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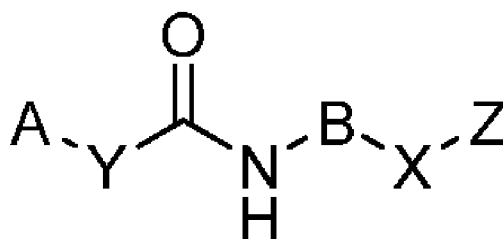
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(54) Title: SUBSTITUTED PYRROLIDINE CARBOXAMIDE COMPOUNDS

**I**

(57) Abstract: The present disclosure provides pyrrolidine carboxamide compounds having Formula I and the pharmaceutically acceptable salts and solvates thereof, wherein A, B, X, Y, and Z are defined as set forth in the specification. The present disclosure is also directed to the use of compounds of Formula I to treat a disorder responsive to the blockade of SMYD proteins such as SMYD3 or SMYD2. Compounds of the present disclosure are especially useful for treating cancer.

SUBSTITUTED PYRROLIDINE CARBOXAMIDE COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure provides substituted pyrrolidine carboxamides as SMYD protein inhibitors, such as SMYD3 and SMYD2 inhibitors, and therapeutic methods of treating conditions and diseases wherein inhibition of SMYD proteins such as SMYD3 and SMYD2 provides a benefit.

Background

[0002] Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases. Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification (*e.g.*, methylation) of DNA and proteins (*e.g.*, histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (*e.g.*, SMYD proteins such as SMYD3 and SMYD2), many of which are associated with genetic alterations that can cause human disease, such as proliferative disorders. Thus, there is a need for the development of small molecules that are capable of inhibiting the activity of SMYD proteins such as SMYD3 and SMYD2.

BRIEF SUMMARY OF THE INVENTION

[0003] In one aspect, the present disclosure provides substituted pyrrolidine carboxamide compounds represented by Formula I below, and the pharmaceutically acceptable salts and solvates thereof, collectively referred to herein as "Compounds of the Disclosure."

[0004] In another aspect, the present disclosure provides a Compound of the Disclosure and one or more pharmaceutically acceptable carriers.

[0005] In another aspect, the present disclosure provides a method of inhibiting SMYD proteins, such as SMYD3 or SMYD2, or both, in a mammal, comprising

administering to the mammal an effective amount of at least one Compound of the Disclosure.

[0006] In another aspect, the present disclosure provides a method of irreversibly inhibiting SMYD proteins, such as SMYD3 or SMYD2, or both, in a mammal, comprising administering to the mammal an effective amount of at least one Compound of the Disclosure.

[0007] In another aspect, the present disclosure provides methods for treating a disease, disorder, or condition, *e.g.*, cancer, responsive to inhibition of SMYD proteins, such as SMYD3 or SMYD2, or both, comprising administering a therapeutically effective amount of a Compound of the Disclosure.

[0008] In another aspect, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of SMYD3.

[0009] In another aspect, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of SMYD2.

[0010] In another aspect, the present disclosure provides the use of Compounds of the Disclosure as inhibitors of SMYD proteins.

[0011] In another aspect, the present disclosure provides a pharmaceutical composition for treating a disease, disorder, or condition responsive to inhibition of SMYD proteins, such as SMYD3 or SMYD2, or both, wherein the pharmaceutical composition comprises a therapeutically effective amount of a Compound of the Disclosure in a mixture with one or more pharmaceutically acceptable carriers.

[0012] In another aspect, the present disclosure provides Compounds of the Disclosure for use in treating cancer in a mammal, *e.g.*, breast, cervical, colon, kidney, liver, head and neck, skin, pancreatic, ovary, esophageal, lung, and prostate cancer.

[0013] In another aspect, the present disclosure provides a Compound of the Disclosure for use in the manufacture of a medicament for treating cancer in a mammal.

[0014] In another aspect, the present disclosure provides kit comprising a Compound of the Disclosure.

[0015] 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.

[0016] 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.

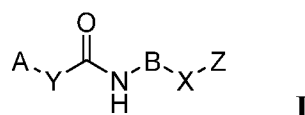
DETAILED DESCRIPTION OF THE INVENTION

[0017] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD proteins. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.*, cancer, responsive to inhibition of SMYD proteins.

[0018] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD3. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.*, cancer, responsive to inhibition of SMYD3.

[0019] One aspect of the present disclosure is based on the use of Compounds of the Disclosure as inhibitors of SMYD2. In view of this property, the Compounds of the Disclosure are useful for treating diseases, disorders, or conditions, *e.g.*, cancer, responsive to inhibition of SMYD2.

[0020] In one embodiment, Compounds of the Disclosure are compounds having Formula I:



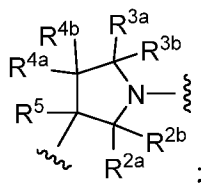
and the pharmaceutically acceptable salts or solvates, *e.g.*, hydrates, thereof, wherein:

[0021] A is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1-imidazolyl, 1-isoquinolyl, 1-pyrazolyl, 2-(1,2,3,4-tetrahydroquinolyl), 2-benzo[d]imidazolyl, 2-benzo[d]thiazolyl, 2-chromenyl-4-one, 2-furanyl, 2-imidazo[1,2-b]pyridazinyl, 2-imidazolyl, 2-indolyl, 2-naphthalenyl, 2-pyrazinyl, 2-pyridyl, 2-pyrimidinyl, 2-pyrrolidinyl, 2-pyrrolyl, 2-quinolyl, 2-quinoxalyl, 2-thiazolo[5,4-c]pyridinyl, 2-thiazolyl, 2-thiophenyl, 3-(1,2,3,4-tetrahydroisoquinoline), 3-(1,2,4-oxadiazolyl), 3-imidazo[1,2-a]pyrimidinyl, 3-indazolyl, 3-indolyl, 3-isothiazolyl, 3-pyrazolyl, 3-pyridazinyl, 3-pyridinyl-2-one, 3-pyridyl, 3-pyrrolo[3,2-b]pyridinyl, 3-quinolyl, 4-(2,2-difluorobenzo[d][1,3]dioxolyl), 4-cyclohexanyl-1-amine, 4-imidazolyl, 4-indolyl-2-one, 4-indolyl, 4-isothiazolyl, 4-oxazolyl, 4-piperidinyl, 4-pyrazolyl, 4-pyridyl, 4-

quinoliny, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one), 5-4H-furo[3,2-b]pyrrolyl, 5-benzo[c][1,2,5]oxadiazolyl, 5-benzo[d][1,3]dioxolyl, 5-benzo[d]oxazolyl-2(3H)-one, 5-bicyclo[2.2.1]heptyl-2-ene, 5-indolinyl-2,3-dione, 5-indolinyl-2-one, 5-indolyl, 5-isoindolinyl-1-one, 5-isoxazolyl, 5-pyrazolo[3,4-c]pyridinyl, 5-pyrazolyl, 5-pyrimidinyl, 5-thiazolyl, 6-(1,2,3,4-tetrahydronaphthalenyl), 6-(3,4-dihydroquinolinyl-2(1H)-one), 6-(3,4-dihydroquinoxalyl-2(1H)-one), 6-(4,5-dihydropyridazinyl-3(2H)-one), 6-benzo[b][1,4]oxazinyl-3-one, 6-benzo[d]imidazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 6-benzo[d]thiazolyl, 6-chromenyl-2-one, 6-imidazo[2,1-b]thiazole, 6-indazolyl, 6-indolinyl-2-one, 6-indolyl, 6-isoquinoliny, 6-quinoliny, 6-quinoxaliny, 6-quinoxaliny-2(1H)-one, 7-(3,4-dihydroquinolinyl-2(1H)-one), 7-(3,4-dihydroquinoxalin-2(1H)-one), 7-benzo[b][1,4]oxazinyl-3-one, 7-indolinyl-2-one, 7-quinoliny, 8-benzo[b][1,4]oxazinyl-3-one, cyclopropanyl, phenyl, 4-(prop-1-en-1-yl)-imidazole, 1-butanyl-imidazole, sec-butylcyclopropane, 2-(ethylsulfonyl)propanyl, 1-isobutylpyrrolidine, 4-pyridyl 1-oxide, and 5-benzo[c][1,2,5]oxadiazolyl 1-oxide, each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, and aralkyl;

[0022] Y is -C(R^{1a})(R^{1b})-; or Y is absent, i.e., A forms a bond with the carbonyl carbon atom;

[0023] B is:



[0024] X is selected from the group consisting of -S(=O)₂-, -S(=O)₂N(R⁶)-, -S(=O)₂C(R⁷)(H)-, -C(=O)-, -C(=O)N(R⁶)-, -C(=O)O-, and -C(=O)C(R⁷)(H)-; or X is absent, i.e., Z forms a bond with the nitrogen atom;

- [0025] Z is selected from the group consisting of hydrogen, optionally substituted C₁₋₆ alkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, alkoxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and heteroaralkyl;
- [0026] R^{1s} and R^{1b} are independently selected from the group consisting of hydrogen and C₁₋₄ alkyl;
- [0027] R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, amino, alkylamino, dialkylamino, cycloalkylamino, halo, hydroxy, C₁₋₆ alkyl, alkoxy, haloalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, alkoxyalkyl, aralkyl, alkoxycarbonyl, sulfonamido, carboxamido, -N(H)C(=O)R^{8a}, and -CH₂N(H)C(=O)R^{8b}; or
- [0028] R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a carbonyl; and R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, alkoxy, hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, aralkyl, -N(H)C(=O)R^{8a}; and -CH₂N(H)C(=O)R^{8b}; or
- [0029] R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a carbonyl; and R^{2a}, R^{2b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, alkoxy, hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, -N(H)C(=O)R^{8a}, and -CH₂N(H)C(=O)R^{8b}; or
- [0030] R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a carbonyl; and R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each independently selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, alkoxy, hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, -N(H)C(=O)R^{8a}; and -CH₂N(H)C(=O)R^{8b}; or
- [0031] R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl or C₃₋₆ heterocyclo; and R^{3a}, R^{3b}, R^{4a}, and R^{4b} are each

independently selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, alkoxy, hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, aralkyl, -N(H)C(=O)R^{8a}; and -CH₂N(H)C(=O)R^{8b}; or

[0032] R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl or C₃₋₆ heterocyclo; and R^{2a}, R^{2b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, alkoxy, hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, -N(H)C(=O)R^{8a}; and -CH₂N(H)C(=O)R^{8b}; or

[0033] R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl or C₃₋₆ heterocyclo; and R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each independently selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, alkoxy, hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, -N(H)C(=O)R^{8a}; and -CH₂N(H)C(=O)R^{8b};

[0034] R⁵ is selected from the group consisting of hydrogen and C₁₋₄ alkyl;

[0035] R⁶ is selected from the group consisting of hydrogen and C₁₋₄ alkyl;

[0036] R⁷ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, and hydroxyalkyl;

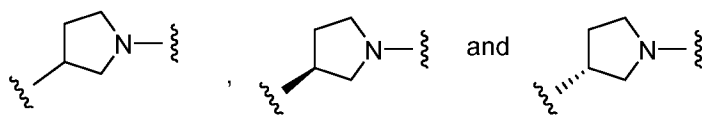
[0037] R^{8a} is selected from the group consisting of C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and heteroaralkyl; and

[0038] R^{8b} is selected from the group consisting of C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted C₄₋₁₄ heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and heteroaralkyl.

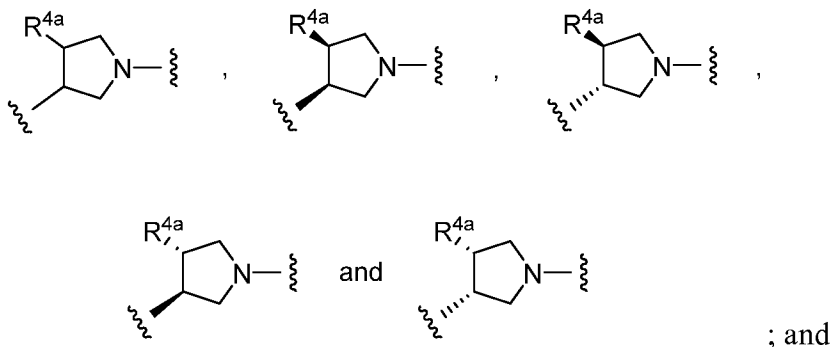
[0039] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, wherein A is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 1-imidazolyl, 1-isoquinolyl, 1-pyrazolyl, 2-(1,2,3,4-tetrahydroquinolyl), 2-benzo[d]imidazolyl, 2-benzo[d]thiazolyl, 2-chromenyl-4-one, 2-furanyl, 2-imidazo[1,2-b]pyridazinyl, 2-imidazolyl, 2-indolyl, 2-naphthalenyl, 2-

pyrazinyl, 2-pyridyl, 2-pyrimidinyl, 2-pyrrolidinyl, 2-pyrrolyl, 2-quinolinyl, 2-quinoxaliny, 2-thiazolo[5,4-c]pyridinyl, 2-thiazolyl, 2-thiophenyl, 3-(1,2,3,4-tetrahydroisoquinoline), 3-(1,2,4-oxadiazolyl), 3-imidazo[1,2-a]pyrimidinyl, 3-indazolyl, 3-indolyl, 3-isothiazolyl, 3-pyrazolyl, 3-pyridazinyl, 3-pyridinyl-2-one, 3-pyridyl, 3-pyrrolo[3,2-b]pyridinyl, 3-quinolinyl, 4-(2,2-difluorobenzo[d][1,3]dioxolyl), 4-cyclohexanyl-1-amine, 4-imidazolyl, 4-indolinyl-2-one, 4-indolyl, 4-isothiazolyl, 4-oxazolyl, 4-piperidinyl, 4-pyrazolyl, 4-pyridyl, 4-quinolinyl, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one), 5-4H-furo[3,2-b]pyrrolyl, 5-benzo[c][1,2,5]oxadiazolyl, 5-benzo[d][1,3]dioxolyl, 5-benzo[d]oxazolyl-2(3H)-one, 5-bicyclo[2.2.1]heptyl-2-ene, 5-indolinyl-2,3-dione, 5-indolinyl-2-one, 5-indolyl, 5-isoindolinyl-1-one, 5-isoxazolyl, 5-pyrazolo[3,4-c]pyridinyl, 5-pyrazolyl, 5-pyrimidinyl, 5-thiazolyl, 6-(1,2,3,4-tetrahydronaphthalenyl), 6-(3,4-dihydroquinolinyl-2(1H)-one), 6-(3,4-dihydroquinoxaliny-2(1H)-one), 6-(4,5-dihydropyridazinyl-3(2H)-one), 6-benzo[b][1,4]oxazinyl-3-one, 6-benzo[d]imidazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 6-benzo[d]thiazolyl, 6-chromenyl-2-one, 6-imidazo[2,1-b]thiazole, 6-indazolyl, 6-indolinyl-2-one, 6-indolyl, 6-isoquinolinyl, 6-quinolinyl, 6-quinoxaliny, 6-quinoxaliny-2(1H)-one, 7-(3,4-dihydroquinolinyl-2(1H)-one), 7-(3,4-dihydroquinoxalin-2(1H)-one), 7-benzo[b][1,4]oxazinyl-3-one, 7-indolinyl-2-one, 7-quinolinyl, 8-benzo[b][1,4]oxazinyl-3-one, cyclopropanyl, phenyl, 4-(prop-1-en-1-yl)-imidazole, 1-butanyl-imidazole, sec-butylcyclopropane, 2-(ethylsulfonyl)propanyl, 1-isobutylpyrrolidine, 4-pyridyl 1-oxide, and 5-benzo[c][1,2,5]oxadiazolyl 1-oxide, each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, and aralkyl.

[0040] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, wherein B is selected from the group consisting of:



[0041] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, wherein B is selected from the group consisting of:



[0042] R^{4a} is selected from the group consisting of hydroxy, C_{1-6} alkyl, alkoxy, hydroxyalkyl, C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, alkoxyalkyl, and aralkyl. In another embodiment, R^{4a} is C_{1-4} alkyl. In another embodiment, R^{4a} is methyl.

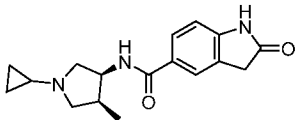
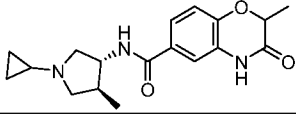
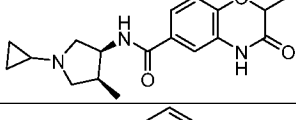
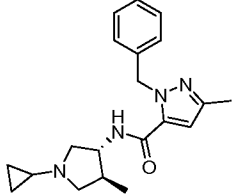
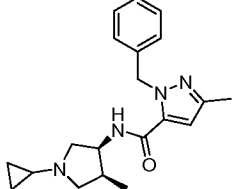
[0043] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, wherein X is selected from the group consisting of $-S(=O)_2-$ and $-C(=O)-$; or X is absent. In another embodiment, X is $-S(=O)_2-$. In another embodiment, X is $-C(=O)-$. In another embodiment, X is absent.

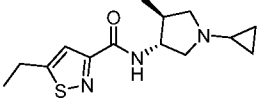
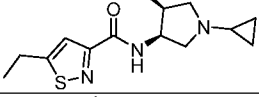
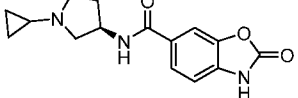
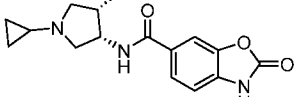
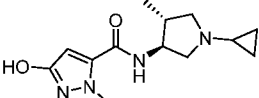
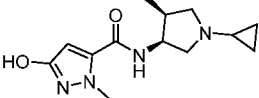
[0044] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, wherein Z is selected from the group consisting of optionally substituted C_{1-6} alkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C_{3-12} cycloalkyl, aralkyl, and heteroaralkyl. In another embodiment, Z is selected from the group consisting of C_{1-6} alkyl and optionally substituted C_{3-12} cycloalkyl. In another embodiment, Z is cyclopropyl.

