

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 April 2009 (16.04.2009)

PCT

(10) International Publication Number
WO 2009/049018 A1

(51) International Patent Classification:
A61K 31/33 (2006.01) **C07D 213/00** (2006.01)

(21) International Application Number:
PCT/US2008/079298

(22) International Filing Date: 9 October 2008 (09.10.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/978,955 10 October 2007 (10.10.2007) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(54) Title: NOVEL COMPOUNDS AND METHODS OF USING THEM

(57) Abstract: The present invention relates to novel compounds and their pharmaceutically acceptable salts, prodrugs, solvates, polymorphs, tautomers and isomers. In some embodiments, the compounds described herein may be used to modulate sirtuins (SIRT). The present invention also relates to methods for modulating sirtuins. The present invention also relates to methods useful in the treatment of diseases.

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NOVEL COMPOUNDS AND METHODS OF USING THEM

CROSS-REFERENCE

- [0001] This application claims the benefit of U.S. Provisional Application No. 60/978,955, filed October 10, 2007, which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

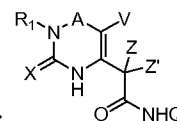
- 5 [0002] Sirtuins are members of the Silent Information Regulator (SIR) family of genes. They are found in both prokaryotes and eukaryotes. The yeast Sir2 protein belongs to a family of histone deacetylases. The Sir2 protein is a deacetylase which can use NAD as a cofactor. Unlike other deacetylases, many of which are involved in gene silencing, Sir2 is relatively insensitive to histone deacetylase inhibitors like trichostatin A (TSA). Mammalian Sir2 homologs, such as SIRT1, have NAD-dependent deacetylase activity, which is involved in gene expression and gene silencing.
- 10 [0003] Exemplary mammalian sirtuins include SIRT1, SIRT2, and SIRT3. A compound described herein may inhibit one or more activities of a mammalian sirtuin. For example, the compound may inhibit deacetylase activity, e.g., with respect to a natural or artificial substrate (e.g. histones, p53, FoxO transcription, deacetylate histones, deacetylate lysines, tubulin, cytochrome c, etc.). Histone deacetylation alters local chromatin structure and consequently can regulate the transcription of a gene in that vicinity. Many of the SIRT1 binding partners are transcription factors, e.g., proteins that recognize specific DNA sites. For example, SIRT1 deacetylates and down regulates forkhead proteins (i.e., FoxO proteins). Interaction between SIRT1 and SIRT1 binding partners can deliver SIRT1 to specific regions of a genome and can result in a local manifestation of substrates, e.g., histones and transcription factors localized to the specific region.
- 15 20 [0004] The present invention relates to novel compounds and compositions containing these compounds. In some embodiments, these compounds of the present invention affect sirtuin activity. Due to its role in the transcriptional mechanism to affect gene expression, compounds affecting sirtuin are useful as a therapeutic or ameliorating agent for diseases involving cellular growth such as malignant tumors, autoimmune diseases, skin diseases, infections, other anti-proliferative therapies, cancer, etc. They are also useful as therapeutic or prophylactic agent for diseases caused by abnormal gene expression such as inflammatory disorders, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, protozoal infections, etc. They also have therapeutic effects in autoimmune diseases (e.g. HIV, AIDS), ocular diseases, neurodegenerative diseases (e.g. Alzheimer), and blood coagulation disorders. They also effects metabolism and be useful as therapeutic agents for treatment of diabetes, diabetic complications, and general obesity control. Compounds affecting sirtuin also have anti-aging effects and can extend cellular life in both prokaryotes and eukaryotes.
- 25 30

SUMMARY OF THE INVENTION

- 35 [0005] The present invention relates to novel compounds and their pharmaceutically acceptable salts, prodrugs, solvates, polymorphs, tautomers and isomers. In some embodiments, the compounds described herein may be used to modulate sirtuins (SIRT). The present invention also relates to compositions comprising novel compounds and their pharmaceutically acceptable salts, prodrugs, solvates,

polymorphs, tautomers and isomers. The present invention also relates to methods for modulating sirtuins. The methods described herein may be used for modulating SIRT1, SIRT2 and/or SIRT3, or homologs thereof. The present invention also relates to methods useful in the treatment of diseases. The compounds and compositions described herein may be useful in the treatment of diseases.

- [0006]** The compounds described herein may be useful in the treatment of diseases such as cancer and other hyperproliferative diseases. The compounds described herein may also be useful in increasing the lifespan of a cell, and treating and/or preventing a wide variety of diseases and disorders including, for example, diseases or disorders related to aging or stress (including increasing radiosensitivity and/or chemosensitivity), diabetes, obesity (including stimulation of appetite or weight gain), neurodegenerative diseases, cardiovascular disease, blood clotting disorders, stroke, ischemia, inflammation, flushing, infections including viral infections (e.g. herpes, HIV, adenovirus, and HTLV-1 associated malignant and benign disorders), autoimmune disorders (e.g., systemic lupus erythematosus, scleroderma, and arthritis, in which autoimmune cells should be removed), fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, tumors, leukemias, neoplasms, carcinomas, metabolic diseases, malignant diseases, stimulation of appetite, and/or stimulation of weight gain.
- [0007]** Compounds of Formula I-XXI, pharmaceutically acceptable salts, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, may modulate the activity of sirtuin enzymes; and, as such, are useful for treating diseases or conditions in which aberrant sirtuin enzyme activity contributes to the pathology and/or symptoms of a disease or condition.

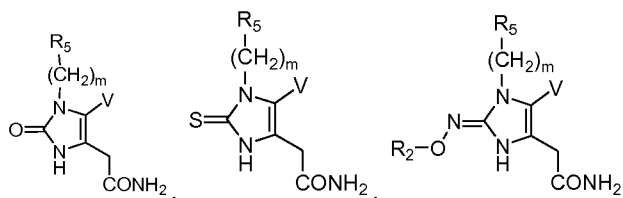


[0008] Provided herein are compounds and pharmaceutically acceptable salts of Formula I:

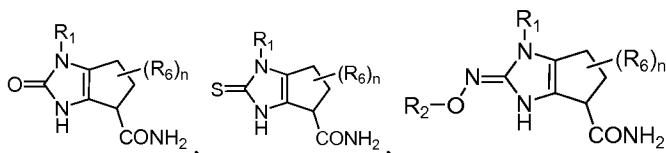
[0009] Provided herein are compounds and pharmaceutically acceptable salts of Formulas IIA-IIC:



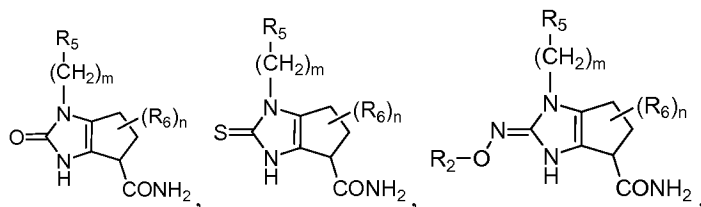
[0010] Provided herein are compounds and pharmaceutically acceptable salts of Formulas IIIA-IIIIC:



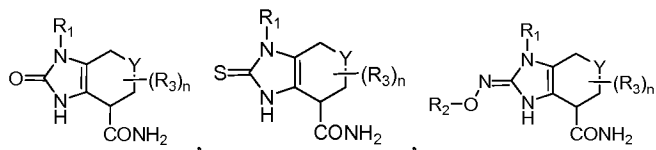
[0011] Provided herein are compounds and pharmaceutically acceptable salts of Formulas IVA-IVC:



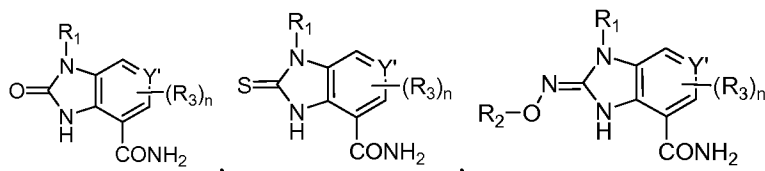
[0012] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VA-VC:



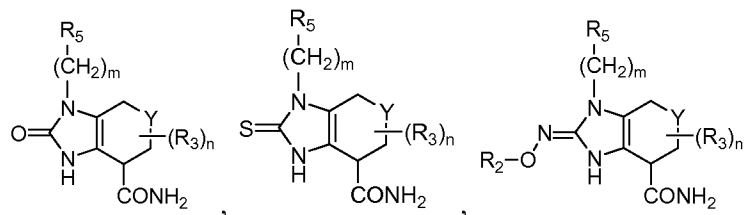
[0013] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIA-VIC:



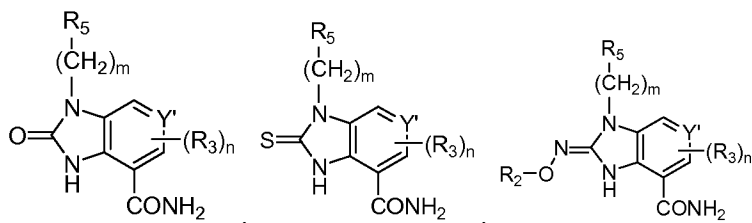
[0014] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIA'-VIC':



