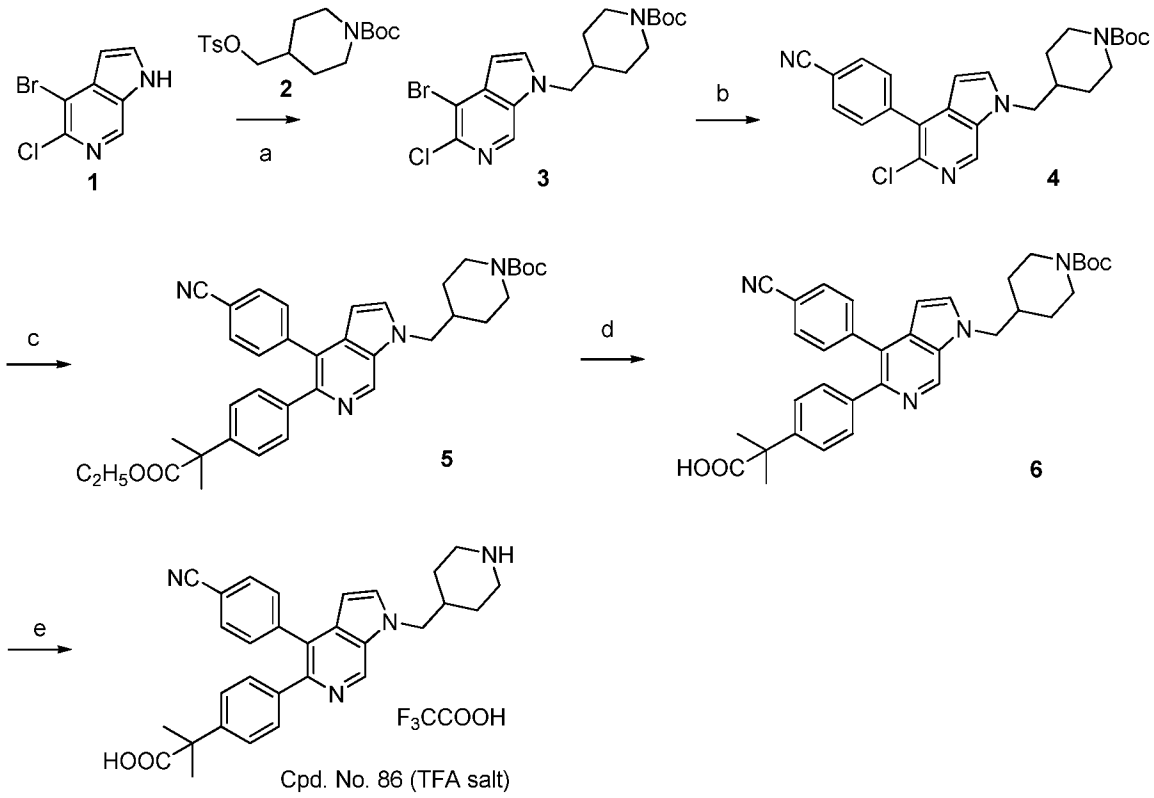


Reagents and conditions for Scheme 5: 2-bromoethan-1-ol, DIPEA, KI, CH_3CN, 90 °C, 22 h.

[0263] To the solution of 10 mg of TFA salt of Cpd. No. 37 in 2 mL of acetonitrile was added 2.85 mg of 2-bromoethan-1-ol, DIPEA (0.13 mL) and catalytic amount of potassium iodide. The resulting mixture was stirred at 80 °C for 22 h and concentrated under vacuum. The residue was dissolved in 2 mL of methanol. The remaining starting material was consumed by addition of Boc anhydride. Then the resulting solution was concentrated under vacuum. The residue was purified by reverse HPLC (15-75% acetonitrile in water containing 0.1% TFA) to give Cpd. No. 51.

EXAMPLE 6

Synthesis of 2-(4-(4-(4-cyanophenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-5-yl)phenyl)-2-methylpropanoic acid (Cpd. No. 86)



[0264] Reagents and conditions for Scheme 6: (a) NaH, DMF, p-toluenesulfonic acid esters, 0-80 °C, overnight; (b) Aryl boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O (4/2/1), 90 °C, 16 h; (c) Aryl boronic acids or esters, $Pd(OAc)_2$, Xphos, K_3PO_4, 110 °C 16 h; (d) LiOH·H_2O, THF/H_2O/MeOH (4.5/4.5/1), rt, overnight; (e) DCM/TFA (4/1), rt.

[0265] Step a:

[0266] Procedure is similar to the one described in step e in Scheme 5 of EXAMPLE 5.

[0267] Step b:

[0268] Procedure is similar to the one described in step f in Scheme 5 of EXAMPLE 5.

[0269] Step c:

[0270] Procedure is similar to the one described in step g in Scheme 5 of EXAMPLE 5.

[0271] Step d:

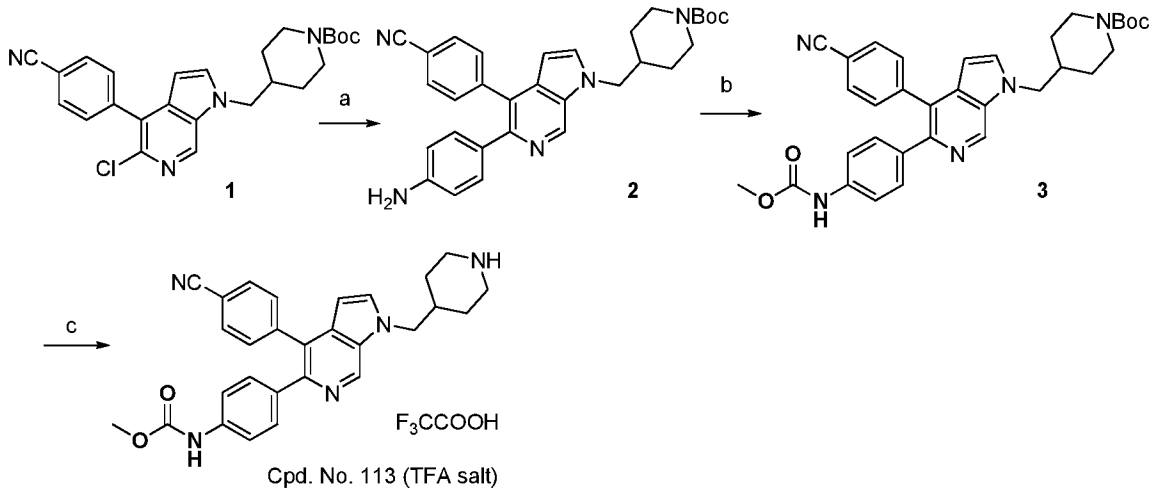
[0272] To the solution of 39 mg of **5** (0.07 mmol) in 2 mL of mixture solvent of THF/H_2O/MeOH (4.5/4.5/1) was added 8.3 mg lithium hydroxide monohydrate (0.21 mmol). The resulting mixture was stirred at room temperature overnight. Then the resulting solution was concentrated under vacuum. The residue was purified by reverse HPLC (25-75% acetonitrile in water) to give the title compound.

[0273] Step e:

[0274] Procedure is similar to the one described in step g in Scheme 1 of EXAMPLE 1 to give Cpd. No. 86 as the TFA salt.

EXAMPLE 7

Synthesis of methyl (4-(4-(4-cyanophenyl)-1-(piperidin-4-ylmethyl)-1H-pyrrolo[2,3-c]pyridin-5-yl)phenyl)carbamate (Cpd. No. 113)



Cpd. No. 113 (TFA salt)

[0275] Reagents and conditions for Scheme 7: (a) Aryl boronic acids or esters, $Pd(OAc)_2$, Xphos, K_3PO_4, 110 °C 16 h; (b) Methyl chloroformate, Et_3N, DCM, rt, overnight; (c) DCM/TFA (4/1), rt.

[0276] Step a:

[0277] Procedure is similar to the one described in step g in Scheme 5 of EXAMPLE 5.

[0278] Step b:

[0279] To the solution of 15 mg of **2** (0.03 mmol) in 1 mL of DCM was added methyl chloroformate (8.3 μL, 0.06 mmol) and Et_3N (12.5 μL, 0.09 mmol). The resulting mixture was stirred at room temperature overnight. Then the resulting solution was concentrated under vacuum. The residue was purified by flash silica gel column (0-10 % MeOH in DCM) to give the title compound.

[0280] Step c:

[0281] Procedure is similar to the one described in step g in Scheme 1 of EXAMPLE 1 to give Cpd. No. 113 as the TFA salt.

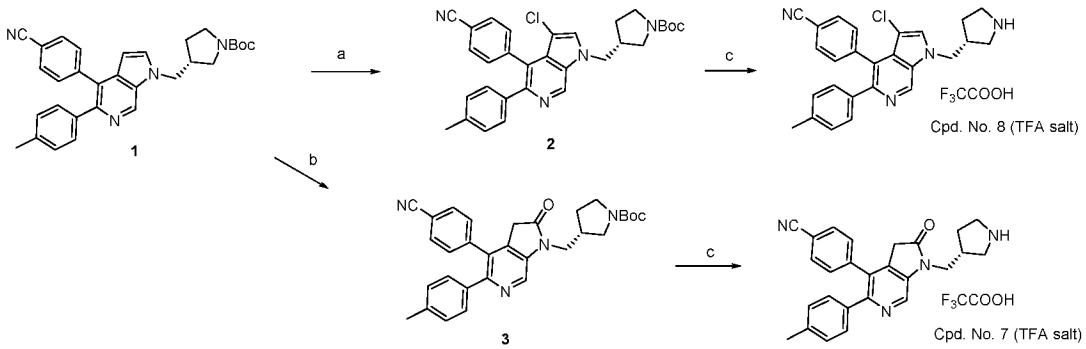
EXAMPLE 8

Synthesis of (R)-4-(3-chloro-1-(pyrrolidin-3-ylmethyl)-5-(p-tolyl)-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile (Cpd. No. 8)

and

(R)-4-(2-oxo-1-(pyrrolidin-3-ylmethyl)-5-(p-tolyl)-2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)benzonitrile (Cpd. No. 7).