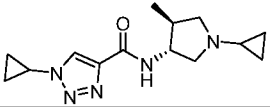
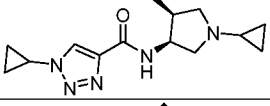
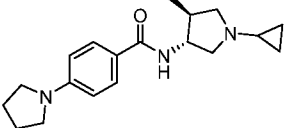
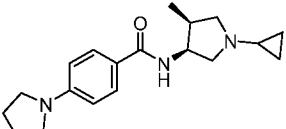
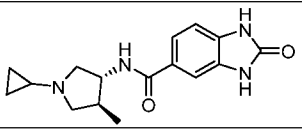
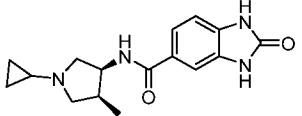
- [0045] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, wherein Y is -CH₂-.
- [0046] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, wherein Y is absent.
- [0047] In another embodiment, Compounds of the Disclosure are compounds having Formula I, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, wherein A is selected from the group consisting of 5-indolinyl-2-one, 6-benzo[b][1,4]oxazinyl-3-one, 5-pyrazolyl, 3-isothiazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 1,2,3-triazolyl, phenyl, and 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one). In another embodiment, A is 5-indolinyl-2-one.
- [0048] In another embodiment, Compounds of the Disclosure are compounds of Tables 1, 3, and 4, and the pharmaceutically acceptable salts or solvates, e.g., hydrates, thereof, or different pharmaceutically acceptable salt thereof.
- [0049] It should be appreciated that the Compounds of the Disclosure in certain embodiments are the free base, various salts, and hydrate forms, and are not limited to the particular salt listed in Tables 1, 3, and 4.

Table 1

Cpd. No.	Structure	Salt Form	Chemical Name	LCMS M+H	SMYD2 Biochem IC50 (μM)*
1		TFA	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	325.2	>50
2		TFA	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2,2-difluorobenzo[d][1,3]dioxole-5-carboxamide	325.2	>50
3		TFA	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)acetamide	330.3	>50
4		TFA	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)acetamide	330.3	>50
5		None	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-oxoindoline-5-carboxamide	300.2	>50

6		None	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-oxoindoline-5-carboxamide	300.2	>50
7		TFA	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	330.7	>50
8		TFA	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine-6-carboxamide	330.3	>50
9		None	(±)- <i>trans</i> -1-benzyl-N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-3-methyl-1H-pyrazole-5-carboxamide	339.4	>50
10		None	(±)- <i>cis</i> -1-benzyl-N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-3-methyl-1H-pyrazole-5-carboxamide	339.5	>50

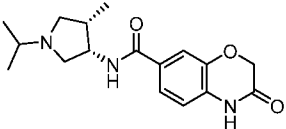
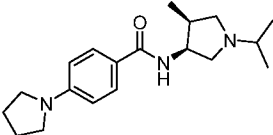
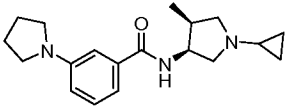
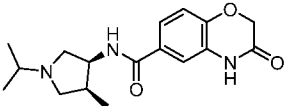
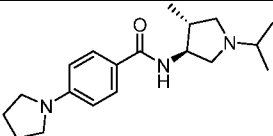
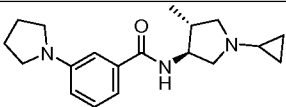
11		None	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-5-ethylisothiazole-3-carboxamide	280.2	>50
12		None	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-5-ethylisothiazole-3-carboxamide	280.2	7.1
13		None	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide	302	>50
14		None	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-oxo-2,3-dihydrobenzo[d]oxazole-6-carboxamide	302	>50
15		None	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-3-hydroxy-1-methyl-1H-pyrazole-5-carboxamide	265	>50
16		None	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-3-hydroxy-1-methyl-1H-pyrazole-5-carboxamide	265	>50

18		TFA	(±)- <i>trans</i> -1-cyclopropyl-N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	276.2	13.2
19		TFA	(±)- <i>cis</i> -1-cyclopropyl-N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-1H-1,2,3-triazole-4-carboxamide	276.3	1.4
20		TFA	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-4-(pyrrolidin-1-yl)benzamide	314.5	>50
21		TFA	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-4-(pyrrolidin-1-yl)benzamide	314.5	>50
22		None	(±)- <i>trans</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide	301.1	>50
23		None	(±)- <i>cis</i> -N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide	301	>50

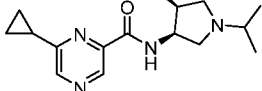
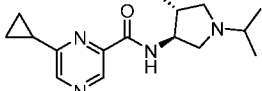
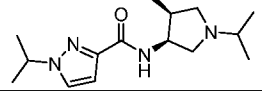
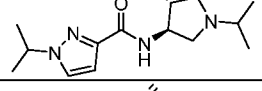
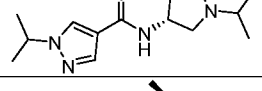
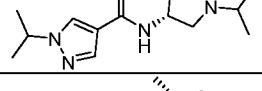
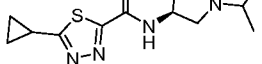
* IC₅₀ values are an average of n=1 to n=50

Table 3

Cpd. No.	Structure	Salt Form	Chemical Name	LCMS M+H	SMYD2 Biochem IC ₅₀ (μM)*
24		None	(±)- <i>trans</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1-(propan-2-yl)-1H-1,2,3-triazole-4-carboxamide	280.2	> 50.0
25		None	(±)- <i>cis</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1-(propan-2-yl)-1H-1,2,3-triazole-4-carboxamide	280.2	6.33619
26		None	(±)- <i>trans</i> -1-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	278.2	19.28126
27		None	(±)- <i>cis</i> -1-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-1,2,3-triazole-4-carboxamide	278.2	0.78114
28		None	(±)- <i>trans</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide	318.3	> 50.0

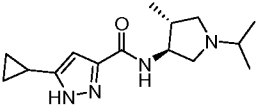
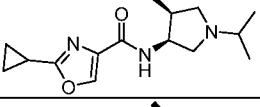
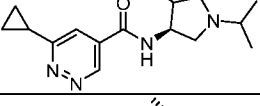
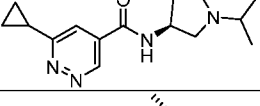
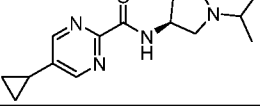
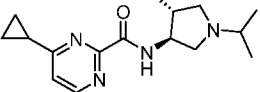
29		None	(±)- <i>cis</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide	318.3	> 50.0
30		None	(±)- <i>cis</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-4-(pyrrolidin-1-yl)benzamide	316.3	> 50.0
31		None	(±)- <i>cis</i> -N-[1-cyclopropyl-4-methylpyrrolidin-3-yl]-3-(pyrrolidin-1-yl)benzamide	314.3	> 50.0
32		None	(±)- <i>cis</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide	318.1	> 50.0
33		None	(±)- <i>trans</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-4-(pyrrolidin-1-yl)benzamide	316.2	> 50.0
34		None	(±)- <i>trans</i> -N-[1-cyclopropyl-4-methylpyrrolidin-3-yl]-3-(pyrrolidin-1-yl)benzamide	314.2	> 50.0

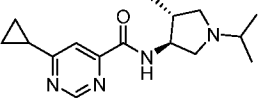
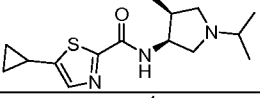
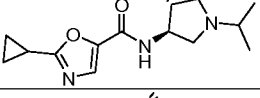
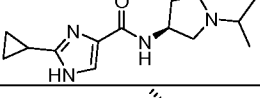
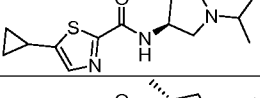
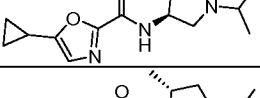
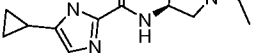
35		None	(±)- <i>cis</i> -4-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-thiazole-2-carboxamide	294.2	> 50.0
36		None	(±)- <i>trans</i> -4-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-thiazole-2-carboxamide	294.2	> 50.0
37		None	(±)- <i>trans</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide	318.2	> 50.0
38		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,2,4-oxadiazole-3-carboxamide	279.2	> 50.0
39		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,2,4-oxadiazole-3-carboxamide	279.2	> 50.0
40		None	(±)- <i>cis</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]acetamide	185.1	> 50.0
41		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3,4-thiadiazole-2-carboxamide	295.1	2.68239

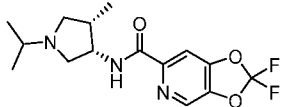
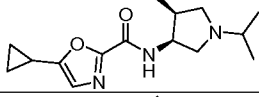
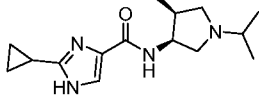
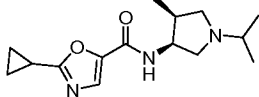
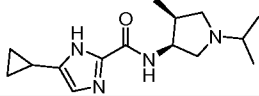
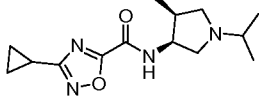
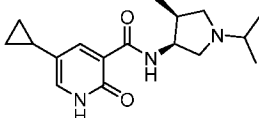
42		None	(±)- <i>cis</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrazine-2-carboxamide	289.2	> 50.0
43		None	(±)- <i>trans</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrazine-2-carboxamide	289.1	> 50.0
44		None	(±)- <i>cis</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1-(propan-2-yl)-1H-pyrazole-3-carboxamide	279.3	> 50.0
45		None	(±)- <i>trans</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1-(propan-2-yl)-1H-pyrazole-3-carboxamide	279.3	> 50.0
46		None	(±)- <i>cis</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1-(propan-2-yl)-1H-pyrazole-4-carboxamide	279.2	> 50.0
47		None	(±)- <i>trans</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1-(propan-2-yl)-1H-pyrazole-4-carboxamide	279.2	> 50.0
48		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3,4-thiadiazole-2-carboxamide	295.1	39.53548

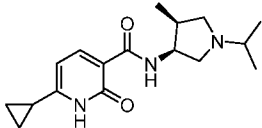
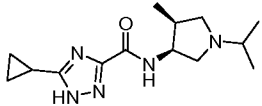
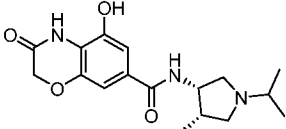
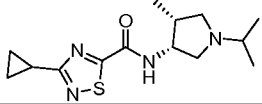
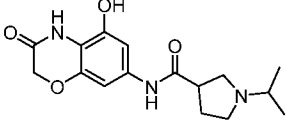
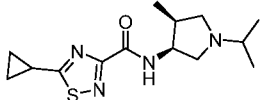
49		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3,4-oxadiazole-2-carboxamide	279.1	26.84323
50		None	(±)- <i>cis</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrimidine-4-carboxamide	289.2	16.71474
51		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrazine-2-carboxamide	289	> 50.0
52		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrazine-2-carboxamide	289.2	> 50.0
53		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3,4-oxadiazole-2-carboxamide	279.1	4.64222
54		None	(±)- <i>trans</i> -2-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-oxazole-4-carboxamide	278.1	> 50.0

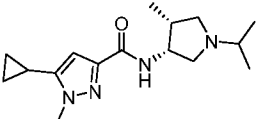
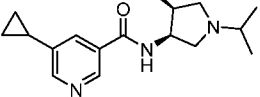
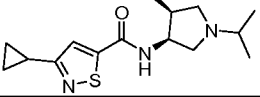
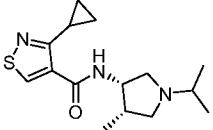
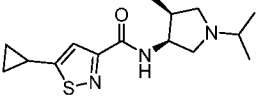
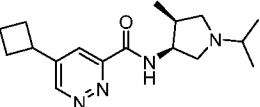
55		None	(±)- <i>trans</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-3-(pyrrolidin-1-yl)propanamide	268.2	> 50.0
56		None	(±)- <i>cis</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-3-(pyrrolidin-1-yl)propanamide	268.2	> 50.0
57		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-6-oxo-1,6-dihydropyridine-2-carboxamide	304.2	> 50.0
58		None	(±)- <i>trans</i> -N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]acetamide	185.1	> 50.0
59		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrimidine-2-carboxamide	289.2	> 50.0
60		None	(±)- <i>cis</i> -4-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrimidine-2-carboxamide	289.2	> 50.0
61		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-pyrazole-3-carboxamide	277.1	> 50.0

62		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-pyrazole-3-carboxamide	277.3	> 50.0
63		None	(±)- <i>cis</i> -2-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-oxazole-4-carboxamide	278.2	> 50.0
64		None	(±)- <i>cis</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-4-carboxamide	289.2	> 50.0
65		None	(±)- <i>trans</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-4-carboxamide	289.2	> 50.0
66		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrimidine-2-carboxamide	289.2	> 50.0
67		None	(±)- <i>trans</i> -4-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrimidine-2-carboxamide	289.3	> 50.0

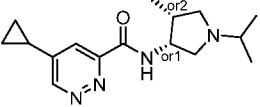
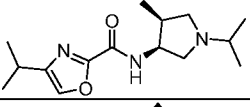
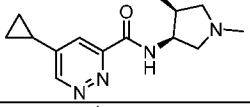
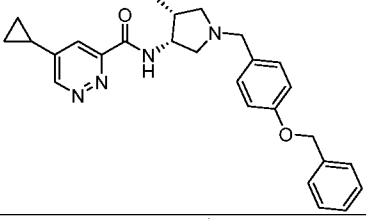
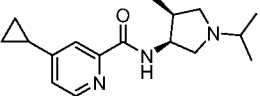
68		None	(±)- <i>trans</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyrimidine-4-carboxamide	289.2	> 50.0
69		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-thiazole-2-carboxamide	294.2	3.2968
70		None	(±)- <i>trans</i> -2-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-oxazole-5-carboxamide	278.2	> 50.0
71		None	(±)- <i>trans</i> -2-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-imidazole-4-carboxamide	277.2	> 50.0
72		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-thiazole-2-carboxamide	294.2	> 50.0
73		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-oxazole-2-carboxamide	278.2	> 50.0
74		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-imidazole-2-carboxamide	277.2	24.25401

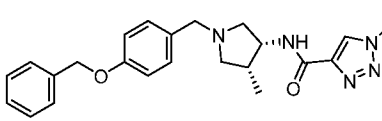
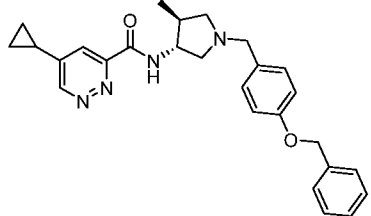
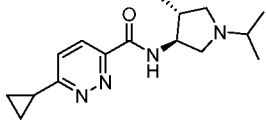
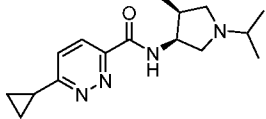
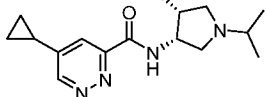
75		None	(±)- <i>cis</i> -2,2-difluoro-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-2H-[1,3]dioxolo[4,5-c]pyridine-6-carboxamide	328.1	> 50.0
76		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-oxazole-2-carboxamide	278.2	6.77179
77		None	(±)- <i>cis</i> -2-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-imidazole-4-carboxamide	277.2	> 50.0
78		None	(±)- <i>cis</i> -2-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,3-oxazole-5-carboxamide	278.2	> 50.0
79		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-imidazole-2-carboxamide	277.3	1.96274
81		None	(±)- <i>cis</i> -3-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,2,4-oxadiazole-5-carboxamide	279.1	> 50.0
82		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-2-oxo-1,2-dihydropyridine-3-carboxamide	304.2	13.56167

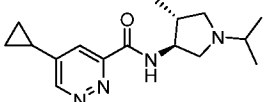
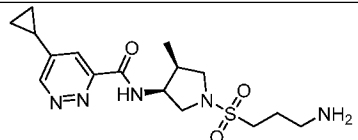
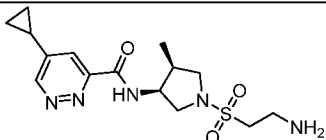
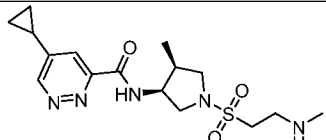
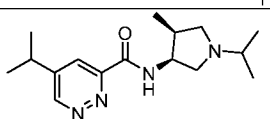
83		None	(±)- <i>cis</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-2-oxo-1,2-dihydropyridine-3-carboxamide	304.3	> 50.0
84		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-1,2,4-triazole-3-carboxamide	278.2	36.77646
85		None	(±)- <i>cis</i> -5-hydroxy-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide	334.1	> 50.0
86		None	(±)- <i>cis</i> -3-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,2,4-thiadiazole-5-carboxamide	295.2	> 50.0
87		None	N-(5-hydroxy-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-7-yl)-1-(propan-2-yl)pyrrolidine-3-carboxamide	320.2	> 50.0
88		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,2,4-thiadiazole-3-carboxamide	295.1	> 50.0

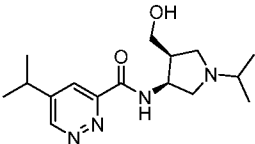
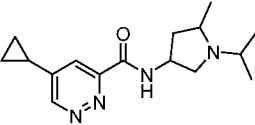
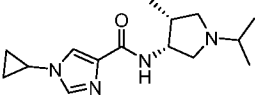
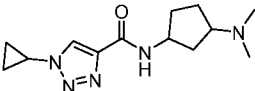
89		None	(±)- <i>cis</i> -5-cyclopropyl-1-methyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1H-pyrazole-3-carboxamide	291.2	> 50.0
90		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridine-3-carboxamide	288.3	> 50.0
91		None	(±)- <i>cis</i> -3-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,2-thiazole-5-carboxamide	294.2	> 50.0
92		None	(±)- <i>cis</i> -3-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,2-thiazole-4-carboxamide	294.2	19.57904
93		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-1,2-thiazole-3-carboxamide	294.2	0.77574
94		None	(±)- <i>cis</i> -5-cyclobutyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide	303.3	> 50.0

95		None	5-cyclopropyl-N-[1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide	275.2	6.06902
96		None	(±)-cis-5-ethyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide	277.2	5.09064
97		None	(±)-trans-N-(1-{[4-(benzyloxy)phenyl]methyl}-4-methylpyrrolidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	432.3	10.45068
98		None	rel-5-cyclopropyl-N-[(3S,4S)-4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide	289.4	2.08912
99		None	(±)-cis-N-(1-benzyl-4-methylpyrrolidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	337.2	0.57363
100		None	(±)-cis-5-cyclopropyl-N-(1-ethyl-4-methylpyrrolidin-3-yl)pyridazine-3-carboxamide	275.2	0.61056

101		None	rel-5-cyclopropyl-N-[(3R,4R)-4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide		0.24471
102		None	(±)-cis-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]-4-(propan-2-yl)-1,3-oxazole-2-carboxamide	280.2	> 50.0
103		None	(±)-cis-5-cyclopropyl-N-(1,4-dimethylpyrrolidin-3-yl)pyridazine-3-carboxamide	261.2	1.66767
104		None	(±)-cis-N-(1-([4-(benzyloxy)phenyl]methyl)-4-methylpyrrolidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	443.3	0.09168
105		None	(±)-cis-4-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridine-2-carboxamide	288.3	0.69415