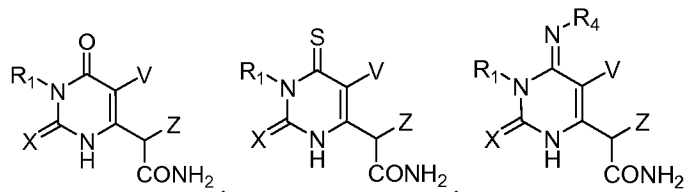
[0015] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIA-VIIC:



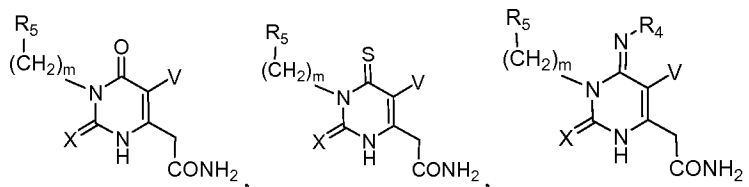
[0016] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIA'-VIIC':



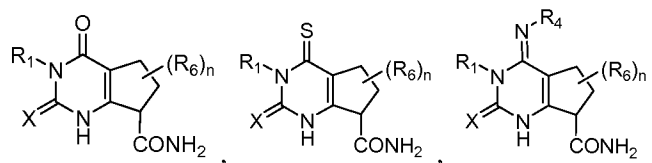
[0017] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIIA-VIIIC:



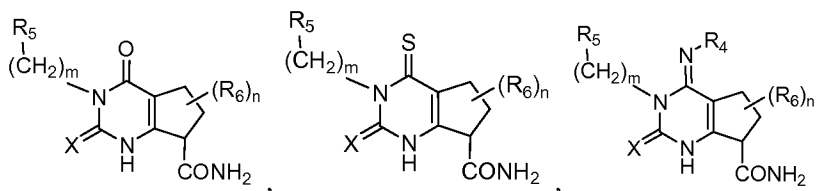
[0018] Provided herein are compounds and pharmaceutically acceptable salts of Formulas IXA-IXC:



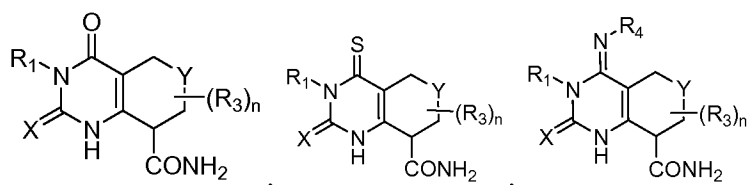
[0019] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XA-XC:



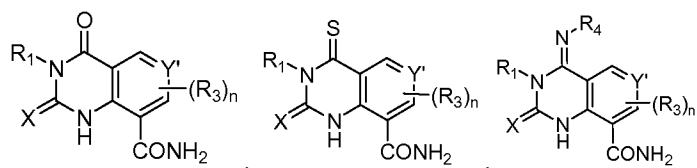
[0020] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XIA-XIC:



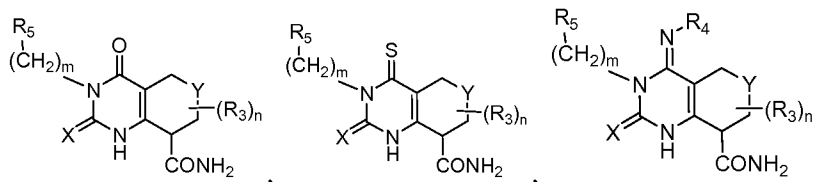
5 [0021] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIA-VIIC:



[0022] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIA'-VIIC':

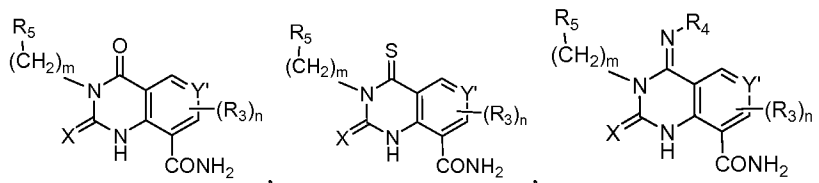


[0023] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIIA-VIIIC:

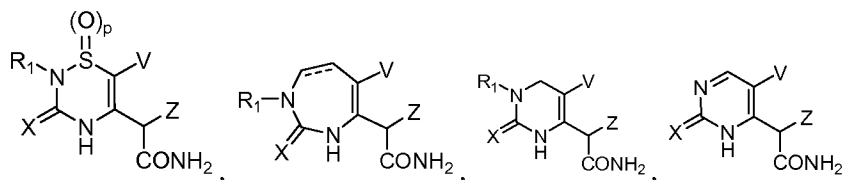


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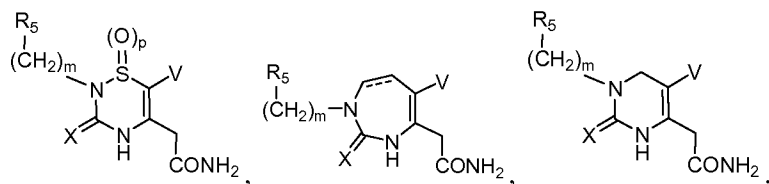
[0024] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIIA'-VIIIC':



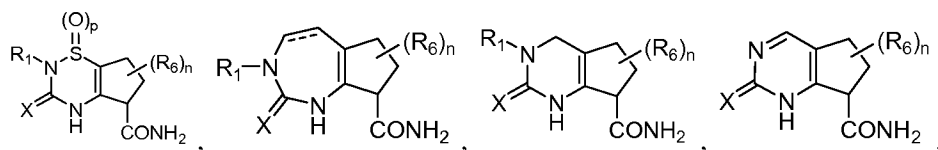
[0025] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XIVA-XIVD:



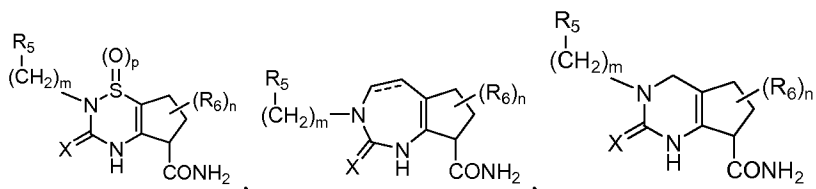
15 [0026] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVA-XVC:



[0027] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVIIA-XVID:

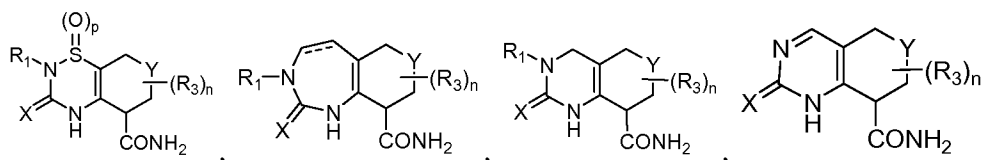


[0028] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVIIA-XVIIC:

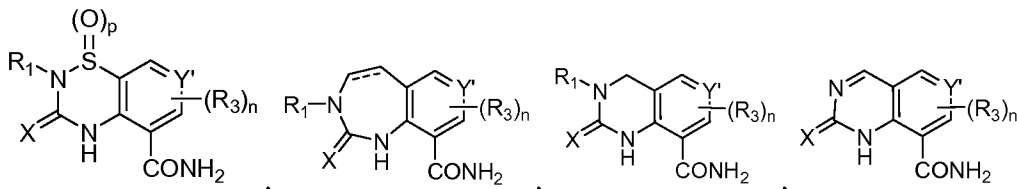


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[0029] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVIIIA-XVIID:

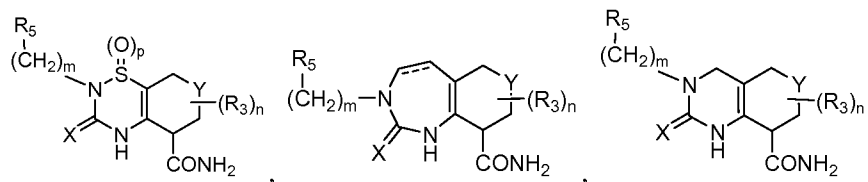


[0030] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVIIIA'-XVIID':

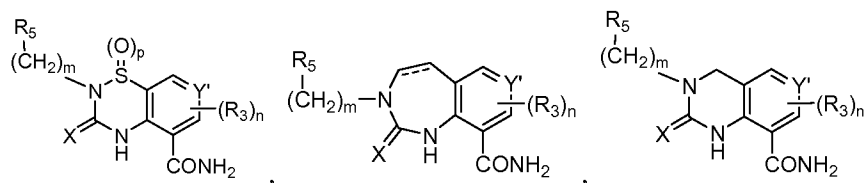


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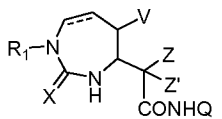
[0031] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XIXA-XIXC:



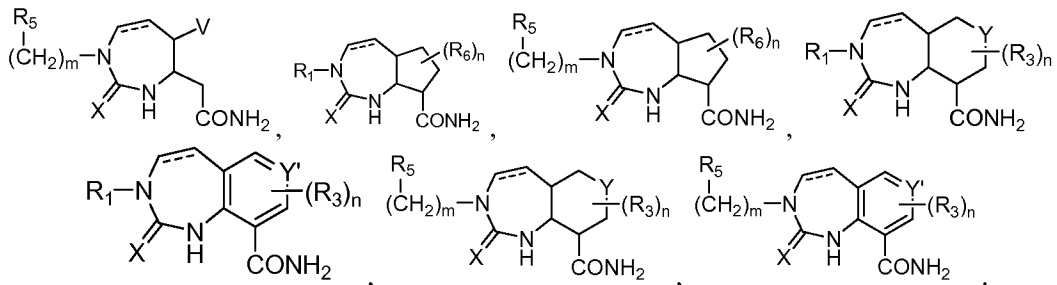
[0032] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XIXA'-XIXC':



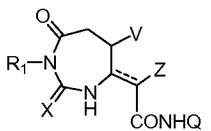
[0033] Provided herein are compounds and pharmaceutically acceptable salts of Formula XX:



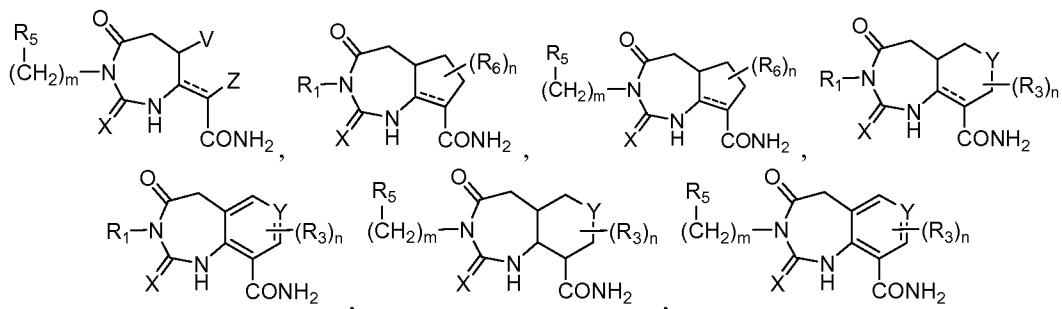
[0034] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XXA-XXG:



[0035] Provided herein are compounds and pharmaceutically acceptable salts of Formula XXI:

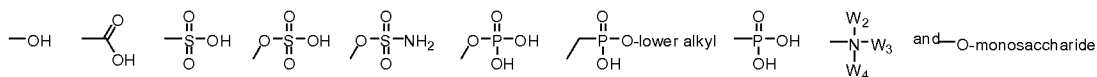


[0036] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XXIA-XXIG:



[0037] In some embodiments, R₁ is hydrogen, halogen, -CN, -L-OH, -L-NH₂, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂. In some embodiments, R₁ is hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-C₁-C₄ alkyl, L-C₂-C₅ alkenyl, L-C₂-C₅ alkynyl, -L-C₃-C₇ cycloalkyl, L-C₃-C₇ cycloalkenyl, -L-C₃-C₇ heterocycloalkyl, -L-C₁-C₄ haloalkyl, -L-C₁-C₄ alkoxy, -L-C₁-C₄ alkylamine, -L-(C₁-C₄)₂dialkylamine, -L-C₅-C₇ aryl and -L-C₅-C₇ heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing

group is: , wherein W is selected from:



, wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom. In some embodiments, R₁ is hydrogen, halogen, -CN, -OH, -NH₂, or a substituted or

unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, R₁ is hydrogen, halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine. In some embodiments, R₁ is hydrogen, -CN, -OH, -NH₂, or a substituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine, wherein the substituted group is substituted with a substituent selected from halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.

[0038] In some embodiments, A is a bond, C=O, C=S, S=O, S(O)₂, C=N-R₄, CR_aR_a, CR_aR_a-CR_aR_a, CR_a=CR_a, or A taken together with the nitrogen to which it is attached is -N=CH- and R₁ is not present, wherein R₄ is hydrogen or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, mercaptoalkyl, haloalkyl and carboxyalkyl; wherein each R_a is independently hydrogen or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, mercaptoalkyl, haloalkyl and carboxyalkyl; and wherein n is 1 or 2. In some embodiments, A is CR_aR_a. In some embodiments, A is CR_aR_a-CR_aR_a. In some embodiments, A is CR_a=CR_a. In some embodiments, A is a bond. In some embodiments, A is C=O. In some embodiments, A is C=S. In some embodiments, A is S=O. In some embodiments, A is S(O)₂. In some embodiments, A taken together with the nitrogen to which it is attached is -N=CH- and R₁ is not present. In some embodiments, A is C=N-R₄. In some embodiments, A is CR_aR_a, CR_aR_a-CR_aR_a or CR_a=CR_a.

[0039] In some embodiments, R₄ is hydrogen or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, R₄ is C₁-C₄ alkyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ aminoalkyl, C₁-C₄ alkylamino, C₁-C₄ alkylthio, C₁-C₄ perfluoroalkyl, C₁-C₄ perfluoroalkoxy, C₁-C₄ alkoxycarbonyl, aryl or heteroaryl. In some embodiments, R₄ is an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.

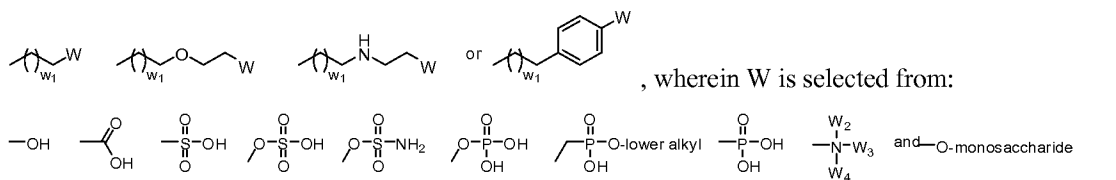
[0040] In some embodiments, each R_a is independently hydrogen or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, each R_a is independently hydrogen, C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, each R_a is independently hydrogen or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine. In some embodiments, R_a is hydrogen.

[0041] In some embodiments, X is O, S or N-O-R², wherein R² is hydrogen or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, mercaptoalkyl, haloalkyl, and carboxyalkyl. In some embodiments, X is O. In some embodiments, X is S. In some embodiments, X is N-O-R².

[0042] In some embodiments, R² is hydrogen or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, R² is C₁-C₄ alkyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ aminoalkyl, C₁-C₄ alkylamino, C₁-C₄ alkylthio, C₁-C₄ perfluoroalkyl, C₁-C₄ perfluoroalkoxy, C₁-C₄ alkoxycarbonyl, aryl or heteroaryl. In some embodiments, R² is an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.

[0043] In some embodiments, V, Z and Z' are each independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O)-, or -S(O)₂-, or when taken together V and Z form a saturated or unsaturated, substituted or unsubstituted 5-7 member ring which incorporates 0, 1 or 2 heteroatoms selected from O, S and N. In some embodiments, Z' is hydrogen.

[0044] In some embodiments, V and Z are each independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-C₁-C₄ alkyl, L-C₂-C₅ alkenyl, L-C₂-C₅ alkynyl, -L-C₃-C₇ cycloalkyl, L-C₃-C₇ cycloalkenyl, -L-C₃-C₇ heterocycloalkyl, -L-C₁-C₄ haloalkyl, -L-C₁-C₄ alkoxy, -L-C₁-C₄ alkylamine, -L-(C₁-C₄)₂dialkylamine, -L-C₅-C₇ aryl and -L-C₅-C₇ heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom. In some embodiments, V and Z are each independently hydrogen or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, Z' is hydrogen and V and Z are each independently hydrogen or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.

[0045] In some embodiments, Z' is hydrogen. In some embodiments, Z' is other than hydrogen.

[0046] In some embodiments, V and Z form a saturated unsubstituted 5-7 member ring. In some embodiments, the saturated unsubstituted 5-7 member ring is a cycloalkyl group. In some embodiments, the saturated unsubstituted 5-7 member ring is a heterocycloalkyl group.

[0047] In some embodiments, V and Z form a partially unsaturated unsubstituted 5-7 member ring. In some embodiments, the partially unsaturated unsubstituted 5-7 member ring is a cycloalkenyl group. In some embodiments, the partially unsaturated unsubstituted 5-7 member ring is a heterocycloalkenyl group.

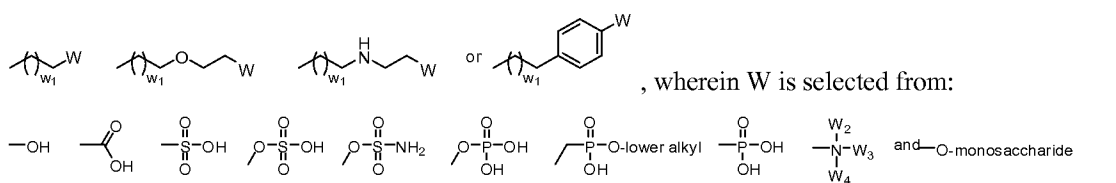
[0048] In some embodiments, V and Z form an unsaturated, unsubstituted 5-7 member ring. In some embodiments, the unsaturated, unsubstituted 5-7 member ring is a heteroaryl group. In some embodiments, the unsaturated, unsubstituted 5-7 member ring is an aryl group.