Scheme 6



[0282] Reagents and conditions for Scheme 8: (a) NCS, CH_3CN, 90 °C, overnight; (b) Br_2, *t*BuOH/H_2O (1:1), rt, 40 min; then Zn, AcOH, rt. (c) DCM/TFA(4/1), rt, 4 h.

[0283] Step a:

[0284] NCS (4.9 mg, 36 µmol) was added to a solution of **1** (18 mg, 36 µmol) in 2 mL of acetonitrile. The resulting mixture was stirred at 80 °C overnight and then concentrated under vacuum. The resulting mixture was purified by flash reverse column with 70% CH_3CN (0.1% TFA) in H_2O (0.1% TFA) as eluent to afford 17 mg of 2 as a TFA salt. $[M+H]^+$: 527.21; 529.21.

[0285] Step b:

[0286] To a solution of **1** (24 mg, 49 µmol) in 2 mL of *t*BuOH/H_2O was added Br_2 (11 µL, 0.22 mmol). The resulting mixture was stirred at room temperature for 40 min. Then the mixture was diluted with saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was dissolved in 2 mL of acetic acid. Zinc powder (32 mg, 0.49 mmol) was added. The resulting mixture was stirred at room temperature overnight. Additional of 100 mg of zinc powder was added. Stirring was continued at room temperature for 4 h. The reaction mixture was filtered and the mother liquors were concentrated and purified by preparative HPLC to give the intermediate 3. $[M+H]^+$: 509.25.

[0287] Step c:

[0288] Procedure is similar to the one described in step g in Scheme 1 of EXAMPLE 1 to give Cpd. Nos. 7 and 8.

EXAMPLE 9

Analytical Characterization of Compounds of the Disclosure

[0289] Table 3 provides ^{1}H NMR and/or mass spectroscopy data for representative Compounds of the Disclosure prepared using methodology described in EXAMPLES 1-8 and known in the art. All compounds in Table 3 were characterized as the TFA salt.

Table 3

Cpd. No.	MS $[M+H]^+$	^{1}H NMR
1	433.25	^{1}H NMR (400 MHz, MeOD) δ 8.40 (s, 1H), 8.14 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.57-7.53 (m, 2H), 7.48-7.41 (m, 3H), 7.01 (dd, *J* = 8.9, 1.6 Hz, 1H), 6.42 (d, *J* = 3.6 Hz, 1H), 4.48 (d, *J* = 7.2 Hz, 2H), 4.19 (s, 3H), 3.51-3.43 (m, 1H), 3.40-3.25 (m, 2H), 3.19-3.13 (m, 1H), 3.09-3.01 (m, 1H), 2.20-2.11 (m, 1H), 1.94-1.84 (m, 1H).
2	393.23	^{1}H NMR (400 MHz, MeOD) δ 8.32 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 3.4 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.38 (d, *J* = 3.5 Hz, 1H), 4.47 (d, *J* = 7.2 Hz, 2H), 3.49-3.41 (m, 1H), 3.40-3.31 (m, 2H), 3.20-3.11 (m, 1H), 3.07-3.06 (m, 1H), 2.30 (s, 3H), 2.21- 2.11 (m, 1H), 1.94-1.82 (m, 1H).
3	451.08	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.16 (s, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.60-7.56 (m, 2H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.27 (t, *J* = 9.2 Hz, 2H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.44 (d, *J* = 3.5 Hz, 1H), 4.49 (d, *J* = 7.1 Hz, 2H), 4.20 (s, 3H), 3.49-3.43 (m, 1H), 3.39-3.25 (m, 2H), 3.20-3.13 (m, 1H), 3.09-3.02 (m, 1H), 2.15 (td, *J* = 13.3, 7.6 Hz, 1H), 1.95-1.85 (m, 1H).
4	434.31	^{1}H NMR (400 MHz, MeOD) δ 9.39 (s, 1H), 8.17 (d, *J* = 12.7 Hz, 2H), 7.74-7.67 (m, 3H), 7.55-7.50 (m, 3H), 7.25 (d, *J* = 9.0 Hz, 2H), 4.80-4.76 (m, 2H), 4.20 (s, 3H), 3.53-3.41 (m, 2H), 3.27-3.22 (m, 1H), 3.17-3.09 (m, 1H), 2.25 (t, *J* = 17.8 Hz, 3H), 2.00-1.88 (m, 1H).
5	434.31	
6	452.11	^{1}H NMR (400 MHz, MeOD) δ 9.39 (s, 1H), 8.76 (s, 1H), 8.04 (d, *J* = 0.7 Hz, 1H), 7.86 (s, 1H), 7.69-7.63 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.46 (dd, *J* = 10.1, 1.3 Hz, 1H), 7.36 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.25 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.75- 4.59 (m, 2H), 4.07 (s, 3H), 3.56-3.48 (m, 2H), 3.36- 3.33 (m, 1H), 3.26-3.24 (m, 1H), 3.21-3.11 (m, 2H), 2.26-2.18 (m, 1H), 1.96-1.87 (m, 1H).
7	409.25	
8	427.02	^{1}H NMR (400 MHz, MeOD) δ 9.47 (s, 1H), 8.34 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.23-7.17 (m, 4H), 4.69-4.58 (m, 2H), 3.57-3.42 (m, 3H), 3.17-3.07 (m, 2H), 2.33 (s, 3H), 2.23-2.14 (m, 1H), 1.90 (dd, *J* = 13.1, 8.4 Hz, 1H).
9	393.64	
10	423.10	

11	408.11	^{1}H NMR (400 MHz, MeOD) δ 9.33 (s, 1H), 8.23 (d, *J* = 3.0 Hz, 1H), 8.05 (s, 1H), 7.80 (s, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.29-7.20 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 3.0 Hz, 1H), 4.66 (t, *J* = 7.1 Hz, 2H), 3.56-3.44 (m, 2H), 3.37-3.31 (m, 1H), 3.14 (dd, *J* = 20.2, 9.2 Hz, 2H), 2.32 (s, 3H), 2.18 (dd, *J* = 19.7, 12.8 Hz, 1H), 1.96 – 1.85 (m, 1H).
12	432.85	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.29 (s, 2H), 7.84 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 1H), 6.77 (d, *J* = 2.9 Hz, 1H), 4.68 (t, *J* = 7.1 Hz, 2H), 4.22 (s, 3H), 3.57-3.44 (m, 2H), 3.36-3.32 (m, 1H), 3.20-3.09 (m, 2H), 2.24-2.14 (m, 1H), 1.93-1.85 (m, 1H).
13	436.14	
14	436.12	^{1}H NMR (400 MHz, MeOD) δ 9.36 (s, 1H), 8.23 (d, *J* = 3.0 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 3.0 Hz, 1H), 4.71-4.59 (m, 2H), 3.54-3.40 (m, 3H), 3.16-3.06 (m, 2H), 2.28-2.05 (m, 4H), 1.93-1.84 (m, 1H).
15	433.06	^{1}H NMR (400 MHz, MeOD) δ 9.42 (s, 1H), 8.29 (d, *J* = 3.0 Hz, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.29 (dd, *J* = 8.8, 1.7 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 4.68 (t, *J* = 7.6 Hz, 2H), 4.07 (s, 3H), 3.55-3.32(m, 3H), 3.18-3.09 (m, 2H), 2.23-2.12 (m, 1H), 1.96-1.86 (m, 1H).
16	303.11	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.47 (s, 1H), 8.34 (d, *J* = 3.1 Hz, 1H), 8.01-7.95 (m, 4H), 7.11 (d, *J* = 2.9 Hz, 1H), 4.67 (dq, *J* = 14.3, 7.1 Hz, 4H), 3.54-3.42 (m, 2H), 3.32-3.30 (m, 1H), 3.16-3.04 (m, 2H), 2.20-2.10 (m, 1H), 1.94-1.84 (m, 1H).
17	423.11	^{1}H NMR (400 MHz, MeOD) δ 9.37 (s, 1H), 8.27 (d, *J* = 3.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 2.9 Hz, 1H), 4.66 (t, *J* = 7.3 Hz, 2H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.55-3.44 (m, 2H), 3.34-3.32 (m, 1H), 3.17-3.07 (m, 2H), 2.21-2.10 (m, 1H), 1.88 (dd, *J* = 21.6, 8.5 Hz, 1H), 1.38 (t, *J* = 7.0 Hz, 3H).
18	451.03	^{1}H NMR (400 MHz, MeOD) δ 9.45 (s, 1H), 8.32 (s, 2H), 7.86 (s, 1H), 7.75 (dd, *J* = 7.9, 6.8 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.42 (dd, *J* = 9.8, 1.4 Hz, 1H), 7.33 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.20 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.81 (d, *J* = 2.9 Hz, 1H), 4.74-4.62 (m, 2H), 4.23 (s, 3H), 3.58-3.44 (m, 2H), 3.35-3.32 (m, 1H), 3.20-3.08 (m, 2H), 2.21-2.14 (m, 1H), 1.96-1.86 (m, 1H).
19	465.25	^{1}H NMR (400 MHz, MeOD) δ 9.45 (s, 1H), 8.33-8.29 (m, 2H), 7.86 (s, 1H), 7.75 (dd, *J* = 7.9, 6.8 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.42 (dd, *J* = 9.8, 1.3 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.20 (dd, *J* = 8.9, 1.6 Hz, 1H), 6.81 (d, *J* = 3.0 Hz, 1H), 4.73-4.60 (m, 2H), 4.23 (s, 3H), 3.88-3.54 (m, 3H), 3.21-2.91 (m, 4H), 2.37-2.16 (m, 1H).
20	446.97	^{1}H NMR (400 MHz, MeOD) δ 9.38 (s, 1H), 8.29 (s, 1H), 8.24 (d, *J* = 3.0 Hz, 1H), 7.83 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.17 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.76 (d, *J* = 2.7 Hz, 1H), 4.52 (d, *J* = 7.4 Hz, 2H), 4.22 (s, 3H), 3.48-3.38 (m, 2H), 3.03-2.92 (m, 2H), 2.45-2.32 (m, 1H), 1.86 (d, *J* = 13.5 Hz, 2H), 1.68-1.57 (m, 2H).