106		None	(±)- <i>cis</i> -N-(1-([4-(benzyloxy)phenyl]methyl)-4-methylpyrrolidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	432.3	0.46
107		None	(±)- <i>trans</i> -N-(1-([4-(benzyloxy)phenyl]methyl)-4-methylpyrrolidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	443.3	2.7
108		None	(±)- <i>trans</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide	289	> 50.0
109		None	(±)- <i>cis</i> -6-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide	289	> 50.0
110		None	(±)- <i>cis</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide	289.2	0.42415

111		None	(±)- <i>trans</i> -5-cyclopropyl-N-[4-methyl-1-(propan-2-yl)pyrrolidin-3-yl]pyridazine-3-carboxamide	289.2	12.0304
112		None	(±)- <i>cis</i> -N-(1-((3-aminopropyl)sulfonyl)-4-methylpyrrolidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide		>50
113		None	(±)- <i>cis</i> -N-(1-((2-aminoethyl)sulfonyl)-4-methylpyrrolidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide		>50
114		None	(±)- <i>cis</i> -5-cyclopropyl-N-(4-methyl-1-((2-(methylamino)ethyl)sulfonyl)pyrrolidin-3-yl)pyridazine-3-carboxamide		>50
118		None	(±)- <i>cis</i> -5-isopropyl-N-(1-isopropyl-4-methylpyrrolidin-3-yl)pyridazine-3-carboxamide		10.4

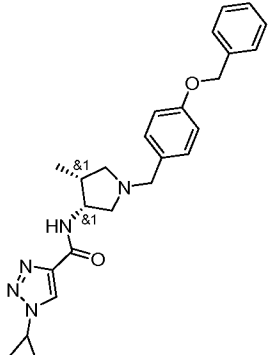
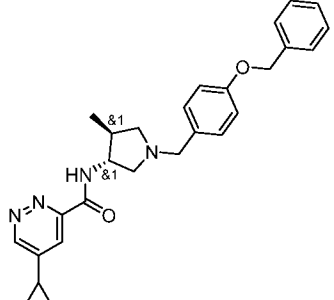
119		None	(±)- <i>cis</i> -N-(4-(hydroxymethyl)-1-isopropylpyrrolidin-3-yl)-5-isopropylpyridazine-3-carboxamide		
120		None	5-cyclopropyl-N-(1-isopropyl-5-methylpyrrolidin-3-yl)pyridazine-3-carboxamide		11.5
121		None	(±)- <i>cis</i> -1-cyclopropyl-N-(1-isopropyl-4-methylpyrrolidin-3-yl)-1H-imidazole-4-carboxamide		2.2
122		None	1-cyclopropyl-N-[3-(dimethylamino)cyclopentyl]-1H-1,2,3-triazole-4-carboxamide	264.2	> 50.0

* IC₅₀ values are an average of n=1 to n=50

Table 4

Cpd. No.	Structure	Salt Form	Chemical Name	LCMS M+H	SMYD2 Biochem IC ₅₀ (μM)*
123		None	rac-1-cyclopropyl-N-((3R,4R)-1-isopropyl-4-methylpyrrolidin-3-yl)-1H-imidazole-4-carboxamide	277.2	2.2
124		None	rac-5-isopropyl-N-((3R,4R)-1-isopropyl-4-methylpyrrolidin-3-yl)pyridazine-3-carboxamide	291.3	10.4
125		None	5-cyclopropyl-N-(1-isopropyl-5-methylpyrrolidin-3-yl)pyridazine-3-carboxamide	289.2	11.5
126		None	rac-N-((3R,4R)-1-((3-aminopropyl)sulfonyl)-4-methylpyrrolidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	368.1	> 50

127		None	rac-N-((3R,4R)-1-((2-aminoethyl)sulfonyl)-4-methylpyrrolidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	354.2	> 50
128		None	rac-5-cyclopropyl-N-((3R,4R)-4-methyl-1-((2-(methylamino)ethyl)sulfonyl)pyrrolidin-3-yl)pyridazine-3-carboxamide	368.2	> 50
129		None	rac-5-cyclopropyl-N-((3R,4R)-4-(hydroxymethyl)-1-isopropylpyrrolidin-3-yl)pyridazine-3-carboxamide	304.9	0.77
130		None	rac-5-cyclopropyl-N-((3R,4R)-1-isopropyl-4-methylpyrrolidin-3-yl)-N-methylpyridazine-3-carboxamide	303.2	6.4

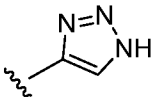
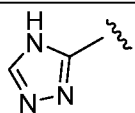
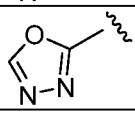
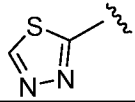
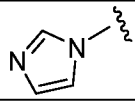
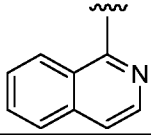
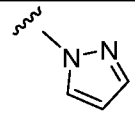
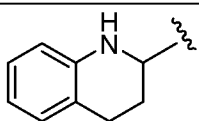
131		None	rac-N-((3R,4R)-1-(4-(benzyloxy)benzyl)-4-methylpyrrolidin-3-yl)-1-cyclopropyl-1H-1,2,3-triazole-4-carboxamide	432.3	0.46
132		None	rac-N-((3R,4S)-1-(4-(benzyloxy)benzyl)-4-methylpyrrolidin-3-yl)-5-cyclopropylpyridazine-3-carboxamide	443.3	2.7

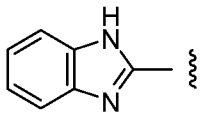
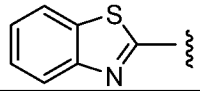
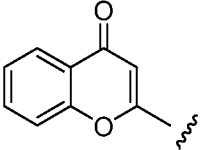
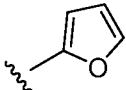
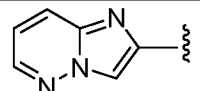
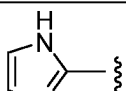
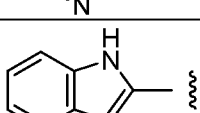
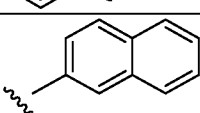
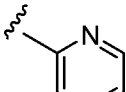
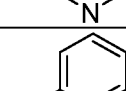
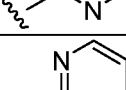
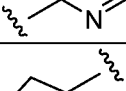
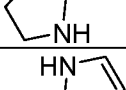
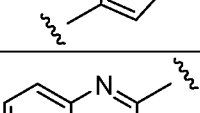
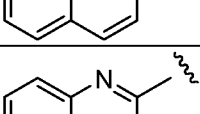
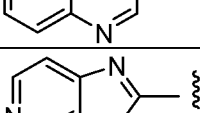
* IC₅₀ values are an average of n=1 to n=50

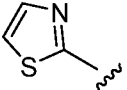
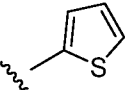
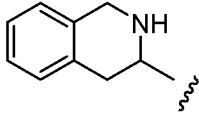
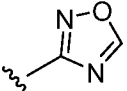
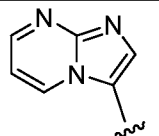
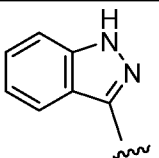
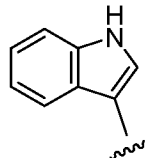
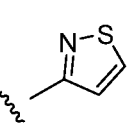
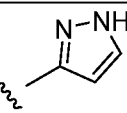
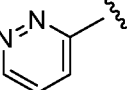
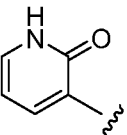
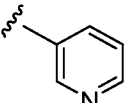
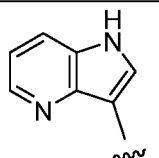
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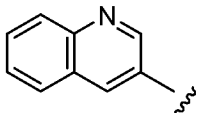
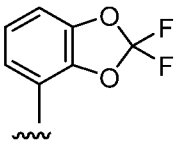
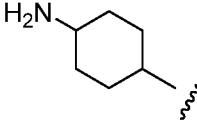
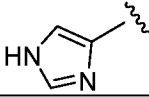
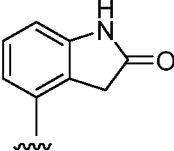
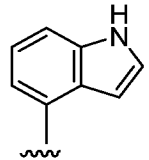
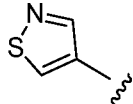
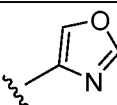
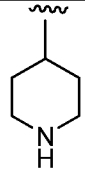
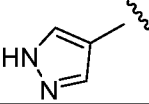
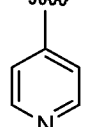
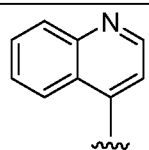
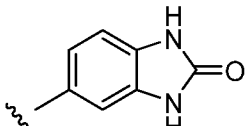
[0050] For the purpose of the present disclosure, the terms used in connection with A have the chemical structures set forth in Table 2, each of which may be optionally substituted with one or more substituents, *e.g.*, 1, 2, 3, 4, or 5 substituents, depending on the nature of the group and the number of available positions. For example, when A is 2-furanyl there are three carbon atoms available for substitution. When A is 2-naphthalenyl there are seven carbon atoms available for substitution. Substitution may occur at any available carbon or nitrogen atom. Optional substituents include, but are not limited to, halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, or aralkyl.

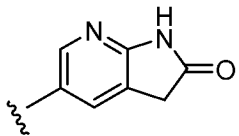
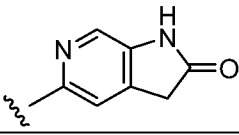
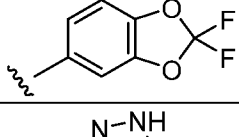
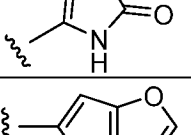
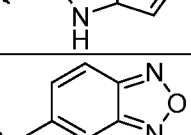
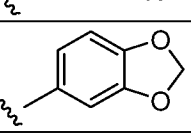
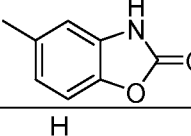
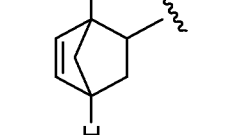
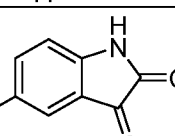
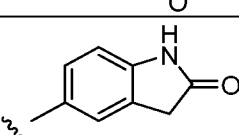
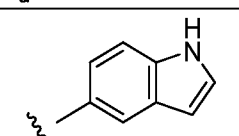
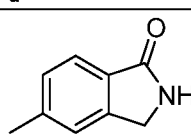

Table 2

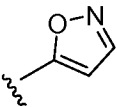
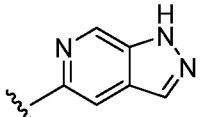
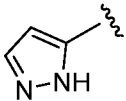
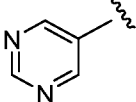
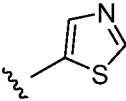
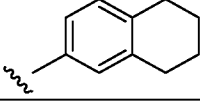
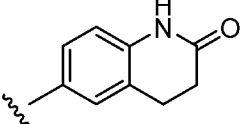
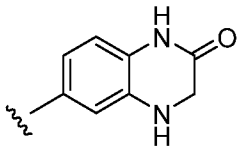
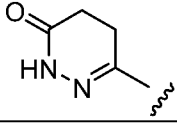
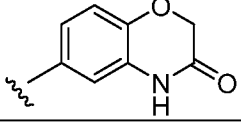
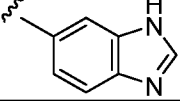
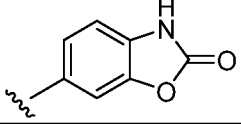
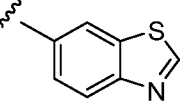
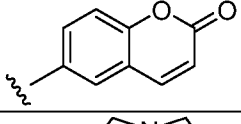
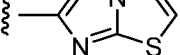
A	Chemical structure
1,2,3-triazolyl	
1,2,4-triazolyl	
1,3,4-oxadizaole	
1,3,4-thiadizaole	
1-imidazolyl	
1-isoquinolinyl	
1-pyrazolyl	
2-(1,2,3,4-tetrahydroquinolinyl)	

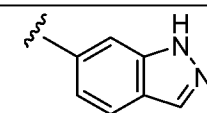
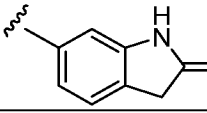
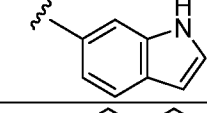
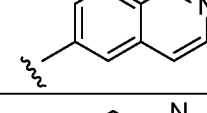
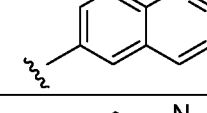
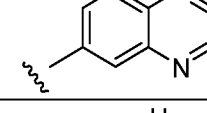
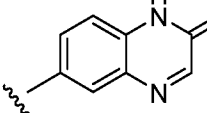
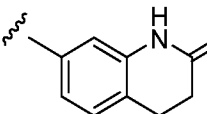
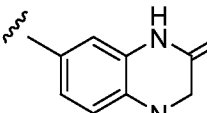
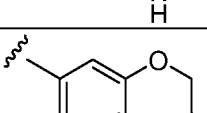
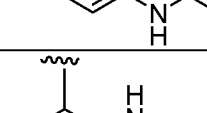
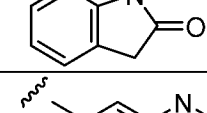
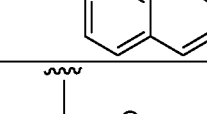
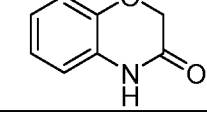
2-benzo[d]imidazolyl	
2-benzo[d]thiazolyl	
2-chromenyl-4-one	
2-furanyl	
2-imidazo[1,2-b]pyridazinyl	
2-imidazolyl	
2-indolyl	
2-naphthalenyl	
2-pyrazinyl	
2-pyridyl	
2-pyrimidinyl	
2-pyrrolidinyl	
2-pyrrolyl	
2-quinolinyl	
2-quinoxaliny	
2-thiazolo[5,4-c]pyridinyl	

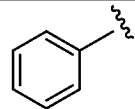
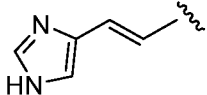
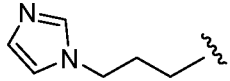
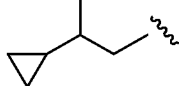
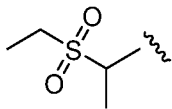
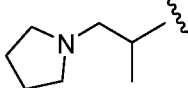
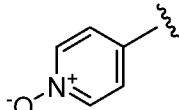
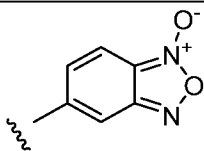
2-thiazolyl	
2-thiophenyl	
3-(1,2,3,4-tetrahydroisoquinoline)	
3-(1,2,4-oxadiazolyl)	
3-imidazo[1,2-a]pyrimidinyl	
3-indazolyl	
3-indolyl	
3-isothiazolyl	
3-pyrazolyl	
3-pyridazinyl	
3-pyridinyl-2-one	
3-pyridyl	
3-pyrrolo[3,2-b]pyridinyl	

3-quinolinyl	
4-(2,2-difluorobenzo[d][1,3]dioxolyl)	
4-cyclohexanyl-1-amine	
4-imidazolyl	
4-indolinyl-2-one	
4-indolyl	
4-isothiazolyl	
4-oxazolyl	
4-piperidiny	
4-pyrazolyl	
4-pyridyl	
4-quinolinyl	
5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one)	

5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one)	
5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one)	
5-(2,2-difluorobenzo[d][1,3]dioxolyl)	
5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one)	
5-4H-furo[3,2-b]pyrrolyl	
5-benzo[c][1,2,5]oxadiazolyl	
5-benzo[d][1,3]dioxolyl	
5-benzo[d]oxazolyl-2(3H)-one	
5-bicyclo[2.2.1]heptyl-2-ene	
5-indolinyl-2,3-dione	
5-indolinyl-2-one	
5-indolyl	
5-isoindolinyl-1-one	

5-isoxazolyl	
5-pyrazolo[3,4-c]pyridinyl	
5-pyrazolyl	
5-pyrimidinyl	
5-thiazolyl	
6-(1,2,3,4-tetrahydronaphthalenyl)	
6-(3,4-dihydroquinolinyl-2(1H)-one)	
6-(3,4-dihydroquinoxalinyl-2(1H)-one)	
6-(4,5-dihydropyridazinyl-3(2H)-one)	
6-benzo[b][1,4]oxazinyl-3-one	
6-benzo[d]imidazolyl	
6-benzo[d]oxazolyl-2(3H)-one	
6-benzo[d]thiazolyl	
6-chromenyl-2-one	
6-imidazo[2,1-b]thiazole	

6-indazolyl	
6-indoliny-2-one	
6-indolyl	
6-isoquinoliny	
6-quinoliny	
6-quinoxaliny	
6-quinoxaliny-2(1H)-one	
7-(3,4-dihydroquinoliny-2(1H)-one)	
7-(3,4-dihydroquinoxalin-2(1H)-one)	
7-benzo[b][1,4]oxazinyl-3-one	
7-indoliny-2-one	
7-quinoliny	
8-benzo[b][1,4]oxazinyl-3-one	
cyclopropanyl	

phenyl	
4-(prop-1-en-1-yl)-imidazole	
1-butanyl-imidazole	
sec-butylcyclopropane	
2-(ethylsulfonyl)propanyl	
1-isobutylpyrrolidine	
4-pyridyl 1-oxide	
5-benzo[c][1,2,5]oxadiazolyl 1-oxide	

[0051] For the purpose of the present disclosure, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one to twelve carbon atoms (*i.e.*, C₁₋₁₂ alkyl) or the number of carbon atoms designated (*i.e.*, a C₁ alkyl such as methyl, a C₂ alkyl such as ethyl, a C₃ alkyl such as propyl or isopropyl, etc.). In one embodiment, the alkyl group is chosen from a straight chain C₁₋₁₀ alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C₃₋₁₀ alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C₁₋₆ alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C₃₋₆ alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C₁₋₄ alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C₃₋₄ alkyl group. In another embodiment, the alkyl group is chosen from a straight or branched chain C₃₋₄ alkyl group. In another embodiment, the alkyl group is partially or completely deuterated, *i.e.*, one or more hydrogen atoms of the alkyl group are replaced with deuterium atoms. Non-limiting exemplary C₁₋₁₀ alkyl groups include methyl (including -CD₃), ethyl, propyl, isopropyl, butyl, *sec*-butyl,