[0049] In some embodiments, V and Z form a saturated, substituted 5-7 member ring. In some embodiments, the saturated, substituted 5-7 member ring is a cycloalkyl group. In some embodiments, the saturated, substituted 5-7 member ring is a heterocycloalkyl group.

[0050] In some embodiments, V and Z form a partially unsaturated, substituted 5-7 member ring. In some embodiments, the partially unsaturated, substituted 5-7 member ring is a cycloalkenyl group. In some embodiments, the partially unsaturated, substituted 5-7 member ring is a heterocycloalkenyl group.

[0051] In some embodiments, V and Z form an unsaturated, substituted 5-7 member ring. In some embodiments, the unsaturated, substituted 5-7 member ring is a heteroaryl group. In some embodiments, the unsaturated, substituted 5-7 member ring is an aryl group.

[0052] In various embodiments, the ring formed by V and Z is substituted with 1-3 substituents selected from halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-C₁-C₄ alkyl, L-C₂-C₅ alkenyl, L-C₂-C₅ alkynyl, -L-C₃-C₇ cycloalkyl, L-C₃-C₇ cycloalkenyl, -L-C₃-C₇ heterocycloalkyl, -L-C₁-C₄ haloalkyl, -L-C₁-C₄ alkoxy, -L-C₁-C₄ alkylamine, -L-(C₁-C₄)₂dialkylamine, -L-C₅-C₇ aryl and -L-C₅-C₇ heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom. In some embodiments, the ring is substituted with 1-3 substituents selected from halogen, -CN, -OH, -NH₂, or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, the ring is substituted with 1-3 substituents selected from halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine. In some embodiments, the ring is substituted with 1-3 substituents selected from halogen, -CN, -OH, -NH₂, or a substituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-

C₄)₂dialkylamine, wherein the substituted group is substituted with a substituent selected from halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.

[0053] In some embodiments, Z and Z' are different and the carbon atom to which they are attached is in the S configuration. In some embodiments, Z and Z' are different and the carbon atom to which they are attached is in the R configuration.

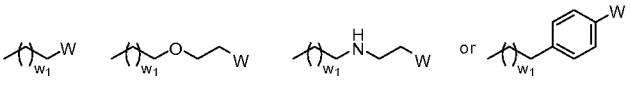
[0054] In some embodiments, V and Z taken together form a saturated or unsaturated, substituted or unsubstituted 5-7 member ring which incorporates 0, 1 or 2 heteroatoms selected from O, S and N; and the carbon atom to Z' is attached is in the S configuration.

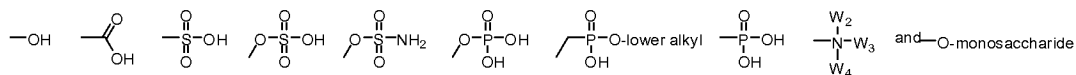
[0055] In some embodiments, V and Z taken together form a saturated or unsaturated, substituted or unsubstituted 5-7 member ring which incorporates 0, 1 or 2 heteroatoms selected from O, S and N; and the carbon atom to Z' is attached is in the R configuration.

[0056] In some embodiments, Q is hydrogen or hydroxyl. In some embodiments, Q is hydrogen. In some embodiments, Q is hydroxyl.

[0057] In some embodiments, R₅ is hydrogen, halogen, -CN, -OH, or -NH₂. In some embodiments, R₅ is H, F, Cl, Br, I, -CN, -OH, or -NH₂.

[0058] In some embodiments, each R₆ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the

water solubilizing group is:  wherein W is selected from:



wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom. In some embodiments, R₆ is hydrogen, halogen, -CN, -OH, -NH₂, or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, R₆ is hydrogen, halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine. In some embodiments, R₆ is hydrogen, -CN, -OH, -NH₂, or a substituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine, wherein the substituted group is substituted with a substituent selected from halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.

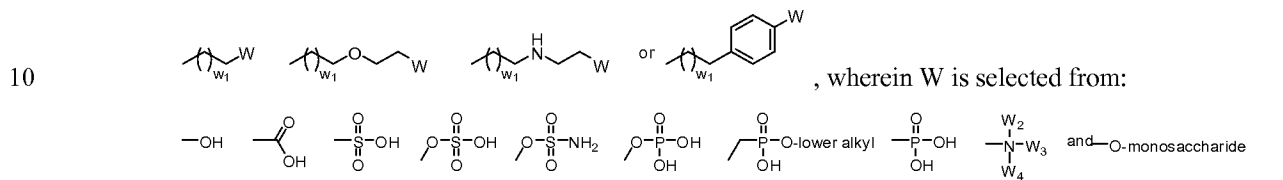
[0059] In some embodiments, m is 1, 2, 3, 4 or 5.

[0060] In some embodiments, n is 0, 1 or 2.

[0061] In some embodiments, p is 1 or 2.

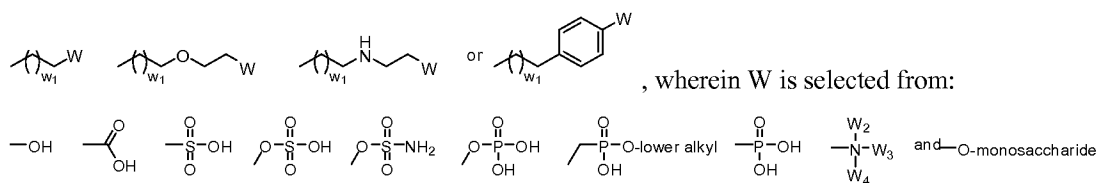
[0062] In some embodiments, ---- represents CH₂-CH₂ or CH=CH. In some embodiments, ---- is CH₂-CH₂. In some embodiments, ---- is CH=CH.

5 [0063] In some embodiments, Y is O, S, NR₃ or CR₃R₃; wherein each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom.

15 [0064] In some embodiments, Y' is N or CR₃; wherein R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom. In some embodiment, Y' is N.

25 [0065] In some embodiments, R₃ is hydrogen, halogen, -CN, -OH, -NH₂, or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl. In some embodiments, R₃ is hydrogen, halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine. In some embodiments, R₃ is hydrogen, -CN, -OH, -NH₂, or a substituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine, wherein the substituted group is substituted with a substituent selected from halogen, -CN, -OH, -NH₂, or an unsubstituted group

selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.

[0066] In some embodiments, when A is a bond and V is OH, then R₁ is not amidoalkyl or carboxyalkyl.

[0067] In some embodiments, X is O and A is C=O or a bond. In some embodiments, X is S and A is C=S or a bond. In some embodiments, X is N-O-R² and A is a bond.

[0068] In some embodiments, Z' is hydrogen, Q is hydrogen and X is O or S.

[0069] In a preferred embodiment, the invention provides for compounds of Formulas I-XXI and their pharmaceutically acceptable salts. In further or additional embodiments, the invention provides for compounds of Formulas I-XXI and their pharmaceutically acceptable solvates. In further or additional embodiments, the invention provides for compounds of Formulas I-XXI and their pharmaceutically acceptable polymorphs. In further or additional embodiments, the invention provides for compounds of Formulas I-XXI and their pharmaceutically acceptable esters. In further or additional embodiments, the invention provides for compounds of Formulas I-XXI and their pharmaceutically acceptable tautomers. In further or additional embodiments, the invention provides for compounds of Formulas I-XXI and their pharmaceutically acceptable prodrugs.

[0070] Provided herein are pharmaceutical compositions comprising a compound of Formula I-XXI or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof. In various embodiments, the pharmaceutical composition comprises at least one pharmaceutically acceptable carrier.

[0071] Provided herein are methods for treating a patient suffering from a sirtuin mediated disorder, comprising administering to said individual an effective amount of a composition comprising a compound of Formula I-XXI or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof. In some embodiments, the compound of Formulas I-XXI is administered in combination with an additional cancer therapy. In some embodiments, the additional cancer therapy is selected from surgery, radiation therapy, and administration of at least one chemotherapeutic agent. In various embodiments, the administration of the compound of Formulas I-XXI occurs after surgery. In other embodiments, the administration of the compound of Formulas I-XXI occurs before surgery. In some embodiments, the sirtuin mediated disorder is selected from the group consisting of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorder, neurological disorders, fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases and malignant diseases. In some embodiments, the sirtuin mediated disorder is cancer, tumors, leukemias, neoplasms, or carcinomas, including but not limited to brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, leukemia, myeloid leukemia, glioblastoma, follicular lymphoma, pre-B acute leukemia, chronic lymphocytic B-leukemia, mesothelioma or small cell line cancer. In yet other embodiments, the sirtuin mediated disorder is a proliferative disease selected from psoriasis, restenosis, autoimmune disease, or atherosclerosis. In some embodiments, the sirtuin mediated disorder is selected from the group consisting of diseases or disorders related to aging or stress (including increasing radiosensitivity and/or chemosensitivity), diabetes, obesity (including stimulation of appetite or weight gain), neurodegenerative diseases, cardiovascular disease, blood clotting disorders, stroke, ischemia,

inflammation, flushing, infections including viral infections (e.g. herpes, HIV, adenovirus, and HTLV-1 associated malignant and benign disorders), autoimmune disorders (e.g., systemic lupus erythematosus, scleroderma, and arthritis, in which autoimmune cells should be removed), fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, tumors, leukemias, neoplasms, carcinomas, metabolic diseases, malignant diseases, stimulation of appetite, and/or stimulation of weight gain.