21	418.91	^{1}H NMR (400 MHz, MeOD) δ 9.37 (s, 1H), 8.29 (s, 1H), 8.25 (d, *J* = 3.1 Hz, 1H), 7.82 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.17 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.76 (d, *J* = 2.9 Hz, 1H), 4.22 (s, 3H), 4.18 (d, *J* = 8.8 Hz, 2H), 4.11 (d, *J* = 7.3 Hz, 2H), 3.67-3.59 (m, 1H).
22	447.54	
23	451.25	^{1}H NMR (400 MHz, MeOD) δ 9.46 (s, 1H), 8.31 (d, *J* = 3.0 Hz, 1H), 8.08 (s, 1H), 7.92 (d, *J* = 0.6 Hz, 1H), 7.77-7.72 (m, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 9.8, 1.1 Hz, 1H), 7.35-7.29 (m, 2H), 6.80 (d, *J* = 2.9 Hz, 1H), 4.84-4.64 (m, 2H), 4.08 (s, 3H), 3.57-3.45 (m, 2H), 3.39-3.32 (m, 1H), 3.30-3.12 (m, 2H), 2.21-2.14 (m, 1H), 1.97 -1.86 (m, 1H).
24	433.07	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.35 (d, *J* = 3.2 Hz, 1H), 8.29 (s, 1H), 7.83 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.18 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.80 (d, *J* = 3.1 Hz, 1H), 5.23-5.11 (m, 1H), 4.23 (s, 3H), 3.69 (d, *J* = 12.7 Hz, 2H), 3.40-3.33 (d, *J* = 9.7 Hz, 2H), 2.52-2.33 (dd, *J* = 33.6, 12.4 Hz, 4H).
25	437.23	^{1}H NMR (400 MHz, MeOD) δ 9.38 (s, 1H), 8.22 (d, *J* = 2.8 Hz, 1H), 8.11 (s, 1H), 7.91 (s, 1H), 7.77-7.71 (m, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 9.8 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 2H), 6.77 (d, *J* = 2.9 Hz, 1H), 4.72-4.59 (m, 2H), 3.56-3.43 (m, 3H), 3.14 (dd, *J* = 20.2, 9.0 Hz, 2H), 2.18 (t, *J* = 16.7 Hz, 1H), 1.98-1.84 (m, 1H).
26	479.31	^{1}H NMR (400 MHz, MeOD) δ 9.38 (s, 1H), 8.23 (d, *J* = 3.0 Hz, 1H), 8.09 (s, 1H), 7.89 (s, 1H), 7.76-7.71 (m, 1H), 7.62 (d, *J* = 8.9 Hz, 1H), 7.42 (d, *J* = 9.9 Hz, 1H), 7.30 (dd, *J* = 8.4, 2.3 Hz, 2H), 6.76 (d, *J* = 2.9 Hz, 1H), 5.07-4.92 (m, 1H), 4.66 (t, *J* = 7.2 Hz, 2H), 3.55-3.43 (m, 2H), 3.36-3.33 (m, 1H), 3.18-3.07 (m, 2H), 2.26-2.13 (m, 1H), 1.96-1.87 (m, 4H), 1.55 (d, *J* = 6.6 Hz, 6H).
27	479.31	^{1}H NMR (400 MHz, MeOD) δ 9.37 (s, 1H), 8.37 (s, 1H), 8.23 (d, *J* = 3.0 Hz, 1H), 7.82 (s, 1H), 7.77-7.72 (m, 2H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.42 (d, *J* = 9.8 Hz, 1H), 7.30 (d, *J* = 9.3 Hz, 1H), 7.20 (dd, *J* = 8.9, 1.5 Hz, 1H), 6.77 (d, *J* = 3.0 Hz, 1H), 4.66 (t, *J* = 7.2 Hz, 2H), 3.55-3.44 (m, 4H), 3.14 (dd, *J* = 20.2, 9.4 Hz, 6H), 2.23 – 2.13 (m, 3H), 1.95-1.87 (m, 3H), 1.64 (d, *J* = 6.7 Hz, 12H).
28	439.96	
29	436.96	^{1}H NMR (400 MHz, MeOD) δ 9.24 (s, 1H), 8.89 (s, 1H), 8.22 (d, *J* = 1.9 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 3.1 Hz, 1H), 7.84-7.76 (m, 3H), 7.48 (dd, *J* = 9.8, 1.4 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.61 (d, *J* = 3.0 Hz, 1H), 4.63-4.58 (m, 2H), 3.54-3.42 (m, 3H), 3.11 (dt, *J* = 15.5, 8.0 Hz, 2H), 2.20-2.11 (m, 1H), 1.94-1.85 (m, 1H).
30	465.14	^{1}H NMR (400 MHz, MeOD) δ 9.42 (s, 1H), 8.36 (s, 1H), 8.29 (d, *J* = 3.0 Hz, 1H), 7.85 (s, 1H), 7.77- 7.73 (m, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 9.8 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.20 (dd, *J* = 8.9, 1.7 Hz, 1H), 6.80 (d, *J* = 3.0 Hz, 1H), 4.71-4.65 (m, 2H), 4.52 (q, *J* = 7.3 Hz, 2H), 3.56-3.44 (m, 3H), 3.14 (dd, *J* = 20.4, 8.6 Hz, 2H), 2.23-2.09 (m, 1H), 1.95-1.82 (m, 1H), 1.60 (t, *J* = 7.3 Hz, 3H).

31	465.15	^{1}H NMR (400 MHz, MeOD) δ 9.44 (d, *J* = 6.3 Hz, 1H), 8.31 (d, *J* = 3.0 Hz, 1H), 8.10 (s, 1H), 7.92 (s, 1H), 7.79-7.73 (m, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.42 (dd, *J* = 9.8, 1.3 Hz, 1H), 7.34-7.28 (m, 2H), 6.81 (d, *J* = 3.0 Hz, 1H), 4.68 (t, *J* = 7.6 Hz, 2H), 4.48 (q, *J* = 7.3 Hz, 2H), 3.57-3.46 (m, 3H), 3.19-3.05 (m, 2H), 2.23-2.13 (m, 1H), 1.95-1.86 (m, 1H), 1.47 (t, *J* = 7.2 Hz, 3H).
32	451.24	/
33	451.04	^{1}H NMR (400 MHz, MeOD) δ 9.40 (s, 1H), 8.24 (d, *J* = 3.0 Hz, 1H), 8.06 (s, 1H), 7.77-7.71 (m, 3H), 7.42 (d, *J* = 10.1 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.05-7.02 (m, 1H), 6.79 (d, *J* = 2.8 Hz, 1H), 4.72-4.61 (m, 2H), 4.06 (s, 3H), 3.52-3.38 (m, 2H), 3.17-3.07 (m, 2H), 2.24-2.15 (m, 1H), 1.92 (d, *J* = 8.7 Hz, 2H).
34	451.02	^{1}H NMR (400 MHz, MeOD) δ 9.39 (s, 1H), 8.29-8.25 (m, 2H), 7.78-7.70 (m, 3H), 7.41 (d, *J* = 11.0 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 3.0 Hz, 1H), 4.73-4.64 (m, 2H), 4.24 (s, 3H), 3.57-3.41 (m, 3H), 3.17-3.04 (m, 2H), 2.38-2.12 (m, 1H), 1.94 (d, *J* = 7.9 Hz, 3H).
35	491.00	^{1}H NMR (400 MHz, MeOD) δ 9.49 (s, 1H), 8.33 (d, *J* = 3.0 Hz, 1H), 7.82 (dd, *J* = 7.9, 6.8 Hz, 1H), 7.57 (s, 4H), 7.43 (dd, *J* = 9.8, 1.3 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.82 (d, *J* = 3.0 Hz, 1H), 6.12 (s, 1H), 4.75-4.63 (m, 2H), 3.56-3.45 (m, 2H), 3.36-3.32 (m, 1H), 3.20-3.06 (m, 2H), 2.31 (s, 3H), 2.25 (s, 3H), 2.21-2.12 (m, 6H), 1.96-1.87 (m, 6H).
36	468.14	^{1}H NMR (400 MHz, MeOD) δ 9.32 (s, 1H), 8.25 (d, *J* = 3.1 Hz, 2H), 7.82 (dd, *J* = 7.9, 6.9 Hz, 1H), 7.39 (dd, *J* = 9.9, 1.4 Hz, 1H), 7.33 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.79-6.66 (m, 4H), 4.85-4.58 (m, 2H), 4.29-4.17 (m, 2H), 3.55-3.42 (m, 3H), 3.35-3.33 (m, 2H), 3.16-3.04 (m, 2H), 2.96- 2.87 (m, 10H), 2.20- 2.11 (m, 4H), 1.95 – 1.84 (m, 4H).
37	464.94	^{1}H NMR (400 MHz, MeOD) δ 9.39 (s, 1H), 8.21 (d, *J* = 3.0 Hz, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.76-7.71 (m, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 9.8, 1.2 Hz, 1H), 7.36-7.28 (m, 2H), 6.79 (d, *J* = 2.9 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 2H), 4.08 (s, 3H), 3.45-3.34 (m, 3H), 2.99-2.88 (m, 2H), 2.61-2.44 (m, 1H), 2.04-1.95 (m, 1H), 1.86-1.75 (m, 2H), 1.54-1.40 (m, 1H).
38	465.05	^{1}H NMR (400 MHz, MeOD) δ 9.39 (s, 1H), 8.24 (d, *J* = 2.8 Hz, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.73 (t, *J* = 7.3 Hz, 1H), 7.59 (d, *J* = 8.9 Hz, 1H), 7.40 (d, *J* = 10.0 Hz, 1H), 7.34-7.28 (m, 2H), 6.78 (d, *J* = 3.1 Hz, 1H), 4.52 (d, *J* = 7.4 Hz, 2H), 4.08 (s, 3H), 3.49-3.38 (m, 2H), 3.03-2.91 (m, 2H), 2.45-2.34 (m, 1H), 1.89-1.81 (m, 2H), 1.67-1.54 (m, 2H).
39	501.21	^{1}H NMR (400 MHz, MeOD) δ 9.52 (s, 1H), 8.33 (d, *J* = 2.9 Hz, 1H), 8.07 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.92 (s, 1H), 7.86-7.80 (m, 2H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 2.9 Hz, 1H), 4.75-4.66 (m, 2H), 4.08 (s, 3H), 3.58-3.45 (m, 2H), 3.35 (d, *J* = 8.4 Hz, 1H), 3.22-3.11 (m, 2H), 2.25-2.16 (m, 1H), 1.98-1.88 (m, 1H).