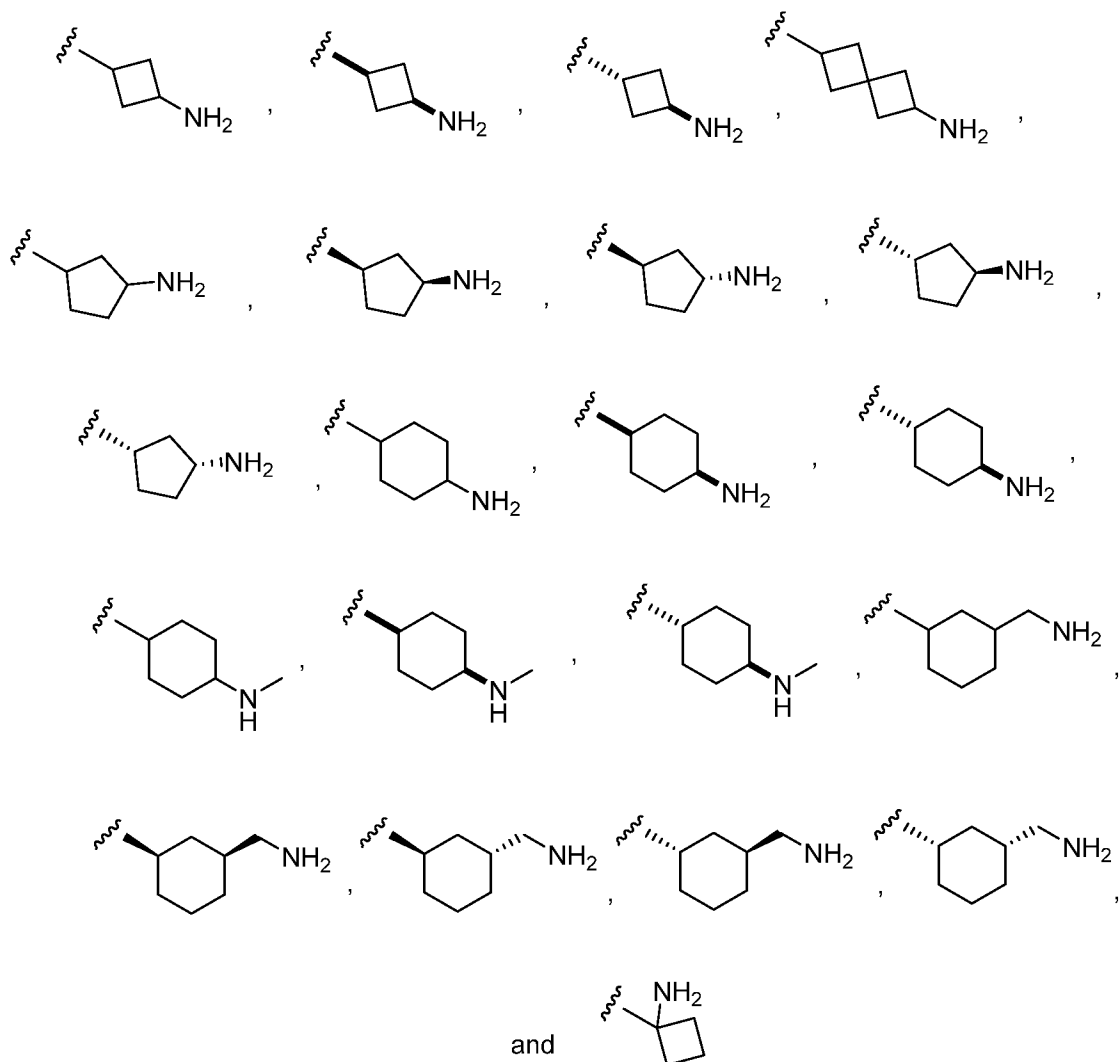
tert-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, and decyl. Non-limiting exemplary C₁₋₄ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, and *iso*-butyl.

[0052] For the purpose of 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 chosen from nitro, haloalkoxy, aryloxy, aralkyloxy, alkylthio, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, alkoxy, carbonyl, and carboxyalkyl. In one embodiment, the alkyl is a C₁₋₄ alkyl. 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 -CH₂CH₂NO₂, -CH₂CH₂CO₂H, -CH₂CH₂SO₂CH₃, -CH₂CH₂COPh, and -CH₂C₆H₁₁.

[0053] For the purpose of 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 to three rings having from three to twelve carbon atoms (*i.e.*, C₃₋₁₂ 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 chosen from a C₃₋₈ cycloalkyl group. In another embodiment, the cycloalkyl group is chosen from a C₃₋₆ cycloalkyl group. Non-limiting exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, and spiro[3.3]heptane.

[0054] For the purpose of 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 chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl,

mercaptoalkyl, (heterocyclo)alkyl, or (heteroaryl)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. In one embodiment, the optionally substituted cycloalkyl is substituted with at least one amino, alkylamino, or dialkylamino group. Non-limiting exemplary optionally substituted cycloalkyl groups include:



[0055] For the purpose of the present disclosure, the term "cycloalkenyl" as used by itself or part of another group refers to a partially unsaturated cycloalkyl group as defined above. In one embodiment, the cycloalkenyl has one carbon-to-carbon double bond. In another embodiment, the cycloalkenyl group is chosen from a C₄₋₈ cycloalkenyl group. Exemplary cycloalkenyl groups include cyclopentenyl and cyclohexenyl.

[0056] For the purpose of the present disclosure, the term "optionally substituted cycloalkenyl" as used by itself or as part of another group means that the cycloalkenyl as

defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, monohydroxyalkyl, dihydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In one embodiment, the optionally substituted cycloalkenyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkenyl is substituted with one substituent. In another embodiment, the cycloalkenyl is unsubstituted.

[0057] For the purpose of 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 chosen from a C₂₋₆ alkenyl group. In another embodiment, the alkenyl group is chosen from a C₂₋₄ alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

[0058] For the purpose of 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 chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclo.

[0059] For the purpose of 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 to 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 chosen from a C₂₋₆ alkynyl group. In another embodiment, the alkynyl group is chosen from a C₂₋₄ alkynyl group.

Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

[0060] For the purpose of 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 chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted heterocyclo.

[0061] For the purpose of 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 chosen from a C₁₋₄ haloalkyl group. Non-limiting exemplary haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

[0062] For the purpose of the present disclosure, the term "hydroxyalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one or more, e.g., 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. In another embodiment, the hydroxyalkyl group is chosen from a C₁₋₄ 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.

[0063] For the purpose of 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 chosen from a C₁₋₄ alkoxy group. In another embodiment, the alkoxy group is chosen from a C₁₋₄ alkyl attached to a terminal oxygen atom, *e.g.*, methoxy, ethoxy, and *tert*-butoxy.

[0064] For the purpose of 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 chosen from a C₁₋₄ alkylthio group. Non-limiting exemplary alkylthio groups include -SCH₃, and -SCH₂CH₃.

[0065] For the purpose of 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.

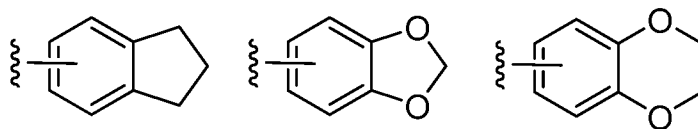
[0066] For the purpose of the present disclosure, the term "haloalkoxy" as used by itself or as part of another group refers to a haloalkyl attached to a terminal oxygen atom. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

[0067] For the purpose of the present disclosure, the term "heteroalkyl" as used by itself or part of another group refers to a stable straight or branched chain hydrocarbon radical containing 1 to 10 carbon atoms and at least two heteroatoms, which can be the same or different, selected from O, N, or S, wherein: 1) the nitrogen atom(s) and sulfur atom(s) can optionally be oxidized; and/or 2) the nitrogen atom(s) can optionally be quaternized. The heteroatoms can be placed at any interior position of the heteroalkyl group or at a position at which the heteroalkyl group is attached to the remainder of the molecule. In one embodiment, the heteroalkyl group contains two oxygen atoms. In one embodiment, the heteroalkyl contains one oxygen and one nitrogen atom. In one embodiment, the heteroalkyl contains two nitrogen atoms. Non-limiting exemplary heteroalkyl groups include -CH₂OCH₂CH₂OCH₃, -OCH₂CH₂OCH₂CH₂OCH₃, -CH₂NHCH₂CH₂OCH₂, -OCH₂CH₂NH₂, -NHCH₂CH₂N(H)CH₃, -NHCH₂CH₂OCH₃ and -OCH₂CH₂OCH₃.

[0068] For the purpose of 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.*, C₆₋₁₄ aryl). Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph"), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl,

biphenyl, biphenylenyl, and fluorenyl groups. In one embodiment, the aryl group is chosen from phenyl or naphthyl. In one embodiment, the aryl group is phenyl.

[0069] For the purpose of 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, heteroaryloxy, aralkyl, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (cycloalkylamino)alkyl, (C₁₋₄ haloalkoxy)alkyl, (heteroaryl)alkyl, -N(R⁴³)(R⁴⁴), and -N(H)C(=O)-R⁴⁵, wherein R⁴³ is hydrogen or C₁₋₄ alkyl; R⁴⁴ is alkoxyalkyl, (heterocyclo)alkyl, (amino)alkyl, (alkylamino)alkyl, or (dialkylamino)alkyl; and R⁴⁵ is alkyl, optionally substituted aryl or optionally substituted heteroaryl. 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. In another embodiment, the optionally substituted phenyl has one amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, or (dialkylamino)alkyl 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-dimethoxyphenyl, 3,5-di-fluorophenyl, 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, 3-chloro-4-fluorophenyl, and 2-phenylpropan-2-amine. The term optionally substituted aryl is meant to include groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Examples include:



[0070] For the purpose of 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-.

[0071] For the purpose of the present disclosure, the term "heteroaryloxy" as used by itself or as part of another group refers to an optionally substituted heteroaryl attached to a terminal oxygen atom.

[0072] For the purpose of the present disclosure, the term "aralkyloxy" or "arylalkyloxy" 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 PhCH₂O-.

[0073] For the purpose of 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) and 1, 2, 3, or 4 heteroatoms independently chosen from oxygen, nitrogen or sulfur. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. In another embodiment, the heteroaryl is a 5- to 10-membered heteroaryl. In one embodiment, the heteroaryl has 5 ring atoms, *e.g.*, thienyl, a 5-membered heteroaryl having four carbon atoms and one sulfur atom. In another embodiment, the heteroaryl has 6 ring atoms, *e.g.*, pyridyl, a 6-membered heteroaryl having five carbon atoms and one nitrogen atom. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranlyl, 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, 4*aH*-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. In one embodiment, the heteroaryl is chosen from thienyl (*e.g.*, thien-2-yl and thien-3-yl), furyl (*e.g.*, 2-furyl and 3-furyl), pyrrolyl (*e.g.*, 1*H*-pyrrol-2-yl and 1*H*-pyrrol-3-yl), imidazolyl (*e.g.*, 2*H*-imidazol-2-yl and 2*H*-imidazol-4-yl), pyrazolyl (*e.g.*, 1*H*-pyrazol-3-yl, 1*H*-pyrazol-4-yl, and 1*H*-pyrazol-5-yl), pyridyl (*e.g.*, pyridin-2-yl,

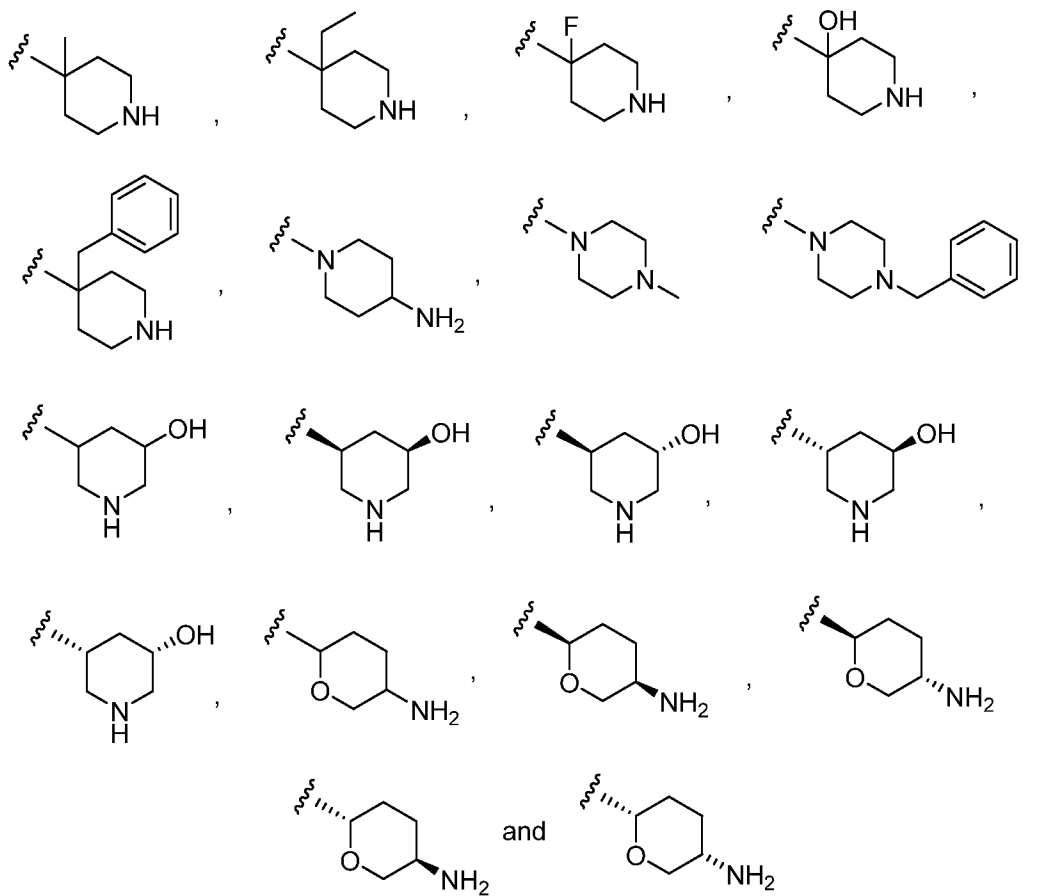
pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (*e.g.*, pyrimidin-2-yl, pyrimidin-4-yl, and pyrimidin-5-yl), thiazolyl (*e.g.*, thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (*e.g.*, isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (*e.g.*, oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl)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

[0074] For the purpose of 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 chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aralkyl, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, optionally substituted cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, $-N(R^{43})(R^{44})$, or $-N(H)C(=O)-R^{45}$, wherein R^{43} is hydrogen or C_{1-4} alkyl; R^{44} is alkoxyalkyl, (heterocyclo)alkyl, (amino)alkyl, (alkylamino)alkyl, or (dialkylamino)alkyl; and R^{45} is alkyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, the optionally substituted heteroaryl has one substituent. In one embodiment, the substituent is amino, alkylamino, dialkylamino, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (heterocyclo)alkyl, $-N(R^{43})(R^{44})$, or $-N(H)C(=O)-R^{45}$. In one embodiment, the optionally substituted is an optionally substituted pyridyl, *i.e.*, 2-, 3-, or 4-pyridyl. Any available carbon or nitrogen atom can be substituted.

[0075] For the purpose of 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) and at least one heteroatom. Each heteroatom is independently selected from the group consisting of oxygen, sulfur, including sulfoxide and sulfone, and/or nitrogen atoms, which can be quaternized. The term "heterocyclo" is meant to include cyclic ureido

groups such as imidazolidinyl-2-one, cyclic amide groups such as β -lactam, γ -lactam, δ -lactam and ϵ -lactam, and cyclic carbamate groups such as oxazolidinyl-2-one. The term "heterocyclo" is also meant to include groups having fused optionally substituted aryl groups, *e.g.*, indolinyl, indolinyl-2-one, benzo[d]oxazolyl-2(3H)-one. In one embodiment, the heterocyclo group is chosen from a 4-, 5-, 6-, 7- or 8-membered cyclic group containing one ring and one or two oxygen and/or nitrogen atoms. In one embodiment, the heterocyclo group is chosen from a 5- or 6-membered cyclic group containing one ring and one or two nitrogen atoms. In one embodiment, the heterocyclo group is chosen from a 8-, 9-, 10-, 11-, or 12-membered cyclic group containing two rings and one or two nitrogen atoms. The heterocyclo can be optionally linked to the rest of the molecule through a carbon or nitrogen atom. Non-limiting exemplary heterocyclo groups include 2-oxopyrrolidin-3-yl, 2-imidazolidinone, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, 8-azabicyclo[3.2.1]octane (nortropene), 6-azaspiro[2.5]octane, 6-azaspiro[3.4]octane, indolinyl, indolinyl-2-one, 1,3-dihydro-2H-benzo[d]imidazol-2-one

[0076] For the purpose of 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, aralkyl aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. Substitution may occur on any available carbon or nitrogen atom, and may form a spirocycle. In one embodiment, the optionally substituted heterocyclo is substituted with at least one amino, alkylamino, or dialkylamino group. Non-limiting exemplary optionally substituted heterocyclo groups include:



[0077] For the purpose of the present disclosure, the term "amino" as used by itself or as part of another group refers to -NH_2 .

[0078] For the purpose of the present disclosure, the term "alkylamino" as used by itself or as part of another group refers to -NHR^{22} , wherein R^{22} is C_{1-6} alkyl. In one embodiment, R^{22} is C_{1-4} alkyl. Non-limiting exemplary alkylamino groups include -N(H)CH_3 and $\text{-N(H)CH}_2\text{CH}_3$.

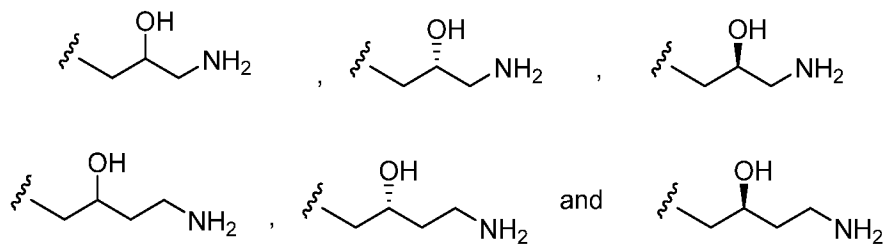
[0079] For the purpose of the present disclosure, the term "dialkylamino" as used by itself or as part of another group refers to $\text{-NR}^{23a}\text{R}^{23b}$, wherein R^{23a} and R^{23b} are each independently C_{1-6} alkyl. In one embodiment, R^{23a} and R^{23b} are each independently C_{1-4} alkyl. Non-limiting exemplary dialkylamino groups include $\text{-N(CH}_3)_2$ and $\text{-N(CH}_3)\text{CH}_2\text{CH(CH}_3)_2$.

[0080] For the purpose of the present disclosure, the term "hydroxyalkylamino" as used by itself or as part of another group refers to -NHR^{24} , wherein R^{24} is hydroxyalkyl.