[0072] Provided herein are methods for degrading, inhibiting the growth of or killing cancer cells comprising contacting the cells with an amount of a composition effective to degrade, inhibit the growth of or kill cancer cells, the composition comprising a compound of Formulas I-XXI or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof. In some embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, leukemia, myeloid leukemia, glioblastoma, follicular lymphoma, pre-B acute leukemia, chronic lymphocytic B-leukemia, mesothelioma or small cell line cancer. In some embodiments, the cancer cells comprise brain, breast, lung, ovarian, pancreatic, prostate, renal, or colorectal cancer cells.

[0073] Provided herein are methods of inhibiting tumor size increase, reducing the size of a tumor, reducing tumor proliferation or preventing tumor proliferation in an individual comprising administering to said individual an effective amount of a composition to inhibit tumor size increase, reduce the size of a tumor, reduce tumor proliferation or prevent tumor proliferation, the composition comprising a compound of Formulas I-XXI or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof. In some embodiments, the tumor occurs in the brain, breast, lung, ovaries, pancreas, prostate, kidney, colon or rectum. In some embodiments the compound of Formulas I-XXI is administered in combination with an additional cancer therapy including, but not limited to surgery, radiation therapy, and administration of at least one chemotherapeutic agent. In some embodiments, the composition is administered before surgery. In other embodiments, the composition is administered after surgery.

INCORPORATION BY REFERENCE

[0074] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0075] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[0076] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application

including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby incorporated by reference.

Certain Chemical Terminology

[0077] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. In the event that there is a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet or other appropriate reference source. Reference thereto evidences the availability and public dissemination of such information.

[0078] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the context clearly dictates otherwise. It should also be noted that use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include”, “includes”, and “included” is not limiting.

[0079] Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York.

Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, IR and UV/Vis spectroscopy and pharmacology, within the skill of the art are employed. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

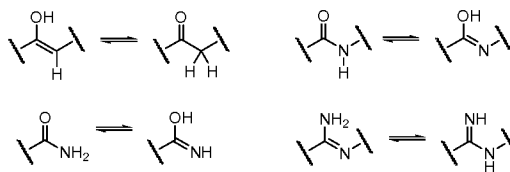
[0080] Where substituent groups are specified by their conventional chemical formulas, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left. As a non-limiting example, -CH₂O- is equivalent to -OCH₂-.

[0081] Unless otherwise noted, the use of general chemical terms, such as though not limited to “alkyl,” “amine,” “aryl,” are equivalent to their optionally substituted forms. For example, “alkyl,” as used herein, includes optionally substituted alkyl.

[0082] The compounds presented herein may possess one or more stereocenters and each center may exist in the R or S configuration, or combinations thereof. Likewise, the compounds presented herein may possess one or more double bonds and each may exist in the E (*trans*) or Z (*cis*) configuration, or

combinations thereof. Presentation of one particular stereoisomer, regioisomer, diastereomer, enantiomer or epimer should be understood to include all possible stereoisomers, regioisomers, diastereomers, enantiomers or epimers and mixtures thereof. Thus, the compounds presented herein include all separate configurational stereoisomeric, regioisomeric, diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. The compounds presented herein include racemic mixtures, in all ratios, of stereoisomeric, regioisomeric, diastereomeric, enantiomeric, and epimeric forms. Techniques for inverting or leaving unchanged a particular stereocenter, and those for resolving mixtures of stereoisomers, or racemic mixtures, are well known in the art and it is well within the ability of one of skill in the art to choose an appropriate method for a particular situation. See, for example, Furniss *et al.* (eds.), VOGEL'S ENCYCLOPEDIA OF PRACTICAL ORGANIC CHEMISTRY 5TH ED., Longman Scientific and Technical Ltd., Essex, 1991, 809-816; and Heller, *Acc. Chem. Res.* 1990, 23, 128.

[0083] The compounds presented herein may exist as tautomers. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Some examples of tautomeric pairs include:



[0084] The terms “moiety”, “chemical moiety”, “group” and “chemical group”, as used herein refer to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0085] The term “bond” or “single bond” refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

[0086] The term “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” means either “alkyl” or “substituted alkyl” as defined below. Further, an optionally substituted group may be un-substituted (e.g., $-\text{CH}_2\text{CH}_3$), fully substituted (e.g., $-\text{CF}_2\text{CF}_3$), mono-substituted (e.g., $-\text{CH}_2\text{CH}_2\text{F}$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, $-\text{CFHCHF}_2$, etc). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*) that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons (except in those instances where macromolecular substituents are clearly intended, e.g., polypeptides, polysaccharides, polyethylene glycols, DNA, RNA and the like).

[0087] As used herein, C₁-C_x includes C₁-C₂, C₁-C₃ . . . C₁-C_x. By way of example only, a group designated as "C₁-C₄" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms, as well as the ranges C₁-C₂ and C₁-C₃. Thus, by way of example only, "C₁-C₄ alkyl" indicates that there are one to four carbon atoms in the alkyl group, i.e., the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; e.g., "1 to 10 carbon atoms" means that the group may have 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, 7 carbon atoms, 8 carbon atoms, 9 carbon atoms, or 10 carbon atoms.

[0088] The term "hydrocarbon" as used herein, alone or in combination, refers to the compound or chemical group containing only carbon and hydrogen atoms.

[0089] The terms "heteroatom" or "hetero" as used herein, alone or in combination, refer to an atom other than carbon or hydrogen. Heteroatoms are may be independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but are not limited to these atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others.

[0090] The term "alkyl" as used herein, alone or in combination, refers to an optionally substituted straight-chain, or optionally substituted branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, *n*-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, isopentyl, neopentyl, *tert*-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as "C₁-C₆ alkyl" or "C₁₋₆ alkyl", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated.

[0091] The term "alkenyl" as used herein, alone or in combination, refers to an optionally substituted straight-chain, or optionally substituted branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH₂), propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "C₂-C₆ alkenyl" or "C₂₋₆ alkenyl", means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated.

[0092] The term "alkynyl" as used herein, alone or in combination, refers to an optionally substituted straight-chain or optionally substituted branched-chain hydrocarbon monoradical having one or more carbon-

carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as "C₂-C₆ alkynyl" or "C₂₋₆ alkynyl", means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated.

[0093] The term "aliphatic" as used herein, alone or in combination, refers to an optionally substituted, straight-chain or branched-chain, non-cyclic, saturated, partially unsaturated, or fully unsaturated nonaromatic hydrocarbon. Thus, the term collectively includes alkyl, alkenyl and alkynyl groups.

[0094] The terms "heteroalkyl", "heteroalkenyl" and "heteroalkynyl" as used herein, alone or in combination, refer to optionally substituted alkyl, alkenyl and alkynyl structures respectively, as described above, in which one or more of the skeletal chain carbon atoms (and any associated hydrogen atoms, as appropriate) are each independently replaced with a heteroatom (i.e. an atom other than carbon, such as though not limited to oxygen, nitrogen, sulfur, silicon, phosphorous, tin or combinations thereof), or heteroatomic group such as though not limited to -O-O-, -S-S-, -O-S-, -S-O-, =N-N=, -N=N-, -N=N-NH-, -P(O)₂-, -O-P(O)₂-, -P(O)₂-O-, -S(O)-, -S(O)₂-, -SnH₂- and the like.

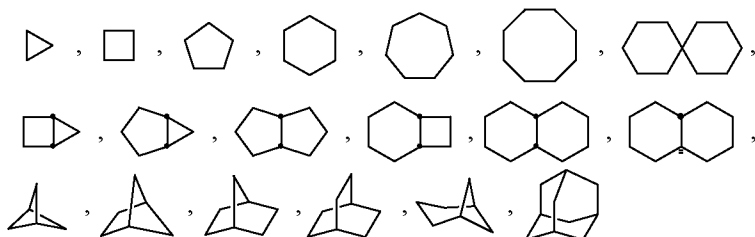
[0095] The terms "haloalkyl", "haloalkenyl" and "haloalkynyl" as used herein, alone or in combination, refer to optionally substituted alkyl, alkenyl and alkynyl groups respectively, as defined above, in which one or more hydrogen atoms is replaced by fluorine, chlorine, bromine or iodine atoms, or combinations thereof. In some embodiments two or more hydrogen atoms may be replaced with halogen atoms that are the same as each other (e.g. difluoromethyl); in other embodiments two or more hydrogen atoms may be replaced with halogen atoms that are not all the same as each other (e.g. 1-chloro-1-fluoro-1-iodoethyl). Non-limiting examples of haloalkyl groups are fluoromethyl and bromoethyl. A non-limiting example of a haloalkenyl group is bromoethenyl. A non-limiting example of a haloalkynyl group is chloroethynyl.