40	450.99	^{1}H NMR (400 MHz, MeOD) δ 9.49 (s, 1H), 8.31 (d, *J* = 3.0 Hz, 1H), 8.06 (s, 1H), 7.88 (s, 1H), 7.65-7.55 (m, 4H), 7.34 (dd, *J* = 8.8, 1.4 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 4.75-4.61 (m, 2H), 4.07 (s, 3H), 3.58-3.46 (m, 2H), 3.37-3.30(m, 1H), 3.19-3.10(m, 2H), 2.23-2.15 (m, 1H), 1.99-1.87 (m, 1H).
41	451.01	^{1}H NMR (400 MHz, MeOD) δ 9.44 (s, 1H), 8.30 (d, *J* = 3.0 Hz, 1H), 8.08 (s, 1H), 7.92 (s, 1H), 7.74 (dd, *J* = 7.9, 6.9 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 9.8, 1.3 Hz, 1H), 7.31 (td, *J* = 9.1, 1.5 Hz, 2H), 6.80 (d, *J* = 2.9 Hz, 1H), 4.73-4.61 (m, 2H), 4.08 (s, 3H), 3.56-3.46 (m, 2H), 3.37-3.33 (m, 1H), 3.20-3.07(m, 2H), 2.21-2.12 (m, 1H), 1.98-1.87 (m, 1H).
42	451.11	^{1}H NMR (400 MHz, MeOD) δ 9.46 (s, 1H), 8.32 (s, 2H), 7.86 (s, 1H), 7.75 (t, *J* = 7.1 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 9.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 6.81 (s, 1H), 4.75-4.61 (m, 2H), 4.23 (s, 3H), 3.57-3.42 (m, 2H), 3.38-3.33 (m, 1H), 3.21-3.06 (m, 2H), 2.24-2.11 (m, 1H), 1.99-1.83 (m, 1H).
43	465.15	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.29 (d, *J* = 3.1 Hz, 1H), 8.09 (s, 1H), 7.91 (s, 1H), 7.78-7.72 (m, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.42 (dd, *J* = 9.8, 1.3 Hz, 1H), 7.34-7.28 (m, 2H), 6.80 (d, *J* = 2.9 Hz, 1H), 4.72-4.61 (m, 2H), 4.47 (q, *J* = 7.2 Hz, 2H), 3.57-3.44 (m, 3H), 3.17-3.08 (m, 2H), 2.22-2.13 (m, 1H), 1.95-1.86 (m, 1H), 1.47 (t, *J* = 7.2 Hz, 3H).
44	465.33	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.28 (d, *J* = 3.0 Hz, 1H), 7.90 (s, 1H), 7.77-7.72 (m, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.43- 7.39 (m, 1H), 7.31 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.25 (dd, *J* = 8.7, 1.4 Hz, 1H), 6.79 (d, *J* = 2.9 Hz, 1H), 4.74- 4.62 (m, 2H), 3.99 (s, 3H), 3.56-3.44 (m, 3H), 3.20-3.08 (m, 2H), 2.52 (s, 3H), 2.23-2.13 (m, 1H), 1.96- 1.87 (m, 1H).
45	467.20	^{1}H NMR (400 MHz, MeOD) δ 9.31 (s, 1H), 8.22 (d, *J* = 3.1 Hz, 1H), 8.08 (s, 1H), 7.92 (s, 1H), 7.74 (dd, *J* = 7.9, 6.9 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.44-7.40 (m, 1H), 7.34-7.28 (m, 2H), 6.79 (d, *J* = 2.9 Hz, 1H), 4.81-4.79 (m, 1H), 4.68 (dd, *J* = 15.2, 7.8 Hz, 1H), 4.28-4.18 (m, 1H), 4.14-4.04 (m, 4H), 3.77 (td, *J* = 12.7, 2.2 Hz, 1H), 3.58 (d, *J* = 12.2 Hz, 1H), 3.28-3.25 (m, 1H), 3.20-3.12 (m, 1H), 3.02 (t, *J* = 12.0 Hz, 1H).
46	448.13	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.83 (s, 1H), 8.28 (d, *J* = 3.1 Hz, 1H), 8.08 (d, *J* = 0.7 Hz, 1H), 7.92 (d, *J* = 0.8 Hz, 1H), 7.73 (t, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.40 (dd, *J* = 9.8, 1.4 Hz, 1H), 7.35-7.28 (m, 2H), 6.81 (d, *J* = 2.9 Hz, 1H), 5.93 (s, 2H), 4.08 (s, 3H).
47	458.50	^{1}H NMR (400 MHz, MeOD) δ 9.36 (s, 1H), 8.80-8.59(m, 2H), 8.37 (d, *J* = 3.1 Hz, 1H), 8.10-8.03 (m, 2H), 7.91 (s, 1H), 7.77-7.72 (m, 1H), 7.67 (dd, *J* = 7.8, 5.3 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.42 (dd, *J* = 9.8, 1.3 Hz, 1H), 7.33 -7.28 (m, 2H), 6.86 (d, *J* = 3.0 Hz, 1H), 5.94 (s, 2H), 4.08 (s, 3H).
48	367.39	

49	478.58	^{1}H NMR (400 MHz, MeOD) δ 9.42 (s, 1H), 8.23 (s, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.74 (t, *J* = 7.3 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 9.6 Hz, 1H), 7.36-7.24 (m, 2H), 6.79 (s, 1H), 4.55 (d, *J* = 7.0 Hz, 2H), 4.08 (s, 2H), 3.56-3.35 (m, 2H), 2.99-2.80 (m, 5H), 2.64-2.53 (m, 1H), 2.07-1.95 (m, 1H), 1.89-1.74 (m, 2H), 1.48-1.37 (m, 1H).
50	493.60	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.24 (d, *J* = 2.8 Hz, 1H), 8.08 (s, 1H), 7.92 (s, 1H), 7.77-7.70 (m, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 9.8 Hz, 1H), 7.34-7.29 (m, 2H), 6.79 (d, *J* = 2.7 Hz, 1H), 4.65-4.49 (m, 2H), 3.54 (dd, *J* = 39.5, 11.8 Hz, 2H), 3.18 (q, *J* = 6.8 Hz, 2H), 2.87 (t, *J* = 12.1 Hz, 2H), 2.68-2.57 (m, 1H), 2.06-1.97 (m, 1H), 1.86-1.75 (m, 2H), 1.49-1.39 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H).
51	509.24	^{1}H NMR (400 MHz, MeOD) δ 9.37 (s, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 10.0 Hz, 1H), 7.34-7.28 (m, 2H), 6.76 (d, *J* = 2.6 Hz, 1H), 4.62-4.49 (m, 2H), 4.08 (s, 3H), 3.91-3.82 (m, 2H), 3.69-3.40 (m, 5H), 2.96 (t, *J* = 12.1 Hz, 2H), 2.70-2.58 (m, 1H), 2.05-1.98 (m, 1H), 1.89-1.77 (m, 2H), 1.49-1.38 (m, 1H).
52	465.07	^{1}H NMR (400 MHz, MeOD) δ 9.41 (s, 1H), 8.25 (d, *J* = 3.0 Hz, 1H), 8.10 (s, 1H), 7.92 (s, 1H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 9.3 Hz, 1H), 7.42 (d, *J* = 9.5 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 3.2 Hz, 1H), 4.71 (t, *J* = 7.8, 2H), 4.11 (s, 3H), 3.69-3.63 (m, 2H), 3.52-3.46 (m, 1H), 2.58-2.48 (m, 1H), 2.45-2.28 (m, 2H), 2.23-2.03 (m, 2H), 1.87-1.76 (m, 1H).
53	479.24	^{1}H NMR (400 MHz, MeOD) δ 9.37 (s, 1H), 8.33 (d, *J* = 3.1 Hz, 1H), 8.06 (d, *J* = 0.8 Hz, 1H), 7.89 (d, *J* = 0.8 Hz, 1H), 7.73 (dd, *J* = 7.9, 6.8 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.39 (dd, *J* = 9.8, 1.4 Hz, 1H), 7.33 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.29 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.77 (d, *J* = 3.0 Hz, 1H), 5.00-4.92 (m, 1H), 4.08 (s, 3H), 3.51-3.47 (m, 1H), 2.82 (s, 3H), 2.29-2.14 (m, 8H).
54	493.21	
55	465.16	^{1}H NMR (400 MHz, MeOD) δ 9.39 (s, 1H), 8.76 (s, 1H), 8.04 (d, *J* = 0.7 Hz, 1H), 7.86 (s, 1H), 7.69-7.63 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.46 (dd, *J* = 10.1, 1.3 Hz, 1H), 7.36 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.25 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.75- 4.59 (m, 2H), 4.07 (s, 3H), 3.56-3.48 (m, 2H), 3.36- 3.33 (m, 1H), 3.26-3.24 (m, 1H), 3.21-3.11 (m, 2H), 2.26-2.18 (m, 1H), 1.96-1.87 (m, 1H).
56	465.16	
57	466.87	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.27 (d, *J* = 2.9 Hz, 1H), 8.08 (d, *J* = 0.9 Hz, 1H), 7.90 (d, *J* = 0.8 Hz, 1H), 7.74 (dd, *J* = 8.0, 6.8 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.40 (dd, *J* = 9.8, 1.4 Hz, 1H), 734-7.28 (m, 2H), 6.79 (d, *J* = 2.8 Hz, 1H), 4.69 (s, 2H), 4.08 (s, 10H), 3.86-3.54 (m, 2H), 3.21-3.02 (m, 3 H), 2.97 (s, 3H), 2.36-2.15 (m, 1H), 2.11-1.89 (m, 1H).
58	481.22	^{1}H NMR (400 MHz, MeOD) δ 9.31 (s, 1H), 8.19 (d, *J* = 3.0 Hz, 1H), 8.07 (s, 1H), 7.90 (s, 1H), 7.76- 7.69 (m, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 9.9 Hz, 1H), 7.34-7.28 (m, 2H), 6.78 (d, *J* = 2.9 Hz, 1H), 4.61 (s, 2H), 4.08 (s, 3H), 3.36-3.20 (m, 4H), 2.06-1.96 (m, 2H), 1.75 (d, *J* = 13.7 Hz, 2H).