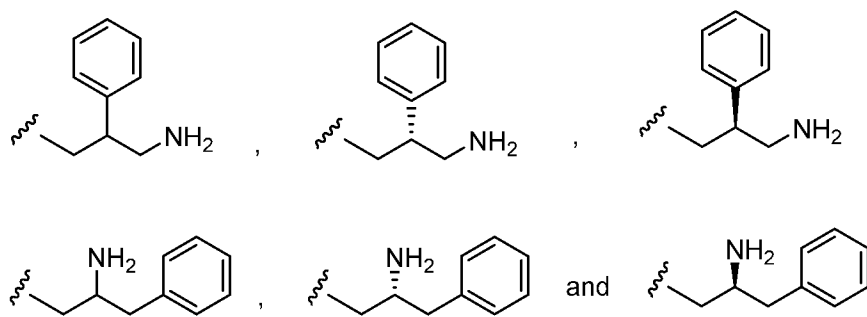
[0081] For the purpose of the present disclosure, the term "cycloalkylamino" as used by itself or as part of another group refers to $\text{-NR}^{25a}\text{R}^{25b}$, wherein R^{25a} is optionally substituted cycloalkyl and R^{25b} is hydrogen or C_{1-4} alkyl.

- [0082] For the purpose of the present disclosure, the term "aralkylamino" as used by itself or as part of another group refers to $-\text{NR}^{26a}\text{R}^{26b}$, wherein R^{26a} is aralkyl and R^{26b} is hydrogen or C_{1-4} alkyl. Non-limiting exemplary aralkylamino groups include $-\text{N}(\text{H})\text{CH}_2\text{Ph}$ and $-\text{N}(\text{CH}_3)\text{CH}_2\text{Ph}$.
- [0083] For the purpose of 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 alkyl is a C_{1-4} alkyl. Non-limiting exemplary (amino)alkyl groups include $-\text{CH}_2\text{NH}_2$, $-\text{C}(\text{NH}_2)(\text{H})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{C}(\text{NH}_2)(\text{H})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$, and $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{NH}_2$.
- [0084] For the purpose of the present disclosure, the term "(alkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an alkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. A non-limiting exemplary (alkylamino)alkyl group is $-\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_3$.
- [0085] For the purpose of the present disclosure, the term "(dialkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a dialkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (dialkylamino)alkyl groups are $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$.
- [0086] For the purpose of the present disclosure, the term "(cycloalkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted by a cycloalkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (cycloalkylamino)alkyl groups include $-\text{CH}_2\text{N}(\text{H})\text{cyclopropyl}$, $-\text{CH}_2\text{N}(\text{H})\text{cyclobutyl}$, and $-\text{CH}_2\text{N}(\text{H})\text{cyclohexyl}$.
- [0087] For the purpose of the present disclosure, the term "(aralkylamino)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with an aralkylamino group. In one embodiment, the alkyl is a C_{1-4} alkyl. A non-limiting exemplary (aralkylamino)alkyl group is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{Ph}$.
- [0088] For the purpose of the present disclosure, the term "(cyano)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one or more cyano, *e.g.*, $-\text{CN}$, groups. In one embodiment, the alkyl is a C_{1-4} alkyl. Non-limiting exemplary (cyano)alkyl groups include $-\text{CH}_2\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CN}$, and $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CN}$.
- [0089] For the purpose of the present disclosure, the term "(amino)(hydroxy)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one amino, alkylamino, or dialkylamino group and one hydroxy group. In one embodiment,

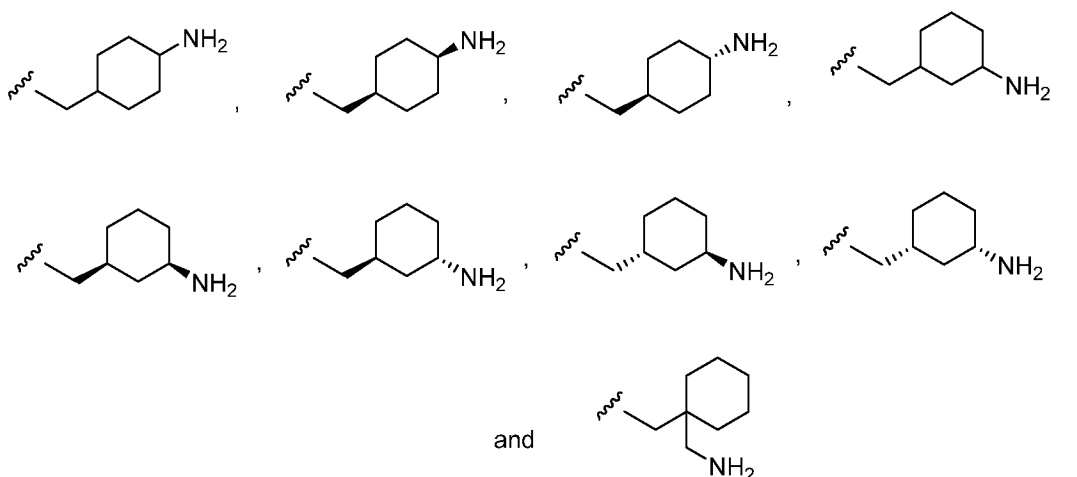
the alkyl is a C₁₋₆ alkyl. In another embodiment, the alkyl is a C₁₋₄ alkyl. Non-limiting exemplary (amino)(hydroxy)alkyl groups include:



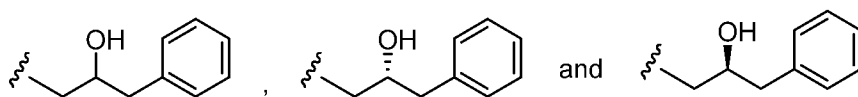
[0090] For the purpose of the present disclosure, the term "(amino)(aryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one amino, alkylamino, or dialkylamino group and one optionally substituted aryl group. In one embodiment, the alkyl is a C₁₋₆ alkyl. In one embodiment, the optionally substituted aryl group is an optionally substituted phenyl. Non-limiting exemplary (amino)(aryl)alkyl groups include:



[0091] For the purpose of the present disclosure, the term "(cycloalkyl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one optionally substituted cycloalkyl group. In one embodiment, the alkyl is a C₁₋₄ alkyl. In one embodiment, the cycloalkyl is a C₃₋₆ cycloalkyl. In one embodiment, the optionally substituted cycloalkyl group is substituted with an amino or (amino)alkyl group. Non-limiting exemplary (cycloalkyl)alkyl groups include:



[0092] For the purpose of the present disclosure, the term "(hydroxy)(aryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one hydroxy group and one optionally substituted aryl group. In one embodiment, the alkyl is a C₁₋₆ alkyl. In one embodiment, the optionally substituted aryl group is an optionally substituted phenyl. Non-limiting exemplary (hydroxy)(aryl)alkyl groups include:



[0093] For the purpose of the present disclosure, the term "carboxamido" as used by itself or as part of another group refers to a radical of formula $-C(=O)NR^{26a}R^{26b}$, wherein R^{26a} and R^{26b} are each independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or R^{26a} and R^{26b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. In one embodiment, R^{26a} and R^{26b} are each independently hydrogen or optionally substituted alkyl. Non-limiting exemplary carboxamido groups include $-CONH_2$, $-CON(H)CH_3$, $CON(CH_3)_2$, and $-CON(H)Ph$.

[0094] For the purpose of the present disclosure, the term "(carboxamido)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with a carboxamido group. Non-limiting exemplary (carboxamido)alkyl groups include $-CH_2CONH_2$, $-C(H)CH_3-CONH_2$, and $-CH_2CON(H)CH_3$.

[0095] For the purpose of the present disclosure, the term "sulfonamido" as used by itself or as part of another group refers to a radical of the formula $-SO_2NR^{27a}R^{27b}$, wherein R^{27a} and R^{27b} are each independently hydrogen, optionally substituted alkyl, or optionally substituted aryl, or R^{27a} and R^{27b} taken together with the nitrogen to which they are

attached from a 3- to 8-membered heterocyclo group. Non-limiting exemplary sulfonamido groups include $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{N(H)CH}_3$, and $-\text{SO}_2\text{N(H)Ph}$.

[0096] For the purpose of the present disclosure, the term "alkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, $-\text{C(=O)-}$, substituted by an alkyl group. A non-limiting exemplary alkylcarbonyl group is $-\text{COCH}_3$.

[0097] For the purpose of the present disclosure, the term "arylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, $-\text{C(=O)-}$, substituted by an optionally substituted aryl group. A non-limiting exemplary arylcarbonyl group is $-\text{COPh}$.

[0098] For the purpose of the present disclosure, the term "alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $-\text{SO}_2-$, substituted by any of the above-mentioned optionally substituted alkyl groups. A non-limiting exemplary alkylsulfonyl group is $-\text{SO}_2\text{CH}_3$.

[0099] For the purpose of the present disclosure, the term "arylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $-\text{SO}_2-$, substituted by any of the above-mentioned optionally substituted aryl groups. A non-limiting exemplary arylsulfonyl group is $-\text{SO}_2\text{Ph}$.

[0100] For the purpose of 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 $-\text{SH}$ group.

[0101] For the purpose of the present disclosure, the term "carboxy" as used by itself or as part of another group refers to a radical of the formula $-\text{COOH}$.

[0102] For the purpose of 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 $-\text{COOH}$. A non-limiting exemplary carboxyalkyl group is $-\text{CH}_2\text{CO}_2\text{H}$.

[0103] For the purpose of the present disclosure, the term "alkoxycarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, $-\text{C(=O)-}$, substituted by an alkoxy group. Non-limiting exemplary alkoxycarbonyl groups are $-\text{CO}_2\text{Me}$ and $-\text{CO}_2\text{Et}$.

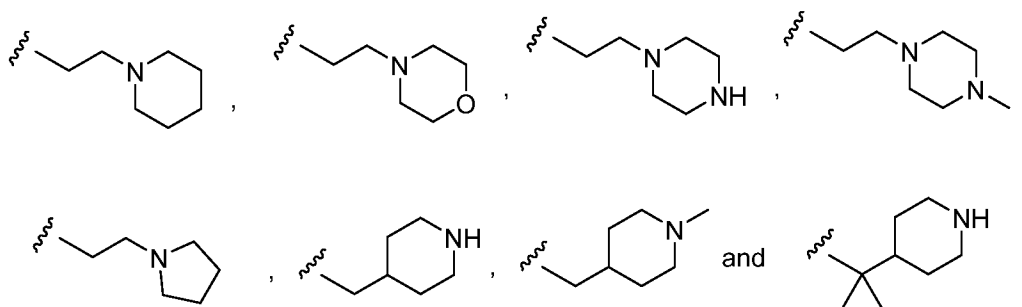
[0104] For the purpose of the present disclosure, the term "aralkyl" or "arylalkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted aryl groups. In one embodiment, the aralkyl group is a

C₁₋₄ alkyl substituted with one optionally substituted aryl group. Non-limiting exemplary aralkyl groups include benzyl, phenethyl, -CHPh₂, -CH₂(4-OH-Ph), and -CH(4-F-Ph)₂.

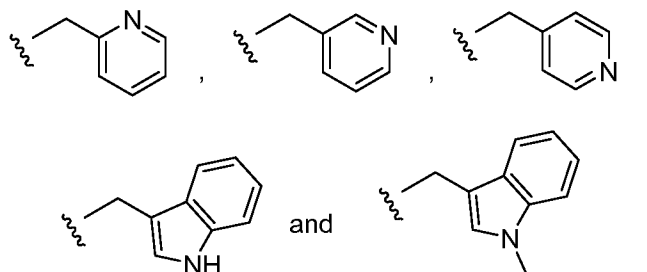
[0105] For the purpose of the present disclosure, the term "ureido" as used by itself or as part of another group refers to a radical of the formula -NR^{30a}-C(=O)-NR^{30b}R^{30c}, wherein R^{22a} is hydrogen, alkyl, or optionally substituted aryl, and R^{30b} and R^{30c} are each independently hydrogen, alkyl, or optionally substituted aryl, or R^{30b} and R^{30c} taken together with the nitrogen to which they are attached form a 4- to 8-membered heterocyclo group. Non-limiting exemplary ureido groups include -NH-C(=O)-NH₂ and -NH-C(=O)-NHCH₃.

[0106] For the purpose of the present disclosure, the term "guanidino" as used by itself or as part of another group refers to a radical of the formula -NR^{28a}-C(=NR²⁹)-NR^{28b}R^{28c}, wherein R^{28a}, R^{28b}, and R^{28c} are each independently hydrogen, alkyl, or optionally substituted aryl, and R²⁹ is hydrogen, alkyl, cyano, alkylsulfonyl, alkylcarbonyl, carboxamido, or sulfonamido. Non-limiting exemplary guanidino groups include -NH-C(=NH)-NH₂, -NH-C(=NCN)-NH₂, and -NH-C(=NH)-NHCH₃.

[0107] For the purpose of the present disclosure, the term "(heterocyclo)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted heterocyclo groups. In one embodiment, the (heterocyclo)alkyl is a C₁₋₄ alkyl substituted with one optionally substituted heterocyclo group. The heterocyclo can be linked to the alkyl group through a carbon or nitrogen atom. Non-limiting exemplary (heterocyclo)alkyl groups include:



[0108] For the purpose of the present disclosure, the term "(heteroaryl)alkyl" as used by itself or as part of another group refers to an alkyl group substituted with one, two, or three optionally substituted heteroaryl groups. In one embodiment, the (heteroaryl)alkyl group is a C₁₋₄ alkyl substituted with one optionally substituted heteroaryl group. Non-limiting exemplary (heteroaryl)alkyl groups include:



[0109] For the purpose of the present disclosure, the term "alkylcarbonylamino" as used by itself or as part of another group refers to an alkylcarbonyl group attached to an amino. A non-limiting exemplary alkylcarbonylamino group is -NHCOCH₃.

[0110] The present disclosure encompasses any of the Compounds of the Disclosure being isotopically-labelled (*i.e.*, radiolabeled) by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ²H (or deuterium (D)), ³H, ¹¹C, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, respectively, *e.g.*, ³H, ¹¹C, and ¹⁴C. In one embodiment, provided is a composition wherein substantially all of the atoms at a position within the Compound of the Disclosure are replaced by an atom having a different atomic mass or mass number. In another embodiment, provided is a composition wherein a portion of the atoms at a position within the Compound of the disclosure are replaced, *i.e.*, the Compound of the Disclosure is enriched at a position with an atom having a different atomic mass or mass number." Isotopically-labelled Compounds of the Disclosure can be prepared by methods known in the art.

[0111] Compounds of the Disclosure may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present disclosure is meant to encompass the use of all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers can be separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present disclosure as well.

[0112] 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).

[0113] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[0114] 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.

[0115] The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.

[0116] 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.

[0117] 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.

[0118] 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 $([\alpha]_{\text{obs}}/[\alpha]_{\text{max}})*100$, where $[\alpha]_{\text{obs}}$ is the optical rotation of the mixture of enantiomers and $[\alpha]_{\text{max}}$ 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.

[0119] 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.

[0120] 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.

[0121] The terms "a" and "an" refer to one or more.

[0122] The term "about," as used herein, includes the recited number $\pm 10\%$. Thus, "about 10" means 9 to 11.

[0123] The present disclosure encompasses the preparation and use of salts of the Compounds of the Disclosure, including non-toxic pharmaceutically acceptable salts. Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts and basic salts. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, phosphate, sulphate and the like; organic acid salts such as citrate, lactate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, formate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; and amino acid salts such as arginate, asparagine, glutamate and the like. The term "pharmaceutically acceptable salt" as used herein, refers to any salt, *e.g.*, obtained by reaction with an acid or a base, of a Compound of the Disclosure that is physiologically tolerated in the target patient (*e.g.*, a mammal, *e.g.*, a human).

[0124] Acid addition salts can be formed by mixing a solution of the particular Compound of the Disclosure with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, or the like. Basic salts can be formed by mixing a solution of the compound of the present disclosure with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

[0125] 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, ethanol, and the like, and it is intended that the disclosure includes both solvated and unsolvated forms of Compounds of the Disclosure. 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 E.C. 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.

[0126] Since Compounds of the Disclosure are inhibitors of SMYD proteins, such as SMYD3 and SMYD2, a number of diseases, conditions, or disorders mediated by SMYD proteins, such as SMYD3 and SMYD2, can be treated by employing these compounds. The present disclosure is thus directed generally to a method for treating a disease, condition, or disorder responsive to the inhibition of SMYD proteins, such as SMYD3 and SMYD2, in an animal suffering from, or at risk of suffering from, the disorder, the method comprising administering to the animal an effective amount of one or more Compounds of the Disclosure.

[0127] The present disclosure is further directed to a method of inhibiting SMYD proteins in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.

[0128] The present disclosure is further directed to a method of inhibiting SMYD3 in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.

- [0129] The present disclosure is further directed to a method of inhibiting SMYD2 in an animal in need thereof, the method comprising administering to the animal a therapeutically effective amount of at least one Compound of the Disclosure.
- [0130] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a Compound of the Disclosure to an individual in need of such treatment.
- [0131] Within the meaning of the disclosure, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy.
- [0132] The term "therapeutically effective amount" or "effective dose" as used herein refers to an amount of the active ingredient(s) that is(are) sufficient, when administered by a method of the disclosure, to efficaciously deliver the active ingredient(s) for the treatment of condition or disease of interest to an individual in need thereof. In the case of a cancer or other proliferation disorder, the therapeutically effective amount of the agent may reduce (i.e., retard to some extent and preferably stop) unwanted cellular proliferation; reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., retard to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., retard to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; modulate protein methylation in the target cells; and/or relieve, to some extent, one or more of the symptoms associated with the cancer. To the extent the administered compound or composition prevents growth and/or kills existing cancer cells, it may be cytostatic and/or cytotoxic.