[0096] The terms "cycle", "cyclic", "ring" and "membered ring" as used herein, alone or in combination, refer to any covalently closed structure, including alicyclic, heterocyclic, aromatic, heteroaromatic and polycyclic fused or non-fused ring systems as described herein. Rings can be optionally substituted. Rings can form part of a fused ring system. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, by way of example only, cyclohexane, pyridine, pyran and pyrimidine are six-membered rings and cyclopentane, pyrrole, tetrahydrofuran and thiophene are five-membered rings.

[0097] The term "fused" as used herein, alone or in combination, refers to cyclic structures in which two or more rings share one or more bonds.

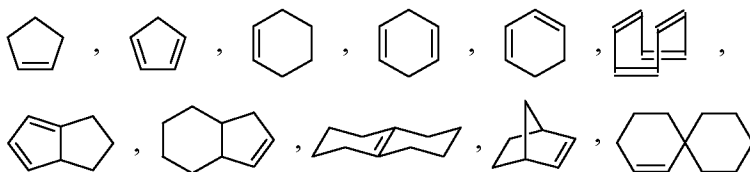
[0098] The term "cycloalkyl" as used herein, alone or in combination, refers to an optionally substituted, saturated, hydrocarbon monoradical ring, containing from three to about fifteen ring carbon atoms or from three to about ten ring carbon atoms, though may include additional, non-ring carbon atoms as substituents (e.g. methylcyclopropyl). Whenever it appears herein, a numerical range such as "C₃-C₆ cycloalkyl" or "C₃₋₆ cycloalkyl", means that the cycloalkyl group may consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, i.e., is cyclopropyl, cyclobutyl, cyclopentyl or

cycloheptyl, although the present definition also covers the occurrence of the term "cycloalkyl" where no numerical range is designated. The term includes fused, non-fused, bridged and spiro radicals. A fused cycloalkyl may contain from two to four fused rings where the ring of attachment is a cycloalkyl ring, and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Examples include, but are not limited to cyclopropyl, cyclopentyl, cyclohexyl, decalyl, and bicyclo [2.2.1] heptyl and adamantyl ring systems. Illustrative examples include, but are not limited to the following moieties:



and the like.

[0099] The term "cycloalkenyl" as used herein, alone or in combination, refers to an optionally substituted hydrocarbon non-aromatic, monoradical ring, having one or more carbon-carbon double-bonds and from three to about twenty ring carbon atoms, three to about twelve ring carbon atoms, or from three to about ten ring carbon atoms. The term includes fused, non-fused, bridged and spiro radicals. A fused cycloalkenyl may contain from two to four fused rings where the ring of attachment is a cycloalkenyl ring, and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Fused ring systems may be fused across a bond that is a carbon-carbon single bond or a carbon-carbon double bond. Examples of cycloalkenyls include, but are not limited to cyclohexenyl, cyclopentadienyl and bicyclo[2.2.1]hept-2-ene ring systems. Illustrative examples include, but are not limited to the following moieties:



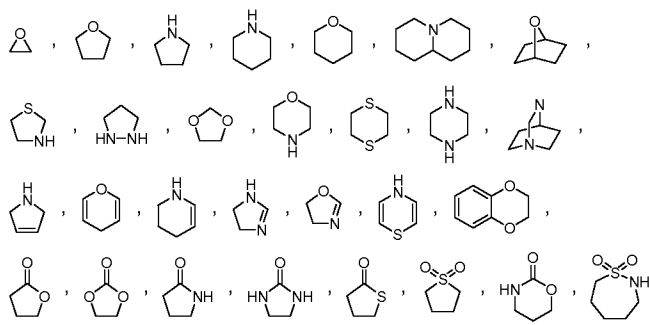
and the like.

[00100] The terms "heterocycloalkyl" as used herein, alone or in combination, refer to optionally substituted, saturated, partially unsaturated, or fully unsaturated nonaromatic ring monoradicals containing from three to about twenty ring atoms, where one or more of the ring atoms are an atom other than carbon, independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but are not limited to these atoms. In embodiments in which two or more heteroatoms are present in the ring, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others. The terms include fused, non-fused, bridged and spiro radicals. A fused non-aromatic heterocyclic radical may contain from two to four fused rings where the attaching ring is a non-aromatic heterocycle, and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Fused ring systems may be fused across a single bond or a double bond, as well as across bonds that are carbon-carbon, carbon-hetero atom or hetero atom-hetero atom. The terms also include radicals having from three to about twelve skeletal ring atoms, as well as those having from three to about ten skeletal ring atoms. Attachment of a

non-aromatic heterocyclic subunit to its parent molecule can be via a heteroatom or a carbon atom.

Likewise, additional substitution can be via a heteroatom or a carbon atom. As a non-limiting example, an imidazolidine non-aromatic heterocycle may be attached to a parent molecule via either of its N atoms (imidazolidin-1-yl or imidazolidin-3-yl) or any of its carbon atoms (imidazolidin-2-yl, imidazolidin-4-yl or imidazolidin-5-yl). In certain embodiments, non-aromatic heterocycles contain one or more carbonyl or thiocarbonyl groups such as, for example, oxo- and thio-containing groups.

Examples include, but are not limited to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



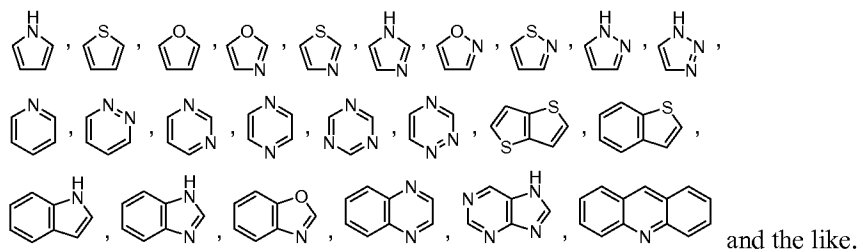
The terms also include all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides.

[00101] The term "aromatic" as used herein, refers to a planar, cyclic or polycyclic, ring moiety having a delocalized π -electron system containing $4n+2$ π electrons, where n is an integer. Aromatic rings can be formed by five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted and can be monocyclic or fused-ring polycyclic. The term aromatic encompasses both all carbon containing rings (*e.g.*, phenyl) and those rings containing one or more heteroatoms (*e.g.*, pyridine).

[00102] The term "aryl" as used herein, alone or in combination, refers to an optionally substituted aromatic hydrocarbon radical of six to about twenty ring carbon atoms, and includes fused and non-fused aryl rings. A fused aryl ring radical contains from two to four fused rings where the ring of attachment is an aryl ring, and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Further, the term aryl includes fused and non-fused rings containing from six to about twelve ring carbon atoms, as well as those containing from six to about ten ring carbon atoms. A non-limiting example of a single ring aryl group includes phenyl; a fused ring aryl group includes naphthyl, phenanthrenyl, anthracenyl, azulenyl; and a non-fused bi-aryl group includes biphenyl.

[00103] The term "heteroaryl" as used herein, alone or in combination, refers to optionally substituted aromatic monoradicals containing from about five to about twenty skeletal ring atoms, where one or more of the ring atoms is a heteroatom independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but not limited to these atoms and with the proviso that the ring of said group

does not contain two adjacent O or S atoms. In embodiments in which two or more heteroatoms are present in the ring, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others. The term heteroaryl includes optionally substituted fused and non-fused heteroaryl radicals having at least one heteroatom. The term heteroaryl also includes fused and non-fused heteroaryls having from five to about twelve skeletal ring atoms, as well as those having from five to about ten skeletal ring atoms. Bonding to a heteroaryl group can be via a carbon atom or a heteroatom. Thus, as a non-limiting example, an imidazole group may be attached to a parent molecule via any of its carbon atoms (imidazol-2-yl, imidazol-4-yl or imidazol-5-yl), or its nitrogen atoms (imidazol-1-yl or imidazol-3-yl). Likewise, a heteroaryl group may be further substituted via any or all of its carbon atoms, and/or any or all of its heteroatoms. A fused heteroaryl radical may contain from two to four fused rings where the ring of attachment is a heteroaromatic ring and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. A non-limiting example of a single ring heteroaryl group includes pyridyl; fused ring heteroaryl groups include benzimidazolyl, quinolinyl, acridinyl; and a non-fused bi-heteroaryl group includes bipyridinyl. Further examples of heteroaryls include, without limitation, furanyl, thienyl, oxazolyl, acridinyl, phenazinyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzothiophenyl, benzoxadiazolyl, benzotriazolyl, imidazolyl, indolyl, isoxazolyl, isoquinolinyl, indolizyl, isothiazolyl, isoindoloxadiazolyl, indazolyl, pyridyl, pyridazyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrazinyl, pyrazolyl, purinyl, phthalazinyl, pteridinyl, quinolinyl, quinazolinyl, quinoxalinyl, triazolyl, tetrazolyl, thiazolyl, triazinyl, thiadiazolyl and the like, and their oxides, such as for example pyridyl-N-oxide. Illustrative examples of heteroaryl groups include the following moieties:



[00104] The terms "halogen", "halo" or "halide" as used herein, alone or in combination refer to fluoro, chloro, bromo and iodo.