59	483.16	^{1}H NMR (400 MHz, MeOD) δ 9.20 (s, 1H), 8.09-8.04 (m, 2H), 7.86 (s, 1H), 7.74-7.70 (m, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.38 (dd, *J* = 9.6, 1.6 Hz, 1H), 7.32 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.28 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.76 (d, *J* = 3.2 Hz, 1H), 4.91 (s, 2H), 4.07 (s, 3H), 3.45-3.39 (m, 2H), 3.23-3.15 (m, 2H), 2.02 (s, 4H).
60	478.23	^{1}H NMR (300 MHz, MeOD) δ 9.46 (s, 1H), 8.30 (d, *J* = 2.9 Hz, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.85 – 7.70 (m, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 10.0 Hz, 1H), 7.39 – 7.24 (m, 2H), 6.82 (d, *J* = 2.8 Hz, 1H), 4.56 (d, *J* = 7.2 Hz, 2H), 4.11 (s, 3H), 3.58 (d, *J* = 12.5 Hz, 2H), 3.00 (t, *J* = 12.0 Hz, 2H), 2.88 (s, 3H), 2.48 – 2.26 (m, 1H), 2.00 – 1.82 (m, 2H), 1.82 – 1.63 (m, 2H).
61	493.20	^{1}H NMR (300 MHz, MeOD) δ 9.47 (s, 1H), 8.30 (d, *J* = 2.9 Hz, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.84 – 7.71 (m, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 9.9 Hz, 1H), 7.39 – 7.26 (m, 2H), 6.82 (d, *J* = 2.8 Hz, 1H), 4.57 (d, *J* = 7.3 Hz, 2H), 4.11 (s, 3H), 3.64 (d, *J* = 12.4 Hz, 2H), 3.19 (q, *J* = 7.2 Hz, 2H), 2.94 (t, *J* = 12.1 Hz, 2H), 2.42 (s, 1H), 2.07 – 1.83 (m, 2H), 1.82 – 1.50 (m, 2H), 1.36 (t, *J* = 7.3 Hz, 3H).
62	425.23	^{1}H NMR (300 MHz, MeOD) δ 9.44 (s, 1H), 8.32 (d, *J* = 3.0 Hz, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 10.3 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 2H), 6.82 (d, *J* = 2.8 Hz, 1H), 4.71 (t, *J* = 7.2 Hz, 2H), 4.11 (s, 3H), 3.19 – 3.00 (m, 2H), 2.49 – 2.22 (m, 2H).
63	453.29	^{1}H NMR (300 MHz, MeOD) δ 9.43 (s, 1H), 8.32 (d, *J* = 3.0 Hz, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 9.9 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 2H), 6.83 (d, *J* = 2.8 Hz, 1H), 4.69 (t, *J* = 7.2 Hz, 2H), 4.11 (s, 3H), 3.30 – 3.20 (m, 2H), 2.94 (s, 6H), 2.58 – 2.37 (m, 2H).
64	411.19	^{1}H NMR (400 MHz, MeOD) δ 9.43 (s, 1H), 8.30 (d, *J* = 3.1 Hz, 1H), 8.12 (s, 1H), 7.95 (d, *J* = 0.7 Hz, 1H), 7.83 – 7.72 (m, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.43 (dd, *J* = 9.8, 1.2 Hz, 1H), 7.38 – 7.28 (m, 2H), 6.85 (d, *J* = 3.0 Hz, 1H), 4.96 – 4.89 (m, 2H), 4.11 (s, 3H), 3.66 (t, *J* = 6.2 Hz, 2H).
65	439.21	^{1}H NMR (300 MHz, MeOD) δ 9.49 (s, 1H), 8.35 (d, *J* = 2.9 Hz, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 9.9 Hz, 1H), 7.33 (t, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 2.9 Hz, 1H), 5.05 (t, *J* = 6.9 Hz, 2H), 4.11 (s, 3H), 3.85 (t, *J* = 6.9 Hz, 2H), 3.06 (s, 6H).
66	350.15	
67	447.24	^{1}H NMR (300 MHz, MeOD) δ 9.45 (s, 1H), 8.28 (d, *J* = 2.2 Hz, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 – 7.48 (m, 3H), 7.32 (d, *J* = 8.8 Hz, 1H), 6.78 (d, 1H), 4.56 (d, *J* = 7.2 Hz, 2H), 4.09 (s, 3H), 3.47 (d, *J* = 12.5 Hz, 2H), 3.01 (t, *J* = 12.2 Hz, 2H), 2.76 – 2.09 (m, 1H), 2.02 – 1.83 (m, 2H), 1.83 – 1.47 (m, 2H).
68	461.24	^{1}H NMR (400 MHz, MeOD) δ 9.34 (s, 1H), 8.16 (d, *J* = 3.0 Hz, 1H), 7.97 (s, 1H), 7.81 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.20 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.66 (d, *J* = 2.9 Hz, 1H), 4.44 (d, *J* = 7.3 Hz, 2H), 4.15 – 3.91 (m, 3H), 3.46 (d, *J* = 12.5 Hz, 2H), 2.89 (dd, *J* = 12.8, 10.6 Hz, 2H), 2.83 – 2.68 (m, 3H), 2.39 – 2.14 (m, 1H), 1.87 – 1.71 (m, 2H), 1.71 – 1.51 (m, 2H).

69	496.98	^{1}H NMR (300 MHz, MeOD) δ 9.37 (s, 1H), 8.27 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.77 (t, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 10.0 Hz, 1H), 7.41 – 7.28 (m, 2H), 6.87 (s, 1H), 5.01 – 4.92 (m, 2H), 4.11 (s, 3H), 3.65 – 3.45 (m, 2H), 3.30 – 3.13 (m, 2H), 2.95 (s, 3H), 2.54 – 2.18 (m, 2H), 2.17 – 1.96 (m, 2H).
70	495.25	^{1}H NMR (300 MHz, MeOD) δ 9.38 (s, 1H), 8.26 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.77 (t, *J* = 7.3 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 9.9 Hz, 1H), 7.40 – 7.27 (m, 2H), 6.82 (s, 1H), 4.66 (s, 2H), 4.11 (s, 3H), 3.52 – 3.39 (m, 2H), 3.32 – 3.18 (m, 2H), 2.91 (s, 3H), 2.49 – 1.98 (m, 2H), 1.96 – 1.65 (m, 2H).
71	509.00	^{1}H NMR (300 MHz, MeOD) δ 9.43 (s, 1H), 8.28 (s, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.65 – 7.49 (m, 2H), 7.32 (d, *J* = 8.8 Hz, 1H), 6.79 (s, 1H), 4.56 (d, *J* = 6.5 Hz, 2H), 4.10 (s, 3H), 3.90 (s, 2H), 3.72 (d, *J* = 12.1 Hz, 2H), 3.31 – 3.16 (m, 2H), 3.14 – 2.94 (m, 2H), 2.57 – 2.27 (m, 1H), 2.12 – 1.52 (m, 4H).
72	406.97	^{1}H NMR (400 MHz, MeOD) δ 9.42 (s, 1H), 8.30 (d, *J* = 3.0 Hz, 1H), 8.09 (s, 1H), 7.97 – 7.90 (m, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.33 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.79 (d, *J* = 3.0 Hz, 1H), 4.71 (t, *J* = 7.3 Hz, 2H), 4.10 (s, 3H), 3.17 – 3.03 (m, 2H), 2.46 – 2.32 (m, 2H).
73	421.33	^{1}H NMR (300 MHz, MeOD) δ 9.39 (s, 1H), 8.30 (s, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.66 – 7.48 (m, 3H), 7.32 (d, *J* = 8.7 Hz, 1H), 6.77 (s, 1H), 4.64 (t, *J* = 6.8 Hz, 2H), 4.09 (s, 3H), 3.04 (t, *J* = 7.4 Hz, 2H), 2.12 (s, 2H), 1.78 (s, 2H).
74	421.38	^{1}H NMR (300 MHz, MeOD) δ 9.41 (s, 1H), 8.29 (d, *J* = 2.9 Hz, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.65 – 7.48 (m, 3H), 7.32 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 2.7 Hz, 1H), 4.70 (t, *J* = 7.1 Hz, 2H), 4.10 (s, 3H), 3.25 – 3.05 (m, 2H), 2.76 (s, 3H), 2.55 – 2.27 (m, 2H).
75	475.38	^{1}H NMR (300 MHz, MeOD) δ 9.43 (s, 1H), 8.28 (s, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.66 – 7.48 (m, 3H), 7.32 (d, *J* = 8.7 Hz, 1H), 6.79 (s, 1H), 4.59 (t, *J* = 12.5 Hz, 2H), 4.10 (s, 3H), 3.64 (d, *J* = 12.3 Hz, 2H), 3.19 (q, *J* = 7.3 Hz, 2H), 2.94 (t, *J* = 12.4 Hz, 2H), 2.55 – 2.29 (m, 1H), 2.02 – 1.85 (m, 2H), 1.82 – 1.62 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H).
76	447.34	^{1}H NMR (300 MHz, MeOD) δ 9.48 (s, 1H), 8.33 (d, *J* = 2.6 Hz, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 – 7.49 (m, 3H), 7.32 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 4.72 (s, 2H), 4.10 (s, 3H), 3.94 – 3.05 (m, 5H), 3.00 (s, 3H), 2.45 – 1.84 (m, 2H).
77	461.43	
78	491.33	
79	475.39	
80	426.31	
81	447.35	
82	461.35	
83	446.33	
84	449.39	
85	436.35	
86	479.36	