- [0133] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.
- [0134] 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.
- [0135] The term "disease" or "condition" or "disorder" 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 inhibit SMYD proteins, such as SMYD3 and SMYD2 and can be used in treating diseases and conditions such as proliferative diseases, wherein inhibition of SMYD proteins, such as SMYD3 and SMYD2 provides a benefit.
- [0136] In some embodiments, the Compounds of the Disclosure can be used to treat a "SMYD protein mediated disorder" (*e.g.*, a SMYD3-mediated disorder or a SMYD2-mediated disorder). A SMYD protein mediated disorder is any pathological condition in which a SMYD protein is known to play a role. In some embodiments, a SMYD-mediated disorder is a proliferative disease.
- [0137] In some embodiments inhibiting SMYD proteins, such as SMYD3 and SMYD2, is the inhibition of the activity of one or more activities of SMYD proteins such as SMYD3 and SMYD2. In some embodiments, the activity of the SMYD proteins such as SMYD3 and SMYD2 is the ability of the SMYD protein such as SMYD3 or SMYD2 to transfer a methyl group to a target protein (*e.g.*, histone). It should be appreciated that the activity of the one or more SMYD proteins such as SMYD3 and SMYD2 may be inhibited *in vitro* or *in vivo*. Exemplary levels of inhibition of the activity one or more SMYD proteins such as SMYD3 and SMYD2 include at least 10% inhibition, at least 20% inhibition, at least 30% inhibition, at least 40% inhibition, at least 50% inhibition, at least 60% inhibition, at least 70% inhibition, at least 80% inhibition, at least 90% inhibition, and up to 100% inhibition.
- [0138] The SMYD (SET and MYND domain) family of lysine methyltransferases (KMTs) plays pivotal roles in various cellular processes, including gene expression regulation and DNA damage response. The family of human SMYD proteins consists of

SMYD1, SMYD2, SMYD3, SMYD4 and SMYD5. SMYD1, SMYD2, and SMYD3 share a high degree of sequence homology and, with the exception of SMYD5, human SMYD proteins harbor at least one C-terminal tetratricopeptide repeat (TPR) domain. (See *e.g.*, Abu-Farha et al. *J Mol Cell Biol* (2011) 3 (5) 301-308). The SMYD proteins have been found to be linked to various cancers (See *e.g.*, Hamamoto et al. *Nat Cell Biol.* 2004, 6: 731-740), Hu et al. *Cancer Research* 2009, 4067-4072, and Komatsu et al. *Carcinogenesis* 2009, 30:1139-1146.)

- [0139] SMYD3 is a protein methyltransferase found to be expressed at high levels in a number of different cancers (Hamamoto, R., *et al.*, *Nat. Cell Biol.*, 6(8):731-40 (2004)). SMYD3 likely plays a role in the regulation of gene transcription and signal transduction pathways critical for survival of breast, liver, prostate and lung cancer cell lines (Hamamoto, R., *et al.*, *Nat. Cell Biol.*, 6(8):731-40 (2004); Hamamoto, R., *et al.*, *Cancer Sci.*, 97(2):113-8 (2006); Van Aller, G.S., *et al.*, *Epigenetics*, 7(4):340-3 (2012); Liu, C., *et al.*, *J. Natl. Cancer Inst.*, 105(22):1719-28 (2013); Mazur, P.K., *et al.*, *Nature*, 510(7504):283-7 (2014)).
- [0140] Genetic knockdown of SMYD3 leads to a decrease in proliferation of a variety of cancer cell lines (Hamamoto, R., *et al.*, *Nat. Cell Biol.*, 6(8):731-40 (2004); Hamamoto, R., *et al.*, *Cancer Sci.*, 97(2):113-8 (2006); Van Aller, G.S., *et al.*, *Epigenetics*, 7(4):340-3 (2012); Liu, C., *et al.*, *J. Natl. Cancer Inst.*, 105(22):1719-28 (2013); Mazur, P.K., *et al.*, *Nature*, 510(7504):283-7 (2014)). Several studies employing RNAi-based technologies have shown that ablation of SMYD3 in hepatocellular carcinoma cell lines greatly reduces cell viability and that its pro-survival role is dependent on its catalytic activity (Hamamoto, R., *et al.*, *Nat. Cell Biol.*, 6(8):731-40 (2004); Van Aller, G.S., *et al.*, *Epigenetics*, 7(4):340-3 (2012)). Moreover, SMYD3 has also been shown to be a critical mediator of transformation resulting from gain of function mutations in the oncogene, KRAS for both pancreatic and lung adenocarcinoma in mouse models. The dependence of KRAS on SMYD3 was also shown to be dependent on its catalytic activity (Mazur, P.K., *et al.*, *Nature*, 510(7504):283-7 (2014)). SMYD3 function has also been implicated in colorectal cancers and RNAi mediated knockdown of SMYD3 has been shown to impair colorectal cell proliferation. (Peserico et al., *Cell Physiol.* 2015 Feb 28. doi: 10.1002/jcp.24975. [Epub ahead of print]).
- [0141] Furthermore, SMYD3 function has also been shown to play a role in immunology and development. For instance, de Almeida reported that SMYD3 plays a role in

generation of inducible regulatory T cells (iTreg) cells. In a mouse model of respiratory syncytial virus (RSV) infection, a model in which iTreg cells have a critical role in regulating lung pathogenesis, SMYD3^{-/-} mice demonstrated exacerbation of RSV-induced disease related to enhanced proinflammatory responses and worsened pathogenesis within the lung (de Almeida et al. *Mucosal Immunol.* 2015 Feb 11. doi: 10.1038/mi.2015.4. [Epub ahead of print]). In addition, as to development, Proserpio et al. have shown the importance of SMYD3 in the regulation of skeletal muscle atrophy (Proserpio et al. *Genes Dev.* 2013 Jun 1;27(11):1299-312), while Fujii et al. have elucidated the role of SMYD3 in cardiac and skeletal muscle development (Fujii et al. *PLoS One.* 2011;6(8):e23491).

[0142] SMYD2 (SET and MYND domain-containing protein 2) was first characterized as protein that is a member of a sub-family of SET domain containing proteins which catalyze the site-specific transfer of methyl groups onto substrate proteins. SMYD2 was initially shown to have methyltransferase activity towards lysine 36 on histone H3 (H3K36) but has subsequently been shown to have both histone and non-histone methyltransferase activity.

[0143] SMYD2 has been implicated in the pathogenesis of multiple cancers. It has been shown to be over-expressed, compared to matched normal samples, in tumors of the breast, cervix, colon, kidney, liver, head and neck, skin, pancreas, ovary, esophagus and prostate, as well as hematologic malignancies such as AML, B- and T-ALL, CLL and MCL, suggesting a role for SMYD2 in the biology of these cancers. More specifically, studies using genetic knock-down of SMYD2 have demonstrated anti-proliferative effects in esophageal squamous cell carcinoma (ESCC), bladder carcinoma and cervical carcinoma cell lines. (See e.g., Komatsu et al., *Carcinogenesis* 2009, 30, 1139, and Cho et al., *Neoplasia*. 2012 Jun;14(6):476-86). Moreover, high expression of SMYD2 has been shown to be a poor prognostic factor in both ESCC and pediatric ALL. (See e.g., Komatsu et al. *Br J Cancer.* 2015 Jan 20;112(2):357-64, and Sakamoto et al., *Leuk Res.* 2014 Apr;38(4):496-502). Recently, Nguyen et al., have shown that a small molecule inhibitor of SMYD2 (LLY-507) inhibited the proliferation of several esophageal, liver and breast cancer cell lines in a dose-dependent manner. (Nguyen et al. *J Biol Chem.* 2015 Mar 30. pii: jbc.M114.626861. [Epub ahead of print]).

[0144] SMYD2 has also been implicated in immunology. For instance, Xu et al. have shown that SMYD2 is a negative regulator of macrophage activation by suppressing

Interleukin-6 and TNF-alpha production. (Xu et al., J Biol Chem. 2015 Feb 27;290(9):5414-23).

[0145] In one aspect, the present disclosure provides a method of treating cancer in a patient comprising administering a therapeutically effective amount of a Compound of the Disclosure. While not being limited to a specific mechanism, in some embodiments, Compounds of the Disclosure can treat cancer by inhibiting SMYD proteins, such as SMYD3 and SMYD2. Examples of treatable cancers include, but are not limited to, adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma,

non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

- [0146] In another embodiment, the cancer is breast, cervix, colon, kidney, liver, head and neck, skin, pancreas, ovary, esophagus, or prostate cancer.

- [0147] In another embodiment, the cancer is a hematologic malignancy such as acute myeloid leukemia (AML), B- and T-acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), or mantle cell lymphoma (MCL).
- [0148] In another embodiment, the cancer is esophageal squamous cell carcinoma (ESCC), bladder carcinoma, or cervical carcinoma.
- [0149] 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.
- [0150] In another embodiment, the present disclosure provides a therapeutic method of modulating protein methylation, gene expression, cell proliferation, cell differentiation and/or apoptosis *in vivo* in the cancers mentioned above by administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need of such therapy.
- [0151] Compounds of the Disclosure can be administered to a mammal in the form of a raw chemical without any other components present. Compounds of the Disclosure can also be administered to a mammal as part of a pharmaceutical composition containing the compound combined with a suitable pharmaceutically acceptable carrier. Such a carrier can be selected from pharmaceutically acceptable excipients and auxiliaries. The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" encompasses any of the standard pharmaceutical carriers, solvents, surfactants, or vehicles. Suitable pharmaceutically acceptable vehicles include aqueous vehicles and nonaqueous vehicles. Standard pharmaceutical carriers and their formulations are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995.

- [0152] Pharmaceutical compositions within the scope of the present disclosure include all compositions where a Compound of the Disclosure is combined with one or more pharmaceutically acceptable carriers. In one embodiment, the Compound of the Disclosure is present in the composition in an amount that is effective to achieve its intended therapeutic purpose. While individual needs may vary, a determination of optimal ranges of effective amounts of each compound is within the skill of the art. Typically, a Compound of the Disclosure can be administered to a mammal, *e.g.*, a human, orally at a dose of from about 0.0025 to about 1500 mg per kg body weight of the mammal, or an equivalent amount of a pharmaceutically acceptable salt or solvate thereof, per day to treat the particular disorder. A useful oral dose of a Compound of the Disclosure administered to a mammal is from about 0.0025 to about 50 mg per kg body weight of the mammal, or an equivalent amount of the pharmaceutically acceptable salt or solvate thereof. For intramuscular injection, the dose is typically about one-half of the oral dose.
- [0153] A unit oral dose may comprise from about 0.01 mg to about 1 g of the Compound of the Disclosure, *e.g.*, about 0.01 mg to about 500 mg, about 0.01 mg to about 250 mg, about 0.01 mg to about 100 mg, 0.01 mg to about 50 mg, *e.g.*, about 0.1 mg to about 10 mg, of the compound. The unit dose can be administered one or more times daily, *e.g.*, as one or more tablets or capsules, each containing from about 0.01 mg to about 1 g of the compound, or an equivalent amount of a pharmaceutically acceptable salt or solvate thereof.
- [0154] A pharmaceutical composition of the present disclosure can be administered to any patient that may experience the beneficial effects of a Compound of the Disclosure. Foremost among such patients are mammals, *e.g.*, humans and companion animals, although the disclosure is not intended to be so limited. In one embodiment, the patient is a human.
- [0155] A pharmaceutical composition of the present disclosure can be administered by any means that achieves its intended purpose. For example, administration can be by the oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, intranasal, transmucosal, rectal, intravaginal or buccal route, or by inhalation. The dosage administered and route of administration will vary, depending upon the circumstances of the particular subject, and taking into account such factors as age,

gender, health, and weight of the recipient, condition or disorder to be treated, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

[0156] In one embodiment, a pharmaceutical composition of the present disclosure can be administered orally. In another embodiment, a pharmaceutical composition of the present disclosure can be administered orally and is formulated into tablets, dragees, capsules, or an oral liquid preparation. In one embodiment, the oral formulation comprises extruded multiparticulates comprising the Compound of the Disclosure.

[0157] Alternatively, a pharmaceutical composition of the present disclosure can be administered rectally, and is formulated in suppositories.

[0158] Alternatively, a pharmaceutical composition of the present disclosure can be administered by injection.

[0159] Alternatively, a pharmaceutical composition of the present disclosure can be administered transdermally.

[0160] Alternatively, a pharmaceutical composition of the present disclosure can be administered by inhalation or by intranasal or transmucosal administration.

[0161] Alternatively, a pharmaceutical composition of the present disclosure can be administered by the intravaginal route.

[0162] A pharmaceutical composition of the present disclosure can contain from about 0.01 to 99 percent by weight, e.g., from about 0.25 to 75 percent by weight, of a Compound of the Disclosure, e.g., about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, or about 75% by weight of a Compound of the Disclosure.

[0163] A pharmaceutical composition of the present disclosure is manufactured in a manner which itself will be known in view of the instant disclosure, for example, by means of conventional mixing, granulating, dragee-making, dissolving, extrusion, or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the active compound with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0164] Suitable excipients include fillers such as saccharides (for example, lactose, sucrose, mannitol or sorbitol), cellulose preparations, calcium phosphates (for example, tricalcium phosphate or calcium hydrogen phosphate), as well as binders such as starch

paste (using, for example, maize starch, wheat starch, rice starch, or potato starch), gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, one or more disintegrating agents can be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate.

[0165] Auxiliaries are typically flow-regulating agents and lubricants such as, for example, silica, talc, stearic acid or salts thereof (*e.g.*, magnesium stearate or calcium stearate), and polyethylene glycol. Dragee cores are provided with suitable coatings that are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate can be used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[0166] Examples of other pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, or soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain a compound in the form of granules, which can be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers, or in the form of extruded multiparticulates. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils or liquid paraffin. In addition, stabilizers can be added.

[0167] Possible pharmaceutical preparations for rectal administration include, for example, suppositories, which consist of a combination of one or more active compounds with a suppository base. Suitable suppository bases include natural and synthetic triglycerides, and paraffin hydrocarbons, among others. It is also possible to use gelatin rectal capsules consisting of a combination of active compound with a base material such as, for example, a liquid triglyceride, polyethylene glycol, or paraffin hydrocarbon.

[0168] Suitable formulations for parenteral administration include aqueous solutions of the active compound in a water-soluble form such as, for example, a water-soluble salt,

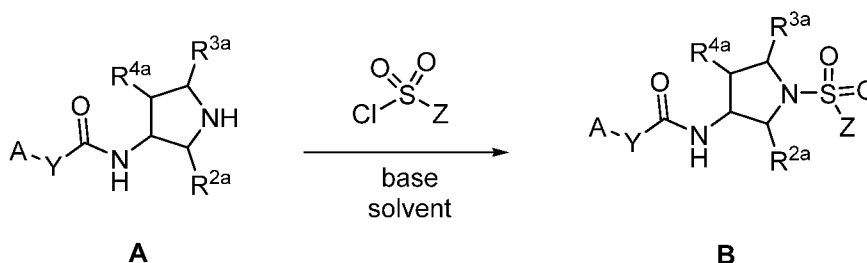
alkaline solution, or acidic solution. Alternatively, a suspension of the active compound can be prepared as an oily suspension. Suitable lipophilic solvents or vehicles for such as suspension may include fatty oils (for example, sesame oil), synthetic fatty acid esters (for example, ethyl oleate), triglycerides, or a polyethylene glycol such as polyethylene glycol-400 (PEG-400). An aqueous suspension may contain one or more substances to increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. The suspension may optionally contain stabilizers.

[0169] 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.

General Synthesis of Compounds

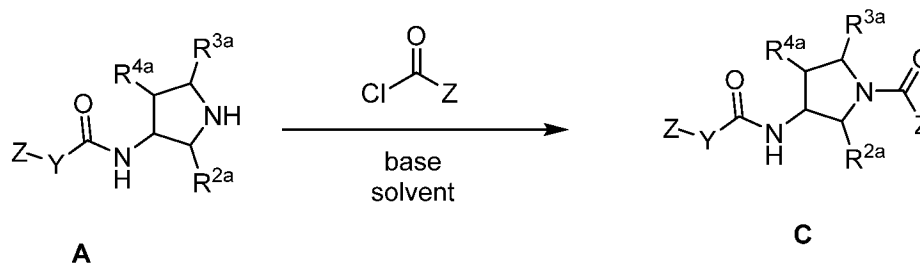
[0170] Compounds of the Disclosure are prepared using methods known to those skilled in the art in view of this disclosure, or by the illustrative methods shown in the General Schemes below. In the General Schemes, R^1 , R^{2a} , R^{3a} , R^{4a} , A, Y, and Z of Formulae **A-D** are as defined in connection with Formula **I**, unless otherwise indicated. In any of the General Schemes, suitable protecting can be employed in the synthesis, for example, when Z is (amino)alkyl or any other group that may require protection. (See, Wuts, P. G. M.; Greene, T. W., "Greene's Protective Groups in Organic Synthesis", 4th Ed., J. Wiley & Sons, NY, 2007).

General Scheme 1



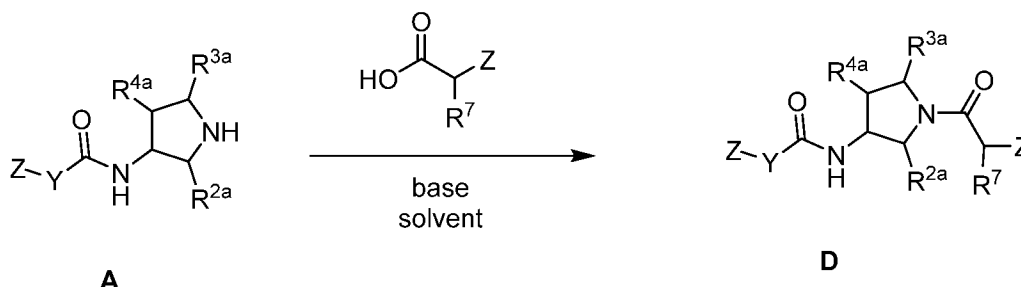
- [0171] Compound A is converted to compound B (i.e., a compound having Formula I, wherein R^{2b} , R^{3b} , R^{4b} , and R^5 are each hydrogen, and X is $-S(=O)_2-$) by coupling with a suitable sulfonyl chloride ($Z-SO_2Cl$) in the presence of a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.

General Scheme 2



- [0172] Compound A is converted to compound C (i.e., a compound having Formula I, wherein R^{2b} , R^{3b} , R^{4b} , and R^5 are each hydrogen, and X is $-C(=O)-$) by coupling with a suitable acid chloride ($Z-COCl$) in the presence of a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF, or by coupling with a suitable carboxylic acid ($Z-CO_2H$) in the presence of a suitable coupling reagent such as HATU and a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.

General Scheme 3



- [0173] Compound A is converted to compound D (i.e., a compound having Formula I, wherein R^{2b} , R^{3b} , R^{4b} , and R^5 are each hydrogen, and X is $-C(=O)C(R^7)(H)-$) by coupling with a suitable carboxylic acid ($Z-C(H)R^7-CO_2H$) in the presence of a suitable coupling reagent such as HATU and a suitable base such as TEA or DIPEA in a suitable solvent such as dichloromethane, acetonitrile, or DMF.

EXAMPLES

General Synthetic Methods

[0174] General methods and experimental procedures for preparing and characterizing Compounds of the Disclosure are set forth in the general schemes above and the examples below. Wherever needed, reactions were heated using conventional hotplate apparatus or heating mantle or microwave irradiation equipment. Reactions were conducted with or without stirring, under atmospheric or elevated pressure in either open or closed vessels. Reaction progress was monitored using conventional techniques such as TLC, HPLC, UPLC, or LCMS using instrumentation and methods described below. Reactions were quenched and crude compounds isolated using conventional methods as described in the specific examples provided. Solvent removal was carried out with or without heating, under atmospheric or reduced pressure, using either a rotary or centrifugal evaporator.