[00105] The term "hydroxy" as used herein, alone or in combination, refers to the monoradical -OH.

[00106] The term "cyano" as used herein, alone or in combination, refers to the monoradical -CN.

[00107] The term "nitro" as used herein, alone or in combination, refers to the monoradical -NO₂.

[00108] The term "oxy" as used herein, alone or in combination, refers to the diradical -O-.

[00109] The term "oxo" as used herein, alone or in combination, refers to the diradical =O.

[00110] The term "carbonyl" as used herein, alone or in combination, refers to the diradical -C(=O)-, which may also be written as -C(O)-.

[00111] The terms "carboxy" or "carboxyl" as used herein, alone or in combination, refer to the moiety -C(O)OH, which may also be written as -COOH.

[00112] The term "alkoxy" as used herein, alone or in combination, refers to an alkyl ether radical, -O-alkyl, including the groups -O-aliphatic and -O-carbocyclyl, wherein the alkyl, aliphatic and carbocyclyl groups may be optionally substituted, and wherein the terms alkyl, aliphatic and carbocyclyl are as

defined herein. Non-limiting examples of alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

[00113] The term "sulfinyl" as used herein, alone or in combination, refers to the diradical $-S(=O)-$.

[00114] The term "sulfonyl" as used herein, alone or in combination, refers to the diradical $-S(=O)_2-$.

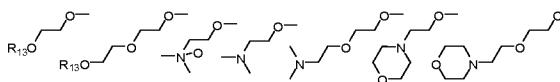
5 [00115] The terms "sulfonamide", "sulfonamido" and "sulfonamidyl" as used herein, alone or in combination, refer to the diradical groups $-S(=O)_2-NH-$ and $-NH-S(=O)_2-$.

[00116] The terms "sulfamide", "sulfamido" and "sulfamidyl" as used herein, alone or in combination, refer to the diradical group $-NH-S(=O)_2-NH-$.

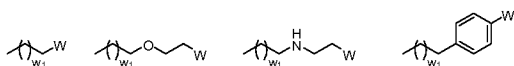
10 [00117] The term "reactant," as used herein, refers to a nucleophile or electrophile used to create covalent linkages.

[00118] The terms "group designed to improve solubility", "solubilizing group" and the like as used herein, alone or in combination, refer to chemical groups and/or substituents that increase the solubility of the compounds described herein compared to the corresponding compound lacking the substituent (i.e. wherein the substituent is hydrogen).

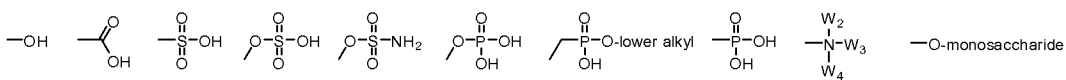
15 [00119] The terms "group designed to improve water solubility", "water solubilizing group" and the like as used herein, alone or in combination, refer to chemical groups and/or substituents that increase the solubility in water of the compounds described herein to the corresponding compound lacking the substituent (i.e. wherein the substituent is hydrogen). Non-limiting examples of water solubilizing groups include substituted or unsubstituted ethyleneoxy or polyethyleneoxy derivatives, such as:



20 , where R_{13} is hydrogen, a sulfate salt, a phosphate salt, an extended PEG moiety and the like. Further non-limiting examples of water solubilizing groups include C_1 - C_6 alkoxy carbonyl (e.g. $-COOMe$), cyano, halo, hydroxy, mercapto, oxo ($=O$), carboxy ($-COOH$), nitro, pyrrolidinyl, piperidinyl, imidazolidinyl, imidazolyl, piperazinyl, morpholinyl, thiomorpholinyl and $-NR_fR_g$, wherein R_f and R_g may be the same or different and are independently chosen from hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, and the corresponding tertiary amine N-oxides. Further non-limiting examples of water solubilizing groups include:



, where W is selected from:



30 where W_1 is 0, 1, 2, or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom.

[00120] It is to be understood that in instances where two or more radicals are used in succession to define a substituent attached to a structure, the first named radical is considered to be terminal and the last named radical is considered to be attached to the structure in question. Thus, for example, the radical arylalkyl is attached to the structure in question by the alkyl group.

Certain Pharmaceutical Terminology

[00121] The terms "SIRT1 protein" and "SIRT1 polypeptide" are used interchangeably herein and refer a polypeptide that is at least 25% identical to the 250 amino acid conserved SIRT1 catalytic domain, amino acid residues 258 to 451 of SEQ ID NO:1. SEQ ID NO:1 depicts the amino acid sequence of human SIRT1. In preferred embodiments, a SIRT1 polypeptide can be at least 30, 40, 50, 60, 70, 80, 85, 90, 95, 99% homologous to SEQ ID NO:1 or to the amino acid sequence between amino acid residues 258 and 451 of SEQ ID NO:1. In other embodiments, the SIRT1 polypeptide can be a fragment, e.g., a fragment of SIRT1 capable of one or more of: deacetylating a substrate in the presence of NAD and/or a NAD analog and capable of binding a target protein, e.g., a transcription factor. Such functions can be evaluated, e.g., by the methods described herein. In other embodiments, the SIRT1 polypeptide can be a "full length" SIRT1 polypeptide.

[00122] The term "full length" as used herein refers to a polypeptide that has at least the length of a naturally-occurring SIRT1 polypeptide (or other protein described herein). A "full length" SIRT1 polypeptide or a fragment thereof can also include other sequences, e.g., a purification tag, or other attached compounds, e.g., an attached fluorophore, or cofactor. The term "SIRT1 polypeptides" can also include sequences or variants that include one or more substitutions, e.g., between one and ten substitutions, with respect to a naturally occurring Sir2 family member.

[00123] The term "SIRT1 activity" refers to one or more activity of SIRT1, e.g., deacetylation of a substrate (e.g., an amino acid, a peptide, or a protein), e.g., transcription factors (e.g., p53) or histone proteins, (e.g., in the presence of a cofactor such as NAD and/or an NAD analog) and binding to a target, e.g., a target protein, e.g., a transcription factor.

[00124] The term "sirtuin modulator" refers to a compound that up regulates (e.g., activate or stimulate), down regulates (e.g., inhibit or suppress) or otherwise changes a functional property or biological activity of a sirtuin protein. Sirtuin modulators may act to modulate a sirtuin protein either directly or indirectly. In certain embodiments, a sirtuin modulator may be a sirtuin activator or a sirtuin inhibitor.

[00125] The term "sirtuin activator" refers to a compound that increases the level of a sirtuin protein and/or increases at least one activity of a sirtuin protein. In an exemplary embodiment, a sirtuin activator may increase at least one biological activity of a sirtuin protein by at least about 10%, 25%, 50%, 75%, 100%, or more. Exemplary biological activities of sirtuin proteins include deacetylation, e.g., of histones and p53; extending lifespan; increasing genomic stability; silencing transcription; and controlling the segregation of oxidized proteins between mother and daughter cells.

[00126] The term "sirtuin inhibitor" refers to a compound that decreases the level of a sirtuin protein and/or decreases at least one activity of a sirtuin protein. In an exemplary embodiment, a sirtuin inhibitor may decrease at least one biological activity of a sirtuin protein by at least about 10%, 25%, 50%, 75%, 100%, or more. Exemplary biological activities of sirtuin proteins include deacetylation, e.g., of histones and p53; extending lifespan; increasing genomic stability; silencing transcription; and controlling the segregation of oxidized proteins between mother and daughter cells.

[00127] The term "subject", "patient" or "individual" as used herein in reference to individuals suffering from a disorder, and the like, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats,

swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

5 **[00128]** The terms "treat," "treating" or "treatment," and other grammatical equivalents as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, 10 or stopping the symptoms of the disease or condition, and are intended to include prophylaxis. The terms further include achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, 15 notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

20 **[00129]** As used herein, the terms "cancer treatment" "cancer therapy" and the like encompasses treatments such as surgery, radiation therapy, administration of chemotherapeutic agents and combinations of any two or all of these methods. Combination treatments may occur sequentially or concurrently. Treatments(s), such as radiation therapy and/or chemotherapy, that is administered prior to surgery, is referred to as neoadjuvant therapy. Treatments(s), such as radiation therapy and/or chemotherapy, administered after surgery is referred to herein as adjuvant therapy.

25 **[00130]** Examples of surgeries that may be used for cancer treatment include, but are not limited to radical prostatectomy, cryotherapy, mastectomy, lumpectomy, transurethral resection of the prostate, and the like.

30 **[00131]** Many chemotherapeutic agents are known and are discussed in greater detail herein. They may operate via a wide variety of modes of action such as, though not limited to, cytotoxic agents, antiproliferatives, targeting agents (such as monoclonal antibodies), and the like. The nature of a combination therapy involving administration of a chemotherapeutic agent will depend upon the type of agent being used.