87	450.38	
88	460.35	
89	465.35	
90	479.25	
91	479.37	
92	349.30	
93	461.35	
94	493.32	
95	475.35	
96	473.33	
97	461.35	
98	464.29	
99	437.29	
100	438.31	
101	475.38	
102	487.32	
103	408.45	
104	421.34	
105	465.47	
106	435.36	
107	473.47	
108	474.61	
109	473.35	
110	487.44	
111	487.37	
112	451.32	
113	466.40	
114	433.40	
115	408.31	
116	397.40	
117	447.39	
118	433.43	
119	451.41	
120	471.34	
121	465.43	
122	447.42	
123	482.37	
124	604.41	
125	461.39	
126	496.35	
127	485.33	
128	479.31	
129	496.32	
130	478.35	
131	461.35	
132	489.34	
133	493.29	
134	407.33	

EXAMPLE 10

LSD1 Activity

[0290] Human recombinant LSD1 protein expressed in E. *coli* cells was purchased from Active Motif (Carlsbad, CA). Biotin-labeled Histone H3K4Me peptide (residues 1-21 with Lys 4 monomethylated) substrate was purchased from Anaspec (Fremont, CA). Enzymatic activity was assessed using the AlphaLISA technology from Perkin Elmer Life Sciences (Waltham, MA). 2.5 μL of compound solution and 5 μL of LSD1 solutions in the assay buffer (50mM Tris, pH 9.0, 50mM NaCl with 0.01% Tween20 and 1mM DTT added right before the assay) were added into a white low volume 384 well microtiter plate. This mixture solution was incubated for 15 minutes with gentle shaking at room temperature. Demethylation reaction was initiated by adding 2.5 μL of Biotin-H3K4Me peptide substrate solution in the assay buffer. Final concentrations of LSD1, Biotin-H3K4Me peptide substrate, and DMSO were 4 nM, 80 nM, and 1%, respectively. The reaction was allowed to proceed for 60 minutes in dark with gentle shaking at room temperature, after which 5 μL of Anti-H3K4 AlphaLISA acceptor beads in detection buffer from the manufacturer was added into the reaction mixture followed by incubation for 60 minutes. 10 μL of Streptavidin labeled AlphaLISA donor beads in detection buffer was added into the mixture followed by 30-minute incubation. Final acceptor and donor beads concentrations were both at 10 μg/mL. Plates were read on a BMG CLARIOStar multimode plate reader from BMG Labtech (Ortenberg, Germany) with an excitation wavelength of 680 nm and emission wavelength of 615 nm. IC_{50} values of inhibitors were obtained by fitting the fluorescence intensity *vs* inhibitor concentrations in a sigmoidal dose-response curve (variable slope) with a non-linear regression using Prism 7 (La Jolla, CA).

[0291] The LSD1 inhibitory activity of representative Compounds of the Disclosure are provided in Table 4. All compounds were tested as the TFA salt.

Table 4

Cpd. No.	LSD1 IC_{50} (nM)
1	62
2	297
3	49
4	19984
5	2341
6	14.55
7	10000

8	5000
9	130
10	10000
11	10000
12	25
13	387
14	52
15	18
16	14071
17	70
18	7
19	69
20	51
21	96
22	20117
23	6
24	444
25	90
26	26
27	60
28	654
29	372
30	27
31	8
32	19
33	167
34	26
35	40
36	8
37	11
38	11
39	9068
40	21
41	2
42	7
43	4
44	61
45	377
46	>10000
47	>10000
49	42.03
50	66.72
51	104.5
52	78.39
53	674.9
54	425.9
55	84.84
56	115.9

57	92.46
58	85.82
59	143.1
60	13.7
61	28.2
62	18.3
63	124
64	244
65	369
67	7.6
68	28.0
69	134
70	28.4
71	16.2
72	28.5
73	13.0
74	39.4
75	30.2
76	32.7
77	4.0
78	14.3
79	4.1
80	154
81	145
82	348
83	7.1
84	75.1
85	23.1
86	241
87	34.6
89	38.1
90	165
91	2.2
92	4935
93	314
94	2.1
95	16.2
96	5.3
97	5.2
98	4.1
99	20.5

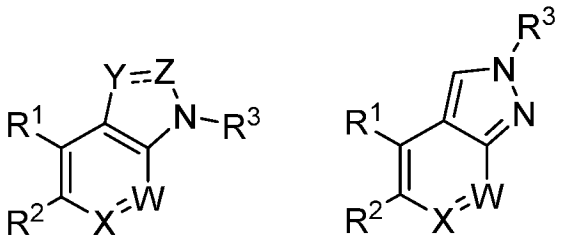
[0292] Having now fully described the methods, compounds, and compositions herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without

affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof.

[0293] 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 **I** or **II**:



I or **II** ,

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is selected from the group consisting of halo, optionally substituted C_6-C_{14} aryl, and optionally substituted 5- to 14-membered heteroaryl;

R^2 is selected from the group consisting of hydrogen, halo, optionally substituted C_6-C_{14} aryl, and optionally substituted 5- to 14-membered heteroaryl;

R^3 is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted 4- to 8-membered heterocyclo, (amino)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl;

X is selected from the group consisting of $=C(R^{6a})-$ and =N-;

W is selected from the group consisting of $=C(R^{6b})-$ and =N-;

$\equiv$ is a single or double bond;

Y is selected from the group consisting of $=C(R^{4a})-$ and =N- when $\equiv$ is a double bond;

Y is $-C(H)R^{4b}-$ when $\equiv$ is a single bond;

Z is selected from the group consisting of $=C(R^5)-$ and =N- when $\equiv$ is a double bond;

Z is -C(=O)- when $\equiv$ is a single bond;

R^{4a} is selected from the group consisting of hydrogen, halo, and C_{1-6} alkyl;

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

R^5 is selected from the group consisting of hydrogen and C_{1-6} alkyl;

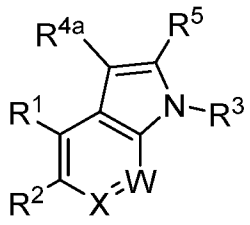
R^{6a} is selected from the group consisting of hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy; and

R^{6b} is selected from the group consisting of hydrogen, halo, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

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

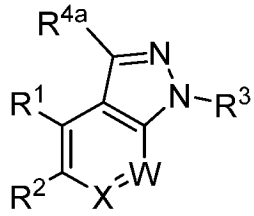
3. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having Formula **II**.

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



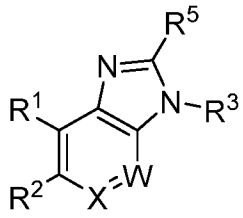
III.

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



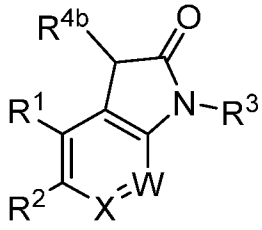
IV.

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



V.

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



VI.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X is =N- and W is =C(H)-.

9. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein X is =C(H)- and W is =N-.

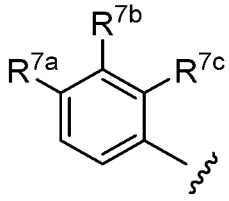
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halo.

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is halo.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halo, R^2 is halo, and R^3 is selected from the group consisting of optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted 4- to 8-membered heterocyclo, (amino)alkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl.

13 The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from the group consisting of optionally substituted phenyl and optionally substituted 9- to 14-membered heteroaryl.

14. The compound of claim 13, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted phenyl having Formula **VII**:

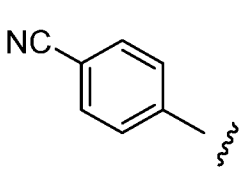
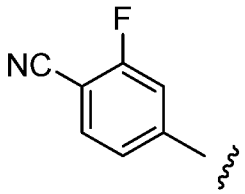
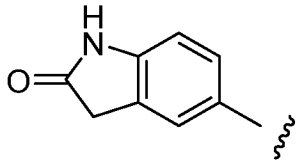
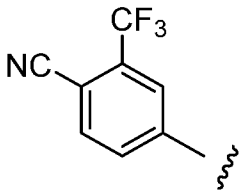
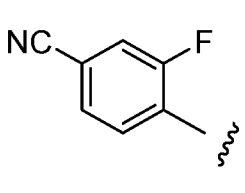
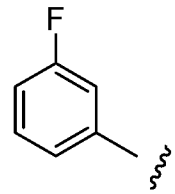
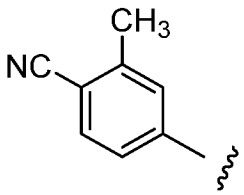
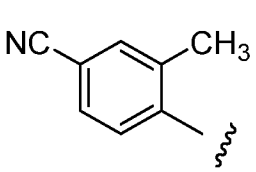
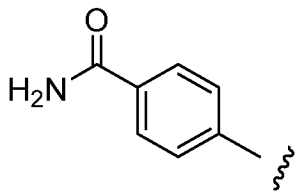
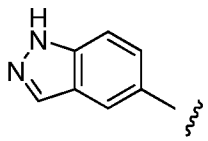
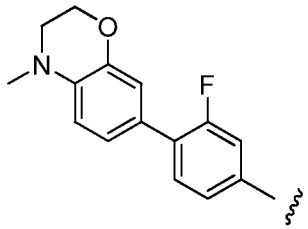


VII,

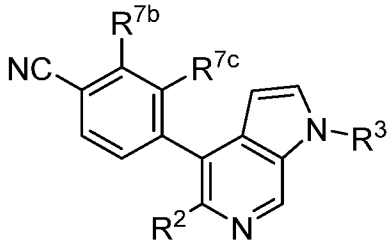
wherein R^{7a}, R^{7b}, and R^{7c} are each independently selected from the group consisting of hydrogen, halo, cyano, amino hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, optionally substituted phenyl, and carboxamido, or R^{7a} and R^{7b} taken together with the carbon atoms to which they are attached form a 5-, 6-, or 7-membered optionally substituted heterocyclo.