[0175] Compound purification was carried out as needed using a variety of traditional methods including, but not limited to, preparative chromatography under acidic, neutral, or basic conditions using either normal phase or reverse phase HPLC or flash columns or Prep-TLC plates. Compound purity and mass confirmations were conducted using standard HPLC and / or UPLC and / or MS spectrometers and / or LCMS and / or GC equipment (*i.e.*, including, but not limited to the following instrumentation: Waters Alliance 2695 with 2996 PDA detector connected with ZQ detector and ESI source; Shimadzu LDMS-2020; Waters Acquity H Class with PDA detector connected with SQ detector and ESI source; Agilent 1100 Series with PDA detector; Waters Alliance 2695 with 2998 PDA detector; AB SCIEX API 2000 with ESI source; Agilent 7890 GC). Exemplified compounds were dissolved in either MeOH or MeCN to a concentration of approximately 1 mg/mL and analyzed by injection of 0.5-10 μ L into an appropriate LCMS system.

[0176] Compound structure confirmations were carried out using standard 300 or 400 MHz NMR spectrometers with nOe's conducted whenever necessary.

[0177] The following abbreviations may be used herein:

Abbreviation	Meaning
ACN	acetonitrile
atm.	atmosphere
DCM	dichloromethane

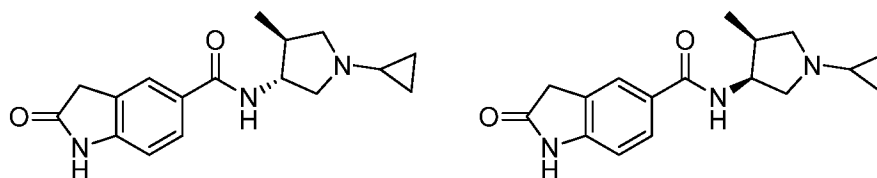
DHP	dihydropyran
DIBAL	diisobutyl aluminum hydride
DIEA	diisopropyl ethylamine
DMF	dimethyl formamide
DMF-DMA	dimethyl formamide dimethyl acetal
DMSO	dimethyl sulfoxide
Dppf	1,1'-bis(diphenylphosphino)ferrocene
EA	ethyl acetate
ESI	electrospray ionization
EtOH	Ethanol
FA	formic acid
GC	gas chromatography
H	hour
Hex	hexanes
HMDS	hexamethyl disilazide
HPLC	high performance liquid chromatography
IPA	Isopropanol
LCMS	liquid chromatography / mass spectrometry
MeOH	Methanol
Min	Minutes
NBS	<i>N</i> -bromo succinimide
NCS	<i>N</i> -chloro succinimide
NIS	<i>N</i> -iodo succinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Prep.	Preparative
PTSA	<i>para</i> -toluene sulfonic acid
R _f	retardation factor
rt	room temperature
RT	retention time
sat.	Saturated
SGC	silica gel chromatography
TBAF	tetrabutyl ammonium fluoride
TEA	Triethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
UPLC	ultra performance liquid chromatography

EXAMPLE 1

Synthesis of (±)-*trans*-N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-oxoindoline-5-carboxamide (Cpd. No. 5)

and

(±)-*cis*-N-(1-cyclopropyl-4-methylpyrrolidin-3-yl)-2-oxoindoline-5-carboxamide (Cpd. No. 6)



[0178] To a solution of 2-oxoindoline-5-carboxylic acid (200 mg, 1.12 mmol) in DMF (3 mL) was added HATU (644 mg, 1.69 mmol) and the reaction mixture was stirred for 30 min at room temperature. After being cooled to 0 °C 1-cyclopropyl-4-methylpyrrolidin-3-amine (174 mg, 1.24 mmol) and DIPEA (0.29 mL, 1.69 mmol) were added successively to the reaction mixture. The reaction was further stirred at room temperature for 2 hrs. Completion of the reaction was confirmed by TLC. After completion, water (30 mL) was added to reaction mixture and product was extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed with brine, and dried over sodium sulfate and concentrated under vacuum to get crude product which was purified by column chromatography. The desire compound started eluting at 4% methanol in DCM. Evaporation of the fractions afforded 70 mg of pure racemic compound as a mixture of *cis* : *trans* isomer. The *cis* and *trans* isomers were separated out using reverse-phase prep. HPLC using 0.1% TFA in ACN and 0.1% TFA in water as mobile phase. Lyophilization of pure fractions afforded the pure title compounds. The yields of the isomers were (18 mg (5.33%) and 23 mg (6.81%). The NMR spectra and LCMS of the isomers were: ¹H NMR (400 MHz, MeOD): δ 7.77-7.75 (m, 2H), 6.97-6.95 (m, 1H), 4.15 (dd, *J* = 6 Hz, 1H), 3.60-3.58 (m, 1H), 3.51 (m, 1H), 3.33-3.32 (q, 1H), 3.18 (dd, *J* = 6 Hz, 1H), 2.82-2.78 (m, 1H), 2.40-2.36 (t, *J* = 8.4 Hz, 1H), 2.25-2.21 (m, 1H), 1.21-1.20 (m, 3H), 0.53-0.49 (m, 4H). LCMS (*m/z*): 300.25 [*M*+H]⁺. ¹H NMR (400 MHz, MeOD): δ 7.78-7.76 (m, 2H), 6.98-6.96 (m, 1H), 4.68 (dd, *J*=5.2 Hz, 1H), 3.61-3.59 (m, 1H), 3.24 (dd, *J*=5.2 Hz, 1H), 3.12 (dd, *J*=7.6 Hz, 1H), 2.72 (dd, *J*=6.4 Hz, 1H), 2.59-2.55 (m, 1H), 2.45 (t, *J*=

9.2 Hz, 1H), 1.86-1.84 (m, 1H), 0.97-0.95 (m, 3H), 0.54-0.48 (m, 4H). LCMS (m/z): 300.25 [M+H]⁺.

EXAMPLE 2

SMYD3 Biochemical Assay

General Materials

[0179] S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), Tris, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well opaque white OptiPlates and SPA beads (Perkin Elmer, catalog # RPNQ0013) were purchased from PerkinElmer.

Substrates

[0180] N-terminally GST-tagged MEKK2 (MAP3K2) protein corresponding to reference sequence AAF63496.3 was purchased from Life Technologies (catalog # PV4010). This protein was expressed in High Five insect cells and purified to >85 % purity. Protein identity was confirmed by MS/MS analysis after proteolytic digestion. The protein sequence used was:

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MAPILGYWKIKGLVQPTRLLEYLEEKYEEHLYERDEGDKWRNK
KFELGLEFPNLPYYIDGDVKLTQSMAIIRYIADKHNMMLGGCPKERA
EISMLEGAVLDIRYGVSRIAYSKDFETLKVDFLSKLPEMLKMFEDR
LCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCF
KKRIEAI PQIDKYLKSSKYIAWPLQGWQATFGGGDHPPKSDLVPRH
NQTSLYKKAGTMDDQQALNSIMQDLAVLHKASRPALSLQETRKA
KSSSPKKQNDVRVKFEHRGEKRILQFPRPVKLEDLRKAKIAFGQS
MDLHYTNNELVIPLTTQDDLDKALELLDRSIHMKSLKILLVINGST
QATNLEPLPSLEDLDNTVFGAERKKRLSIIGPTSRDRSSPPPGYIPDE
LHQVARNGSFTSINSEGEFIPESMEQMLDPLSLSSPENSGSGSCPSL
DSPLDGESYPKSRMPRAQSYPDNHQEFSDYDNPIFEKFGKGGTYPR
RYHVSYYHHQEYNDGRKTFPRARRTQGNQLTSPVSFSPTDHSLSSTSS

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GSSIFTPEYDDSRIRRRGSDIDNPTLTVMDISPPSRSPRAPTNWRLG
 KLLGQGAFGRVYLCYDVDGTGRELAVKQVQFDPDSPETSKEVNAL
 ECEIQLLKNLLHERIVQYYGCLRDPQEKTLSIFMEYMPGGSIKDQL
 KAYGALTENVTRKYTRQILEGVHYLHSNMIVHRDIKGANILRDST
 GNVKLGDFGASKRLQTICLSGTGMKSVTGTPTYWMSPEVISGQGYG
 RKADIWSVACTVVEMLTEKPPWAEFEAMAAIFKIATQPTNPKLPP
 HVSDYTRDFLKRIFVEAKLRPSADELLRHMFVHYH.

(SEQ ID No. 1).

Molecular Biology

- [0181] Full-length human SMYD3 isoform 1 (BAB86333) was inserted into a modified pET21b plasmid containing a His6 tag and TEV and SUMO cleavage sites. Because two common variants of SMYD3 exist in the population, site directed mutagenesis was subsequently performed to change amino acid 13 from an asparagine to a lysine, resulting in plasmid pEPZ533. A lysine at position 13 conforms to the more commonly occurring sequence (NP_001161212).

Protein Expression

- [0182] *E. coli* (BL21 codonplus RIL strain, Stratagene) were transformed with plasmid pEPZ553 by mixing competent cells and plasmid DNA and incubating on ice for 30 minutes followed by heat shock at 42 °C for 1 minute and cooling on ice for 2 minutes. Transformed cells were grown and selected on LB agar with 100 µg/mL ampicillin and 17 µg/mL chloramphenicol at 37 °C overnight. A single clone was used to inoculate 200 mL of LB medium with 100 µg/mL ampicillin and 17 µg/mL chloramphenicol and incubated at 37 °C on an orbital shaker at 180 rpm. Once in log growth, the culture was diluted 1:100 into 2 L of LB medium and grown until OD₆₀₀ was about 0.3 after which the culture was incubated at 15 °C and 160 rpm. Once OD₆₀₀ reached about 0.4, IPTG was added to a final concentration of 0.1 mM and the cells were grown overnight at 15 °C and 160 rpm. Cells were harvested by centrifugation at 8000 rpm, for 4 minutes at 4 °C and stored at -80 °C for purification.

Protein Purification

- [0183] Expressed full-length human His-tagged SMYD3 protein was purified from cell paste by Nickel affinity chromatography after equilibration of the resin with Buffer A (25

mM Tris, 200 mM NaCl, 5% glycerol, 5 mM β -mercaptoethanol, pH7.8). The column was washed with Buffer B (Buffer A plus 20 mM imidazole) and His-tagged SMYD3 was eluted with Buffer C (Buffer A plus 300 mM imidazole). The His tag, TEV and SUMO cleavage sites were removed generating native SMYD3 by addition of ULP1 protein at a ratio of 1:200 (ULP1:SMYD3). Imidazole was removed by dialysis overnight in Buffer A. The dialyzed solution was applied to a second Nickel column and the native SMYD3 protein was collected from the column flow-through. The flow-through was dialyzed in Buffer D (25 mM Tris, 5% glycerol, 5 mM β -mercaptoethanol, 50 mM NaCl, pH7.8) and ULP1 was removed using a Q sepharose fast flow column. SMYD3 was eluted in Buffer A and further purified using an S200 size-exclusion column equilibrated with Buffer A. SMYD3 was concentrated to 2 mg/mL with a final purity of 89%.

Predicted Translation:

[0184] SMYD3 (Q9H7B4)
 MEPLKVEKFATAKRGNGLRVTPLRPGELLFRSDPLAYTVCKGSR
 GVVCDRCLLGKEKLMRCSQCRVAKYCSAKCQKKAWPDHKRECK
 CLKSCKPRYPDSVRLLGRVVFKLMDGAPSESEKLYSFYDLESNIN
 KLTEDKKEGLRQLVMTFQHFMREEIQDASQLPPAFDLFEAFKVIC
 NSFTICNAEMQEVGVGLYPSISLLNHSCDPNCSIVFNPHLLLRV
 RDIEVGEELTICYLDMLMTSEERRKQLRDQYCFECDCFRCQTQDK
 DADMLTGDEQVWKEVQESLKKIEELKAHWKWEQVLAMCQAISS
 NSERLPDINIYQLKVLDACAMDACINLGLLEEALFYGTRTMEPYRIFF
 PGSHPVVRGVQVMKVGKLQLHQGMFPQAMKNLRLAFDIMRVTHG
 REHSLIEDLILLEECDANIRAS. (SEQ ID No. 2).

General Procedure for SMYD3 Enzyme Assays on MEKK2 protein substrate

[0185] The assays were all performed in a buffer consisting of 25 mM Tris-Cl pH 8.0, 1 mM TCEP, 0.005% BSG, and 0.005% Tween 20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a 384-well white opaque OptiPlate using a Bravo automated liquid handling platform outfitted with a 384-channel head (Agilent Technologies). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of

SMYD3, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the SMYD3 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with SMYD3 for 30 min at room temperature, then a cocktail (10ul) containing SAM and MEKK2 was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: SMYD3 was 0.4 nM, ³H-SAM was 8 nM, MEKK2 was 12 nM, SAH in the minimum signal control wells was 1 mM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radiolabeled SAM (10ul) to a final concentration of 100 uM, which dilutes the ³H-SAM to a level where its incorporation into MEKK2 is no longer detectable. Radiolabeled MEKK2 was detected using a scintillation proximity assay (SPA). 10 uL of a 10 mg/mL solution of SPA beads in 0.5 M citric acid was added and the plates centrifuged at 600 rpm for 1 min to precipitate the radiolabeled MEKK2 onto the SPA beads. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ³H-labeled MEKK2 as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% \text{ inh} = 100 - \left(\frac{\text{dpm}_{\text{compd}} - \text{dpm}_{\text{min}}}{\text{dpm}_{\text{max}} - \text{dpm}_{\text{min}}} \right) \times 100$$

[0186] Where dpm = disintegrations per minute, compd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$Y = \text{Bottom} + \frac{(\text{Top} - \text{Bottom})}{\left(1 + \left(\frac{X}{\text{IC}_{50}}\right)^{\text{Hill Coefficient}}\right)}$$

[0187] Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

EXAMPLE 3

SMYD3 Cell Assay

Trimethyl-MEKK2-In-Cell Western Assay

[0188] 293T/17 adherent cells were purchased from ATCC (American Type Culture Collection), Manassas, VA, USA. MEM/Glutamax medium, Optimem Reduced Serum medium, penicillin-streptomycin, 0.05% trypsin and 1x D-PBS were purchased from Life Technologies, Grand Island, NY, USA. PBS-10X was purchased from Ambion, Life Technologies, Grand Island, New York, USA. PBS with Tween 20 (PBST (10x)) was purchased from KPL, Gaithersburg, Maryland, USA. Tet System FBS- approved FBS US Source was purchased from Clontech, Mountain View, California, USA. Odyssey blocking buffer, 800CW goat anti-rabbit IgG (H+L) antibody, 680CW Goat anti-mouse IgG (H+L) and Licor Odyssey infrared scanner were purchased from Licor Biosciences, Lincoln, NE, USA. Tri-methyl-Lysine [A260]-MEKK2 antibody, MEKK2 and SMYD3 plasmids were made at Epizyme. Anti-flag monoclonal mouse antibody was purchased from Sigma, St. Louis, MO, USA. Methanol was purchased from VWR, Franklin, MA, USA. 10% Tween 20 was purchased from KPL, Inc., Gaithersburg, Maryland, USA. Fugene was purchased from Promega, Madison, WI, USA. The Biotek ELx405 was purchased from BioTek, Winooski, Vermont, USA. The multidrop combi was purchased from Thermo Scientific, Waltham, Massachusetts, USA.

[0189] 293T/17 adherent cells were maintained in growth medium (MEM/Glutamax medium supplemented with 10% v/v Tet System FBS and cultured at 37 °C under 5% CO₂.

Cell treatment, In Cell Western (ICW) for detection of trimethyl-lysine-MEKK2 and MEKK2.

[0190] 293T/17 cells were seeded in assay medium at a concentration of 33,333 cells per cm² in 30 mL medium per T150 flask and incubated at 37 °C under 5% CO₂. Plasmids were prepared for delivery to cells by first mixing 1350 µL Opti-MEM with Fugene (81 µL) in a sterile Eppendorf and incubated for five minutes at room temperature (RT). MEKK2-flag (13.6 ug/T150) MEKK2 p3XFlag-CMV-14 with C-3XFlag and SMYD3 (0.151 ug/T150) SMYD3 p3XFlag-CMV-14 without C-3XFlag plasmids were aliquotted to a 1.7 mL sterile microfuge tube. The gene ID for MEKK2 and SMYD3 is

NM_006609.3 and Q9H7B4, respectively. Entire volume of Opti-MEM/Fugene mixture was then added to a microfuge tube containing DNA plasmid, mixed and then incubated x 15 minutes at RT. The medium on the 293T/17 cells was refreshed, and the DNA/Fugene complex is added aseptically to each flask, rocked gently, and incubated at 37 °C for 5 hours. Medium was then removed, and cells were washed once with PBS in the flask. Trypsin 0.05% (3mL) was added and cells incubated for three minutes. Room temperature MEM+10% Tet system FBS was added and cells were mixed gently, and counted using the Vi-cell. Cells were seeded at 100,000 cells/mL in 50 µL MEM/10%Tet FBS/Pen/Strep to a 384 well black/clear poly-D-lysine coated plate containing test agent diluted in DMSO. The final top concentration of test compound was 40 µM. The total concentration of DMSO did not exceed 0.2% (v/v). Plates were incubated x 30 minutes at RT in low-airflow area, followed by incubation at 37 °C under 5% CO₂ for 24 hours. Medium was aspirated from all wells of assay plates prior to fixation and permeabilization with ice cold (-20 °C) methanol (90 µL/well) for ten minutes. Plates were rinsed with PBS three times on BioTek ELx405. PBS was removed with a final aspiration, and Odyssey blocking buffer (50 µL/well) was added to each well and incubated for one hour at RT. Primary antibody solution was prepared (anti-trimethyl-MEKK2 at 1:600 dilution plus mouse anti-flag antibody at 1:10,000 dilution in diluent (Odyssey Blocking buffer + 0.1% Tween 20)) and 20 µL per well was dispensed using the Multidrop Combi. Assay plates were then sealed with foil, and incubated overnight at 4° C. Plates were washed five times with PBS-Tween (1X) on Biotek ELx405 and blotted on paper towel to remove excess reagent. Detection antibody solution (IRDye 800 CW goat anti-rabbit IgG diluted 1:400 in diluent (Odyssey Blocking buffer + 0.1% Tween 20), plus IRDye 680CW goat anti-mouse IgG at 1:500 in diluent (Odyssey Blocking buffer + 0.1% Tween 20) was added (20 µL/well) and incubated in dark for one hour at RT. Plates were then washed four times with PBS-T (1X) on ELx405. A final rinse with water was performed (115 µL/well x three washes on the ELx405). Plates were then centrifuged upside down, on paper towel, at 200 x g to remove excess reagent. Plates were left to dry in dark for one hour. The Odyssey Imager was used to measure the integrated intensity of 700 and 800 wavelengths at resolution of 84 µm, medium quality, focus offset 4.0, 700 channel intensity = 3.5 to measure the MEKK2-flag signal, 800 channel intensity = 5 to measure the Trimethyl-MEKK2 signal of each well.

Calculations:

[0191] First, the ratio for each well was determined by:

$$\left(\frac{\text{Trimethyl MEKK2 800nm value}}{\text{Flag tagged MEKK2 700nm value}} \right)$$

[0192] Each plate included fourteen control wells of DMSO only treatment (Minimum Inhibition) as well as fourteen control wells for maximum inhibition (Background). The average of the ratio values for each control type was calculated and used to determine the percent inhibition for each test well in the plate. Reference compound was serially diluted two-fold in DMSO for a total of nine test concentrations, beginning at 40 μ M. Percent inhibition was calculated (below).

$$\text{Percent Inhibition} = 100 - \left(\frac{(\text{Individual Test Sample Ratio}) - (\text{Background Avg Ratio})}{(\text{Minimum Inhibition Ratio}) - (\text{Background Average Ratio})} \right) * 100$$

[0193] Non-linear regression curves were generated to calculate the IC₅₀ and dose-response relationship using triplicate wells per concentration of compound.

EXAMPLE 4 SMYD2 ASSAY

General Materials

[0194] S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

Substrates

[0195] Peptide was synthesized with a N-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was high high-performance liquid chromatography (HPLC) purified to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was ARTKQTARKSTGGKAPRKQLATKAARKSA(K-Biot)-amide. (SEQ ID NO: 3)

Production of Recombinant SMYD2 Enzymes for Biochemical Enzyme Activity Assays

[0196] Full length SMYD2 (NP_064582.2) was cloned into a pFastbac-Htb-lic vector with an N-terminal His6 tag and *FLAG tag*, preceded by a *TEV protease cleavage site*. The protein was expressed in Sf9 insect cells. Cells were resuspended in lysis buffer (25 mM HEPES-NaOH, pH 7.5, 200 mM NaCl, 5% glycerol, and 5 mM β -ME) and lysed by sonication. The protein was purified by Ni-NTA (Qiagen), followed by TEV cleavage to remove the His6 tag, subtractive Ni-NTA (Qiagen), and gel filtration chromatography using an S200 column (GE Healthcare). Purified protein was stored in 20 mM Tris-HCl, pH 8.0, 100 mM NaCl, and 1 mM TCEP.

General Procedure for SMYD2 Enzyme Assays on Peptide Substrates

[0197] The assays were all performed in a buffer consisting of 20mM Bicine (pH=7.6), 1mM TCEP, 0.005% Bovine Skin Gelatin, and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a polypropylene 384-well V-bottom plates (Greiner) using a Platemate Plus outfitted with a 384-channel head (Thermo Scientific). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of SMYD2, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the SMYD2 enzyme was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with SMYD2 for 30 min at room temperature, then a cocktail (10ul) containing ^3H -SAM and peptide was added to initiate the reaction (final volume = 51ul). The final concentrations of the components were as follows: SMYD2 was 1.5nM, ^3H -SAM was 10nM, and peptide was 60nM, SAH in the minimum signal control wells was 1000uM, and the DMSO concentration was 2%. The assays were stopped by the addition of non-radioactive SAM (10ul) to a final concentration of 600uM, which dilutes the ^3H -SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50ul of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1 hour before being washed three times with 0.1%Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ^3H -labeled peptide bound

to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% inh = 100 - \left(\frac{dpm_{compd} - dpm_{min}}{dpm_{max} - dpm_{min}} \right) \times 100$$

[0198] Where dpm = disintegrations per minute, compd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$\% inhibition = Bottom + \frac{Top - Bottom}{(1 + (IC_{50}/[I])^{Hill\ slope/Hill\ slope})}$$

[0199] Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. *I* is the compound concentration.

[0200] SMYD2 biochemical assay data for representative Compounds of the Disclosure are presented in Tables 1, 3, and 4 in the column titled "SMYD2 Biochem IC₅₀ (μM)."

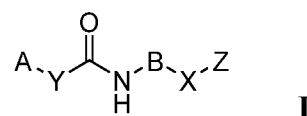
[0201] Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof.

[0202] Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

[0203] All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What is Claimed Is:

1. A compound having Formula I:



or a pharmaceutically acceptable salt or hydrate thereof,

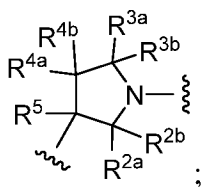
wherein:

A is selected from the group consisting of 1,2,3-triazolyl, 1,2,4-triazolyl, 1-imidazolyl, 1-isoquinolyl, 1-pyrazolyl, 2-(1,2,3,4-tetrahydroquinolyl), 2-benzo[d]imidazolyl, 2-benzo[d]thiazolyl, 2-chromenyl-4-one, 2-furanyl, 2-imidazo[1,2-b]pyridazinyl, 2-imidazolyl, 2-indolyl, 2-naphthalenyl, 2-pyrazinyl, 2-pyridyl, 2-pyrimidinyl, 2-pyrrolidinyl, 2-pyrrolyl, 2-quinolyl, 2-quinoxalyl, 2-thiazolo[5,4-c]pyridinyl, 2-thiazolyl, 2-thiophenyl, 3-(1,2,3,4-tetrahydroisoquinoline), 3-(1,2,4-oxadiazolyl), 3-imidazo[1,2-a]pyrimidinyl, 3-indazolyl, 3-indolyl, 3-isothiazolyl, 3-pyrazolyl, 3-pyridazinyl, 3-pyridinyl-2-one, 3-pyridyl, 3-pyrrolo[3,2-b]pyridinyl, 3-quinolyl, 4-(2,2-difluorobenzo[d][1,3]dioxolyl), 4-cyclohexanyl-1-amine, 4-imidazolyl, 4-indolyl-2-one, 4-indolyl, 4-isothiazolyl, 4-oxazolyl, 4-piperidinyl, 4-pyrazolyl, 4-pyridyl, 4-quinolyl, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-b]pyridinyl-2-one), 5-(1,3-dihydro-2H-pyrrolo[2,3-c]pyridinyl-2-one), 5-(2,2-difluorobenzo[d][1,3]dioxolyl), 5-(2,4-dihydro-3H-1,2,4-triazolyl-3-one), 5-4H-furo[3,2-b]pyrrolyl, 5-benzo[c][1,2,5]oxadiazolyl, 5-benzo[d][1,3]dioxolyl, 5-benzo[d]oxazolyl-2(3H)-one, 5-bicyclo[2.2.1]heptyl-2-ene, 5-indolyl-2,3-dione, 5-indolyl-2-one, 5-indolyl, 5-isoindolyl-1-one, 5-isoxazolyl, 5-pyrazolo[3,4-c]pyridinyl, 5-pyrazolyl, 5-pyrimidinyl, 5-thiazolyl, 6-(1,2,3,4-tetrahydronaphthalenyl), 6-(3,4-dihydroquinolyl-2(1H)-one), 6-(3,4-dihydroquinoxalyl-2(1H)-one), 6-(4,5-dihydropyridazinyl-3(2H)-one), 6-benzo[b][1,4]oxazinyl-3-one, 6-benzo[d]imidazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 6-benzo[d]thiazolyl, 6-chromenyl-2-one, 6-imidazo[2,1-b]thiazole, 6-indazolyl, 6-indolyl-2-one, 6-indolyl, 6-isoquinolyl, 6-quinolyl,

6-quinoxaliny, 6-quinoxaliny-2(1H)-one, 7-(3,4-dihydroquinoliny-2(1H)-one), 7-(3,4-dihydroquinoxalin-2(1H)-one), 7-benzo[b][1,4]oxaziny-3-one, 7-indoliny-2-one, 7-quinoliny, 8-benzo[b][1,4]oxaziny-3-one, cyclopropanyl, phenyl, 4-(prop-1-en-1-yl)-imidazole, 1-butanyl-imidazole, sec-butylcyclopropane, 2-(ethylsulfonyl)propanyl, 1-isobutylpyrrolidine, 4-pyridyl 1-oxide, and 5-benzo[c][1,2,5]oxadiazolyl 1-oxide, each of which is optionally substituted with one, two, or three substituents independently selected from the group consisting of halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (carboxamido)alkyl, (cycloalkyl)alkyl, optionally substituted C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 5- to 14-membered heteroaryl, optionally substituted 4- to 14-membered heterocyclo, and aralkyl;

Y is -C(R^{1a})(R^{1b})-; or Y is absent;

B is:



X is selected from the group consisting of -S(=O)₂-, -S(=O)₂N(R⁶)-, -S(=O)₂C(R⁷)(H)-, -C(=O)-, -C(=O)N(R⁶)-, -C(=O)O-, and -C(=O)C(R⁷)(H)-; or X is absent;

Z is selected from the group consisting of hydrogen, optionally substituted C₁₋₆ alkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, (amino)(hydroxy)alkyl, (amino)(aryl)alkyl, (hydroxy)(aryl)alkyl, (aralkylamino)alkyl, alkoxyalkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and heteroaralkyl;

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

R^{2a} , R^{2b} , R^{3a} , R^{3b} , R^{4a} , and R^{4b} are each independently selected from the group consisting of hydrogen, amino, alkylamino, dialkylamino, cycloalkylamino, halo, hydroxy, C_{1-6} alkyl, alkoxy, haloalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, alkoxyalkyl, aralkyl, alkoxycarbonyl, sulfonamido, carboxamido, $-N(H)C(=O)R^{8a}$; and $-CH_2N(H)C(=O)R^{8b}$; or

R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a carbonyl; and R^{3a} , R^{3b} , R^{4a} , and R^{4b} are each independently selected from the group consisting of hydrogen, hydroxy, C_{1-6} alkyl, alkoxy, hydroxyalkyl, C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, alkoxyalkyl, aralkyl, $-N(H)C(=O)R^{8a}$; and $-CH_2N(H)C(=O)R^{8b}$; or

R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a carbonyl; and R^{2a} , R^{2b} , R^{4a} , and R^{4b} are each independently selected from the group consisting of hydrogen, hydroxy, C_{1-6} alkyl, alkoxy, hydroxyalkyl, C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, alkoxyalkyl, $-N(H)C(=O)R^{8a}$; and $-CH_2N(H)C(=O)R^{8b}$; or

R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a carbonyl; and R^{2a} , R^{2b} , R^{3a} , and R^{3b} are each independently selected from the group consisting of hydrogen, hydroxy, C_{1-6} alkyl, alkoxy, hydroxyalkyl, C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, alkoxyalkyl, $-N(H)C(=O)R^{8a}$; and $-CH_2N(H)C(=O)R^{8b}$; or

R^{2a} and R^{2b} taken together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl or C_{3-6} heterocyclo; and R^{3a} , R^{3b} , R^{4a} , and R^{4b} are each independently selected from the group consisting of hydrogen, hydroxy, C_{1-6} alkyl, alkoxy,

hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, aralkyl, -N(H)C(=O)R^{8a}; and -CH₂N(H)C(=O)R^{8b}; or

R^{3a} and R^{3b} taken together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl or C₃₋₆ heterocyclo; and R^{2a}, R^{2b}, R^{4a}, and R^{4b} are each independently selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, alkoxy, hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, -N(H)C(=O)R^{8a}; and -CH₂N(H)C(=O)R^{8b}; or

R^{4a} and R^{4b} taken together with the carbon atom to which they are attached form a C₃₋₆ cycloalkyl or C₃₋₆ heterocyclo; and R^{2a}, R^{2b}, R^{3a}, and R^{3b} are each independently selected from the group consisting of hydrogen, hydroxy, C₁₋₆ alkyl, alkoxy, hydroxyalkyl, C₃₋₁₂ cycloalkyl, optionally substituted C₆₋₁₄ aryl, alkoxyalkyl, -N(H)C(=O)R^{8a}; and -CH₂N(H)C(=O)R^{8b};

R⁵ is selected from the group consisting of hydrogen and C₁₋₄ alkyl;

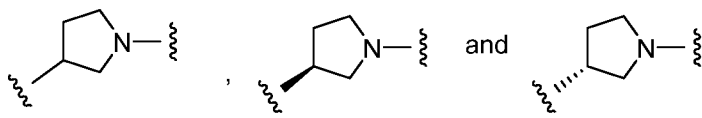
R⁶ is selected from the group consisting of hydrogen and C₁₋₄ alkyl;

R⁷ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, amino, alkylamino, dialkylamino, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, and hydroxyalkyl;

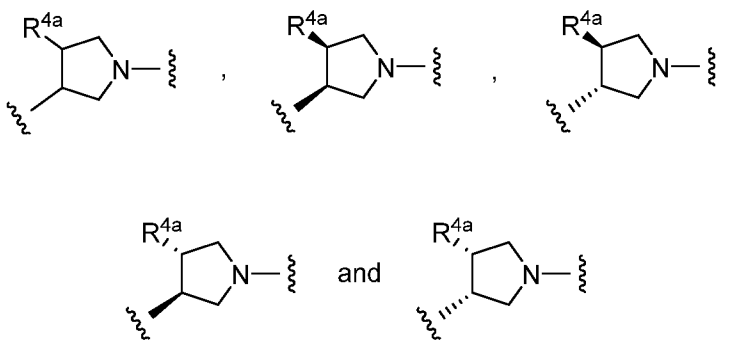
R^{8a} is selected from the group consisting of C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and heteroaralkyl; and

R^{8b} is selected from the group consisting of C₁₋₆ alkyl, haloalkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and heteroaralkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



3. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, wherein B is selected from the group consisting of:



R^{4a} is selected from the group consisting of hydroxy, C_{1-6} alkyl, alkoxy, hydroxyalkyl, C_{3-12} cycloalkyl, optionally substituted C_{6-14} aryl, alkoxyalkyl, and aralkyl.

4. The compound of claim 3, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{4a} is C_{1-4} alkyl.

5. The compound of claim 4, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{4a} is methyl.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or solvate thereof, wherein X is selected from the group consisting of $-S(=O)_2-$ and $-C(=O)-$; or X is absent.

7. The compound of claim 6, or a pharmaceutically acceptable salt or solvate thereof, wherein X is $-S(=O)_2-$.

8. The compound of claim 6, or a pharmaceutically acceptable salt or solvate thereof, wherein X is $-C(=O)-$.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein X is absent.
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is selected from the group consisting of optionally substituted C₁₋₆ alkyl, hydroxyalkyl, (amino)alkyl, (alkylamino)alkyl, (dialkylamino)alkyl, (cycloalkylamino)alkyl, (heterocyclo)alkyl, optionally substituted C₆₋₁₄ aryl, optionally substituted 4- to 14-membered heterocyclo, optionally substituted 5- to 14-membered heteroaryl, optionally substituted C₃₋₁₂ cycloalkyl, aralkyl, and heteroaralkyl.
11. The compound of claim 10, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is selected from the group consisting of C₁₋₆ alkyl and optionally substituted C₃₋₁₂ cycloalkyl.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -CH₂-.
13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is absent.
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt or solvate thereof, wherein A is selected from the group consisting of 5-indolinyl-2-one, 6-benzo[b][1,4]oxazinyl-3-one, 5-pyrazolyl, 3-isothiazolyl, 6-benzo[d]oxazolyl-2(3H)-one, 1,2,3-triazolyl, phenyl, 5-(1,3-dihydro-2H-benzo[d]imidazolyl-2-one), 3-pyridazinyl, 1,2,3-triazolyl, 3-isothiazolyl, 2-imidazolyl, 2-pyridyl, 1,3,4-thiadiazole, and 1,3,4-oxadiazole.
15. The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein A is 5-indolinyl-2-one.

16. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from any one or more of the compounds provided in Tables 1, 3, and 4 of the specification.

17. A pharmaceutical composition comprising the compound of any one of claims 1-16, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

18. A method of treating a patient comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-16, or a pharmaceutically acceptable salt or hydrate thereof, wherein the patient has cancer.

19. The method of claim 18, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer,

ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocyoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preprimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial

carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

20. The pharmaceutical composition of claim 17 for use in treating cancer.

21. The pharmaceutical composition of claim 20, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell

lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preprimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

22. A compound of any one of claims 1-16, or a pharmaceutically acceptable salt or hydrate thereof, for use in treatment of cancer.

23. The compound of claim 22, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer,

MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocyoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preprimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

24. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt or hydrate thereof, for the manufacture of a medicament for treatment of cancer.

25. The use of claim 24, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute

promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor,

multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

26. A kit comprising the compound of any one of claims 1-16, or a pharmaceutically acceptable salt or hydrate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or hydrate thereof, to a patient having cancer.

27. The kit of claim 26, wherein the cancer is selected from the group consisting of adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentigious melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part

sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer, brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hairy cell leukemia, hemangioblastoma, head and neck cancer, hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, lethal midline carcinoma, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocyoma, optic nerve sheath meningioma, optic nerve tumor, oral

cancer, osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine cancer, squamous carcinoma, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor, and Wilms' tumor.

28. A method of treating a SMYD protein mediated disorder comprising administering to a subject in need thereof a compound of any one of claims 1-16, or a pharmaceutically acceptable salt or hydrate thereof in an effective amount to treat the SMYD protein mediated disorder.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/49225

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 55/02 (2015.01)

CPC - A61K 31/555; A61K 31/28; A61K 33/24

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)

IPC(8): A01N 55/02 (2015.01)

CPC: A61K 31/555; A61K 31/28; A61K 33/24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/186Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; Keyword limited: Isoxazole carboxamide, pyrrolidine, substituted pyrrolidine, pyrrolidine compounds, SMYD proteins, SMYD blockade/inhibition, SMYD blockade/inhibition and response, SMYD3/SMYD2, cancer, treating cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	PubChem-CID-62379165 Create Date: 22 October 2012 (22.10.2012), pg 3, Fig, pg 4, Fig.	1-2,6 ----- 3-5,7-8,16
Y	PubChem-CID-72928190 Create Date: 28 February 2014 (28.02.2014), pg 3, Fig, pg 4, Fig.	3-5,7-8
Y	US 2006/0252811 A1 (KIM et al.) 09 November 2006 (09.11.2006), entire document, especially: para [0013]; para [0341]; pg 55, col 1, box.	16

☐

Further documents are listed in the continuation of Box C.

☐

* 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

20 November 2015 (20.11.2015)

Date of mailing of the international search report

07 JAN 2016

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/49225

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 9-15, 17-28
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 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.