15. The compound of claim 14, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{7a} is cyano.

16. The compound of claim 13, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted phenyl or optionally substituted 9- to 14-membered heteroaryl selected from the group consisting of:


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17. The compound of claim 15, or a pharmaceutically acceptable salt or solvate thereof, having Formula **VIII**:

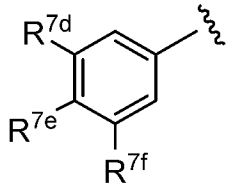


VIII,

wherein R^{7b} and R^{7c} are independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and C_{1-4} haloalkyl.

18. The compound of any one of claims 1-9 or 13-17, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted phenyl.

19. The compound of claim 18, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted phenyl having Formula **IX**:



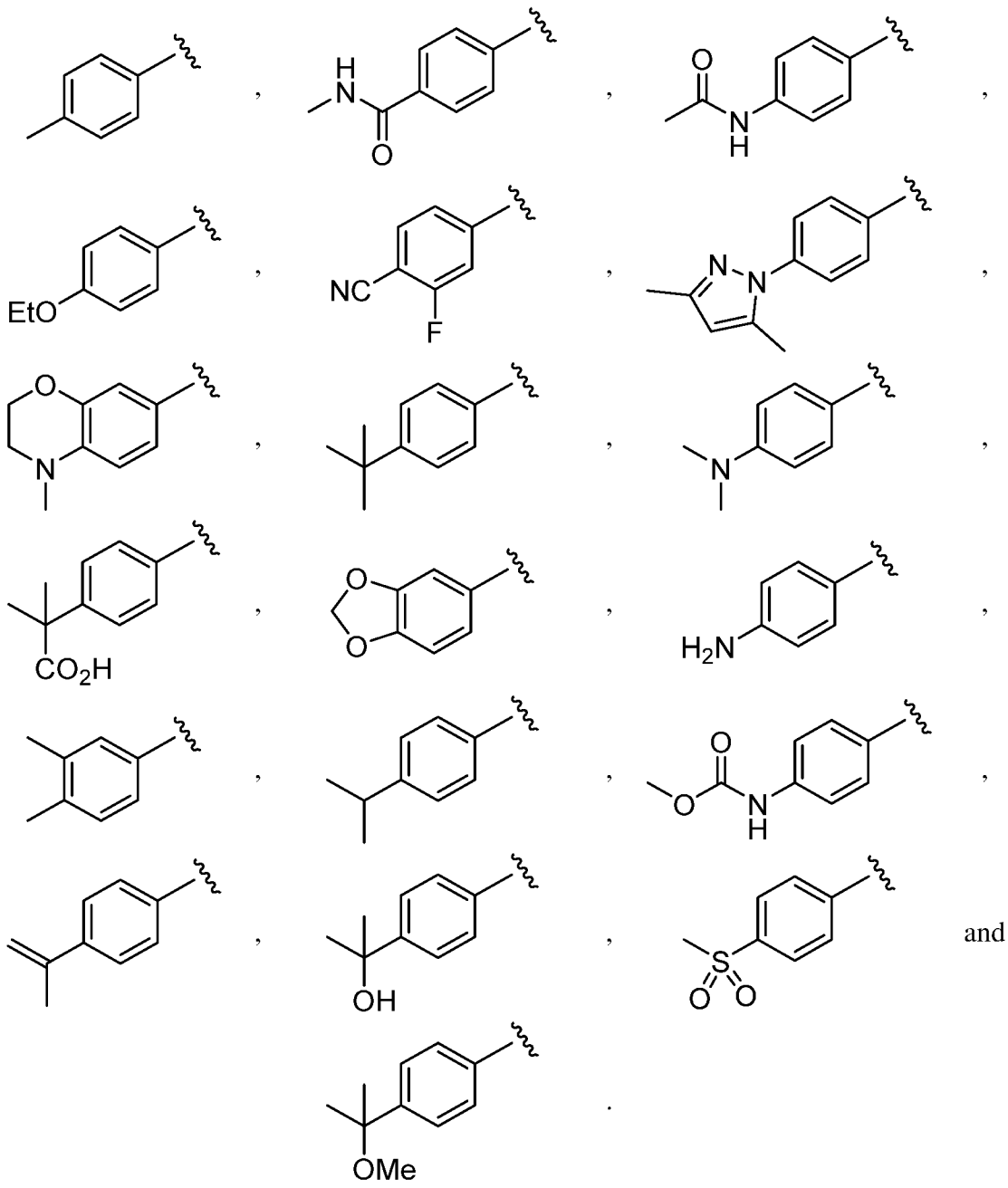
IX,

wherein:

R^{7d}, R^{7e}, and R^{7f} are each independently selected from the group consisting of hydrogen, halo, cyano, amino, hydroxy, optionally substituted C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, carboxamido, amido, optionally substituted C_{3-6} cycloalkyl, optionally substituted phenyl, and optionally substituted 5- to 9-membered heteroaryl; or

R^{7d} and R^{7e} taken together with the carbon atoms to which they are attached form an optionally substituted 5-, 6-, or 7-membered optionally substituted heterocyclo.

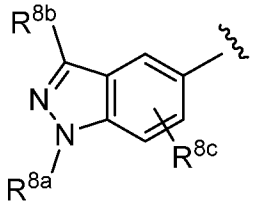
20. The compound of claim 18, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted phenyl selected from the group consisting of:



and

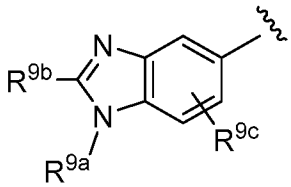
21. The compound of any one of claims 1-9 or 13-17, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted 5- to 14-membered heteroaryl.

22. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 optionally substituted 5- to 14-membered heteroaryl having Formula **X**, **XI**, or **XII**:



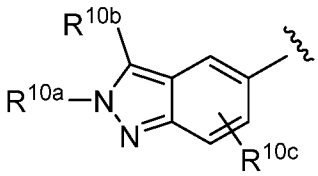
X

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XI

or



XII

wherein:

R^{8a} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{8b} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

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

R^{9a} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{9b} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

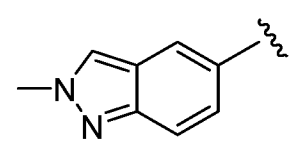
R^{9c} is selected from the group consisting of hydrogen, halo, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy;

R^{10a} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

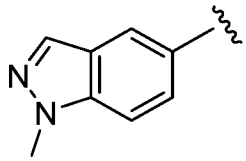
R^{10b} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R^{10c} is selected from the group consisting of hydrogen, halo, cyano, amino, hydroxy, C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkoxy.

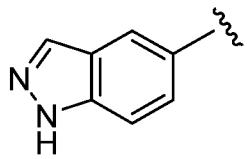
23. The compound of claim 21, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is optionally substituted 5- to 14-membered heteroaryl selected from the group consisting of:



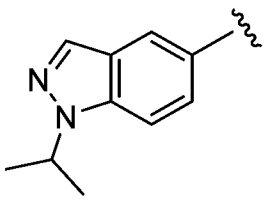
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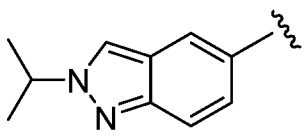
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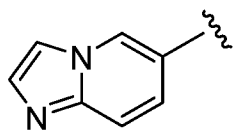
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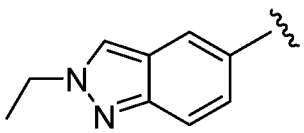
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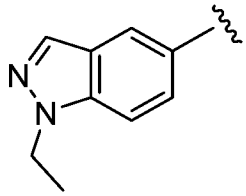
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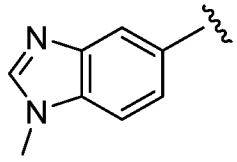
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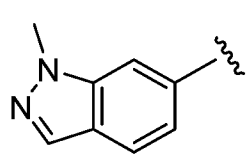
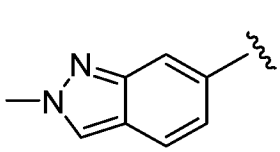
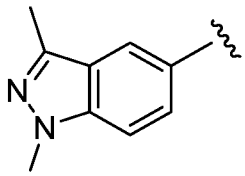
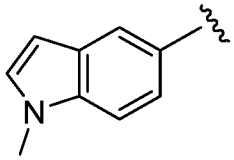
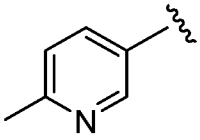
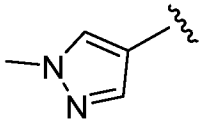
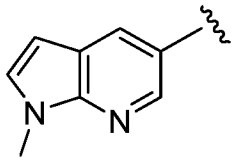
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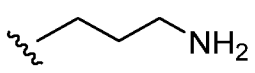
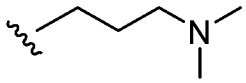
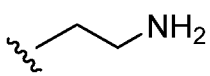
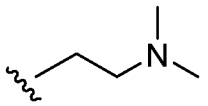
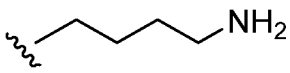
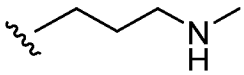


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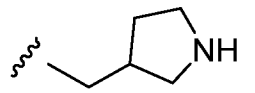
24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is (amino)alkyl.

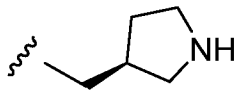
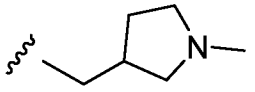
25. The compound of claim 24, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is (amino)alkyl selected from the group consisting of:

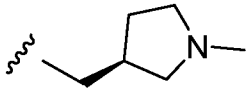
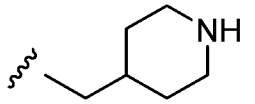
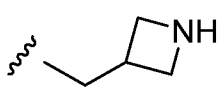
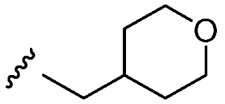
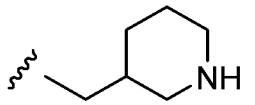
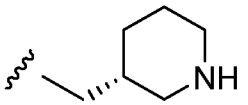
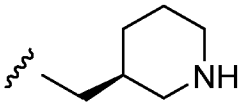

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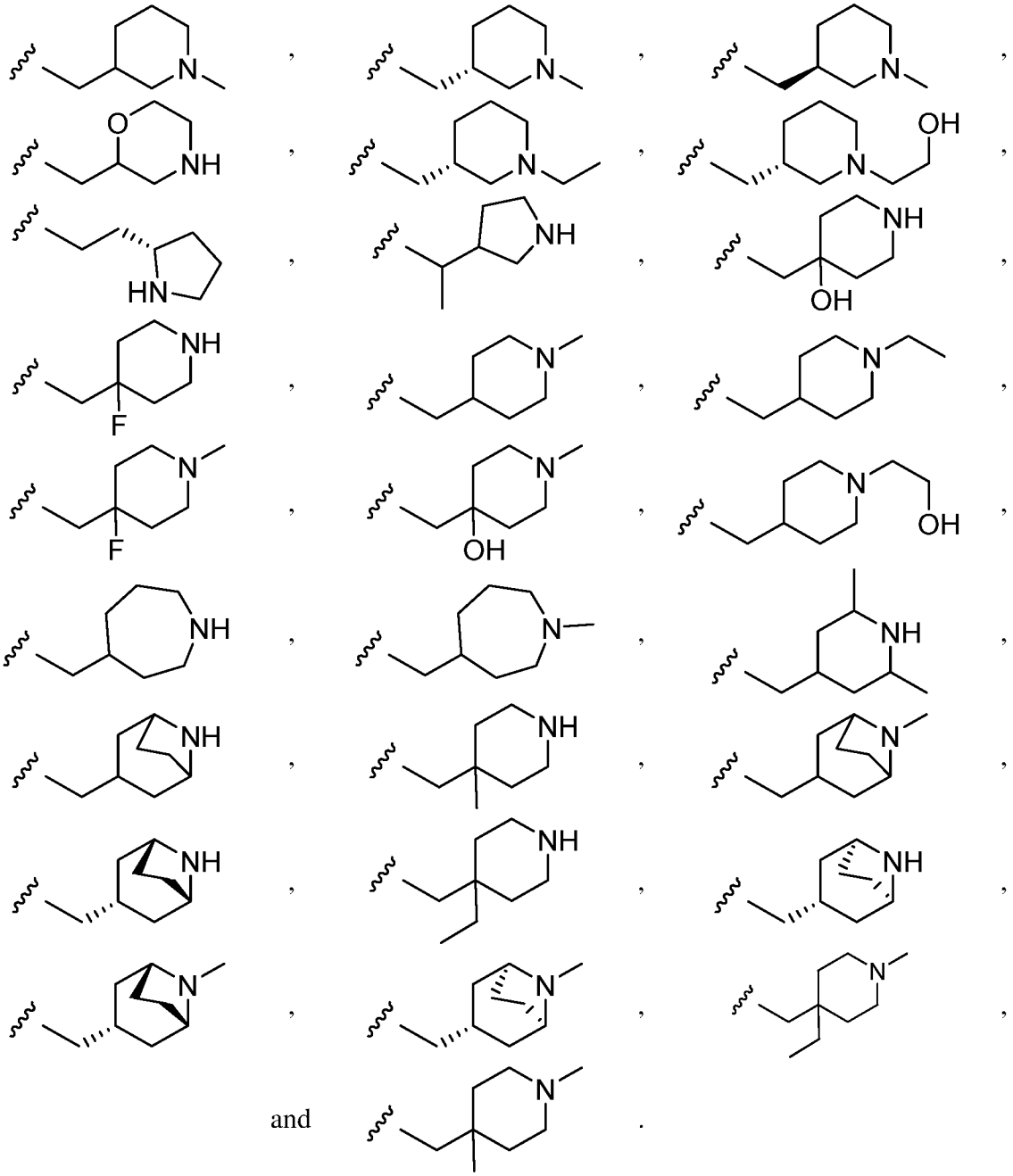
26. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is (heterocyclo)alkyl.

27. The compound of claim 26, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is (heterocyclo)alkyl selected from the group consisting of:


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and .

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

29. A pharmaceutical composition comprising the compound of any one of claim 1-28, or a pharmaceutically acceptable salt or solvate 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 or solvate thereof, wherein the patient has cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

31. The method 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 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, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

34. The method of any one of claims 31-33 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 myelogenous

leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

39. A compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate 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 myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

43. Use of a compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

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 myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

47. A kit comprising the compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or solvate thereof, to a patient having cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection.

48. The kit of claim 47, wherein the patient has cancer.

49. The kit of claim 48, wherein the cancer is any one or more of the cancers of Table 2.

50. The kit of claim 48, 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, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

51. The kit of any one of claims 47-50 further comprising one or more additional therapeutic agents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/032619

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D519/00 A61P35/00 A61K31/437
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, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2016/161282 A1 (INCYTE CORP [US]) 6 October 2016 (2016-10-06) the whole document in particular abstract, examples 1-138 and claims 1-57	1-51

Y	US 2016/009720 A1 (WU LIANGXING [US] ET AL) 14 January 2016 (2016-01-14) cited in the application the whole document in particular abstract, examples 4-6 and claims 1-58	1-51

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[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
26 July 2018	14/08/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Papathoma, Sofia

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MOULD DANIEL P ET AL: "Development of 5-hydroxypyrazole derivatives as reversible inhibitors of lysine specific demethylase 1", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 27, no. 14, 8 May 2017 (2017-05-08), pages 3190-3195, XP085062060, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2017.05.018 the whole document in particular figure 1	1-51
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 16 November 1984 (1984-11-16), XP002783352,accession no. STN Database accession no. 17374-26-4 RN: 17374-26-4	1,2,10, 11
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2 September 2003 (2003-09-02), XP002783353,accession no. STN Database accession no. 577779-57-8 RN: 577779-57-8	1,2,6, 10,11
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 26 November 2007 (2007-11-26), XP002783354,accession no. STN Database accession no. 955978-88-8 RN:955978-88-8	1,2,4, 10,11
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 8 December 2008 (2008-12-08), XP002783355,accession no. STN Database accession no. 1082041-85-7 RN: 1082041-85-7	1,2,5, 10,11
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 11 December 2008 (2008-12-11), XP002783356, Database accession no. 1083096-61-0 RN: 1083096-61-0	1,2,7, 11,13,14

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/079521 A2 (VERTEX PHARMA [US]; BENNANI YOUSSEFF [US]; WANG TIANSHENG [US]; SALITU) 3 July 2008 (2008-07-03) page 63; compound 1009	1,2,4,9, 11,13,14
X	MITKIN O D ET AL: "Indoles from 3-nitropyridinium salts:^1 an extension of the transformation method on 5-substituted indoles", TETRAHE, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 57, no. 9, 25 February 2001 (2001-02-25), pages 1827-1831, XP004317644, ISSN: 0040-4020, DOI: 10.1016/S0040-4020(00)01162-5 page 1829; figure 1; table 2; compound 6A	1,2,4, 11,13,14
X	WO 2016/201266 A1 (USHER III INITIATIVE INC [US]) 15 December 2016 (2016-12-15) pages 44,46,60; compounds Va, Vb,Vp, Vr, Vt, Vu, Vv, Vw, Vbb,Vhh, XIIId pages 69,70; compounds 112, 114-117 claims 9,16,22,23	1,3,5, 10,18,19
X	KR 2015 0024669 A (CHEIL IND INC [KR]) 9 March 2015 (2015-03-09) page 33; compounds I-4, I-5	1,2,4,9, 10,13, 14,22
A	WO 02/088078 A2 (VERTEX PHARMA [US]; TER HAAR ERNST [US]; SWENSON LOVORKA [US]; GREEN J) 7 November 2002 (2002-11-07) claims 10-13	1-51

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/032619

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.: 1-51(partially)
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:

see FURTHER INFORMATION sheet PCT/ISA/210

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:

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.:

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.

Continuation of Box II.2

Claims Nos.: 1-51(partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims.
The search of the claims / claim 1 was restricted to:
compounds of the formulae I or II for which R 1 is defined as in claim 15 (i.e. R1 is a phenyl ring para-substituted with a cyano group) and R2 is an optionally substituted C6 -C14 aryl or an optionally substituted 5- to 14- membered heteroaryl, which is supported by 130 of the 134 compounds exemplified in the present application.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/032619

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