35 **[00132]** The compounds described herein may be administered in combination with surgery, as an adjuvant, or as a neoadjuvant agent. The compounds described herein may be useful in instances where radiation and chemotherapy are indicated, to enhance the therapeutic benefit of these treatments, including induction chemotherapy, primary (neoadjuvant) chemotherapy, and both adjuvant radiation therapy and adjuvant chemotherapy. Radiation and chemotherapy frequently are indicated as adjuvants to surgery in the treatment of cancer. For example, radiation can be used both pre- and post-surgery as components of the treatment strategy for rectal carcinoma. The compounds described herein may be useful following surgery in the treatment of cancer in combination with radio- and/or chemotherapy.

[00133] Where combination treatments are contemplated, it is not intended that the compounds described herein be limited by the particular nature of the combination. For example, the compounds described herein may be administered in combination as simple mixtures as well as chemical hybrids. An example of the latter is where the compound is covalently linked to a targeting carrier or to an active pharmaceutical.

5 Covalent binding can be accomplished in many ways, such as, though not limited to, the use of a commercially available cross-linking compound.

[00134] As used herein, the terms "pharmaceutical combination", "administering an additional therapy", "administering an additional therapeutic agent" and the like refer to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that at least one of the compounds described herein, and at least one co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that at least one of the compounds described herein, and at least one co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the patient. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients.

[00135] As used herein, the terms "co-administration", "administered in combination with" and their grammatical equivalents or the like are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different times. In some embodiments the compounds described herein will be co-administered with other agents. These terms encompass administration of two or more agents to an animal so that both agents and/or their metabolites are present in the animal at the same time. They include simultaneous administration in separate compositions, administration at different times in separate compositions, and/or administration in a composition in which both agents are present. Thus, in some embodiments, the compounds described herein and the other agent(s) are administered in a single composition. In some embodiments, the compounds described herein and the other agent(s) are admixed in the composition.

[00136] The terms "effective amount", "therapeutically effective amount" or "pharmaceutically effective amount" as used herein, refer to a sufficient amount of at least one agent or compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising the compound as disclosed herein required to provide a clinically significant decrease in a disease. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[00137] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular

or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein, e.g., as discussed in Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa. In preferred
5 embodiments, the compounds and compositions described herein are administered orally.

[00138] The term "acceptable" as used herein, with respect to a formulation, composition or ingredient, means having no persistent detrimental effect on the general health of the subject being treated.

[00139] The term "pharmaceutically acceptable" as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein, and is
10 relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00140] The term "pharmaceutical composition," as used herein, refers to a biologically active compound, optionally mixed with at least one pharmaceutically acceptable chemical component, such as, though
15 not limited to carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

[00141] The term "carrier" as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of the compound into cells or tissues.

[00142] The term "agonist," as used herein, refers to a molecule such as the compound, a drug, an enzyme
20 activator or a hormone modulator which enhances the activity of another molecule or the activity of a receptor site.

[00143] The term "antagonist," as used herein, refers to a molecule such as the compound, a drug, an enzyme inhibitor, or a hormone modulator, which diminishes, or prevents the action of another molecule or the activity of a receptor site.

[00144] The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the
25 target.

[00145] The term "modulator," as used herein, refers to a molecule that interacts with a target either directly or
30 indirectly. The interactions include, but are not limited to, the interactions of an agonist and an antagonist.

[00146] The term "pharmaceutically acceptable derivative or prodrug" as used herein, refers to any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of the compound of Formula I, Formula XX or Formula XXI, which, upon administration to a recipient, is capable of providing,
35 either directly or indirectly, the compound of this invention or a pharmaceutically active metabolite or residue thereof. Particularly favored derivatives or prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e.g., by allowing orally administered compound to be more readily absorbed into blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system).

[00147] The term "pharmaceutically acceptable salt" as used herein, refers to salts that retain the biological effectiveness of the free acids and bases of the specified compound and that are not biologically or otherwise undesirable. Compounds described herein may possess acidic or basic groups and therefore may react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral or organic acid or an inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate undeconate and xylenesulfonate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. (See for example Berge *et al.*, *J. Pharm. Sci.* **1977**, *66*, 1-19.) Further, those compounds described herein which may comprise a free acid group may react with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they may contain. Water or oil-soluble or dispersible products may be obtained by such quaternization. See, for example, Berge *et al.*, *supra*.

[00148] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

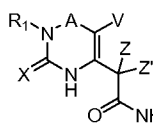
[00149] The term "metabolite," as used herein, refers to a derivative of the compound which is formed when the compound is metabolized.

[00150] The term "active metabolite," as used herein, refers to a biologically active derivative of the compound that is formed when the compound is metabolized.

5 [00151] The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to the compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic
10 alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996).

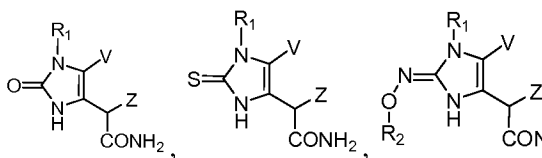
Compounds

[00152] Provided herein are compounds and pharmaceutically acceptable salts of Formula I:



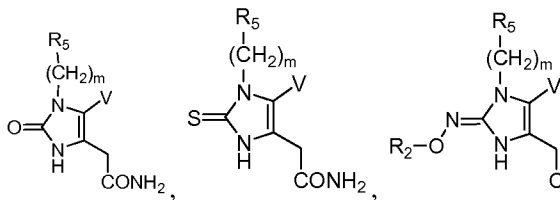
15 $\text{O}=\text{NHQ}$, wherein the substituents are as defined herein.

[00153] Provided herein are compounds and pharmaceutically acceptable salts of Formulas IIA-IIC:



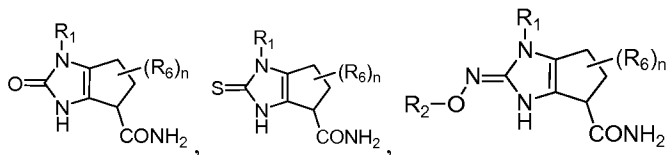
wherein the substituents are as defined herein.

[00154] Provided herein are compounds and pharmaceutically acceptable salts of Formulas IIIA-IIIIC:



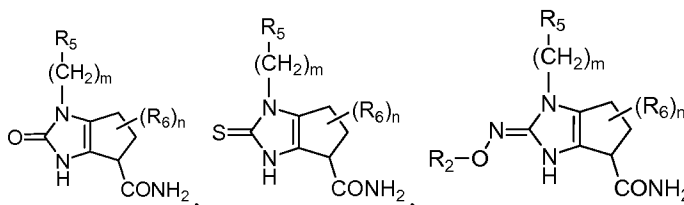
wherein the substituents are as defined herein.

20 [00155] Provided herein are compounds and pharmaceutically acceptable salts of Formulas IVA-IVC:



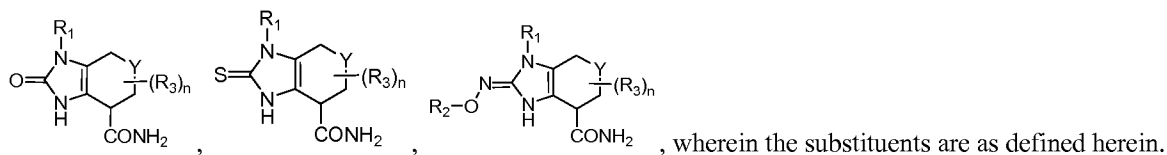
wherein the substituents are as defined herein.

[00156] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VA-VC:

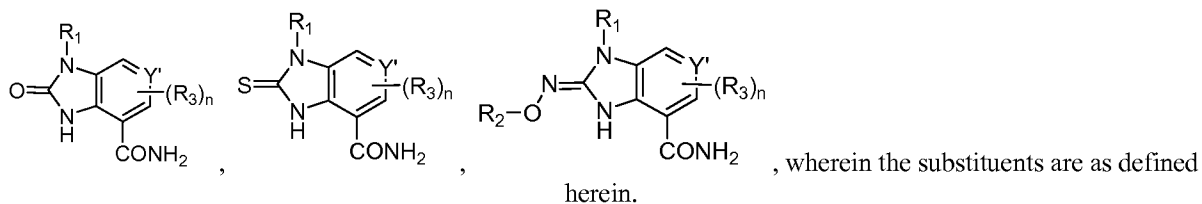


wherein the substituents are as defined herein.

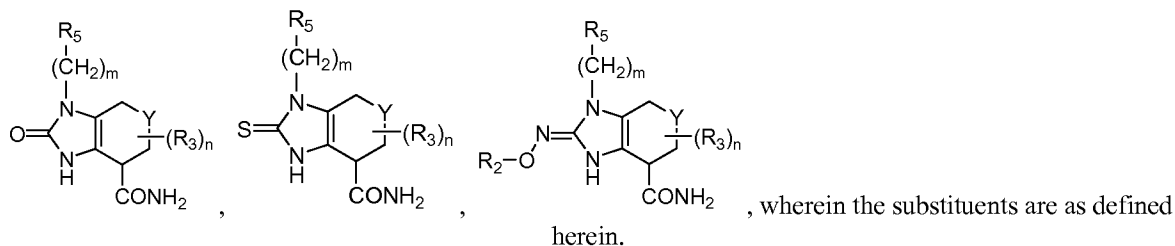
[00157] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIA-VIC:



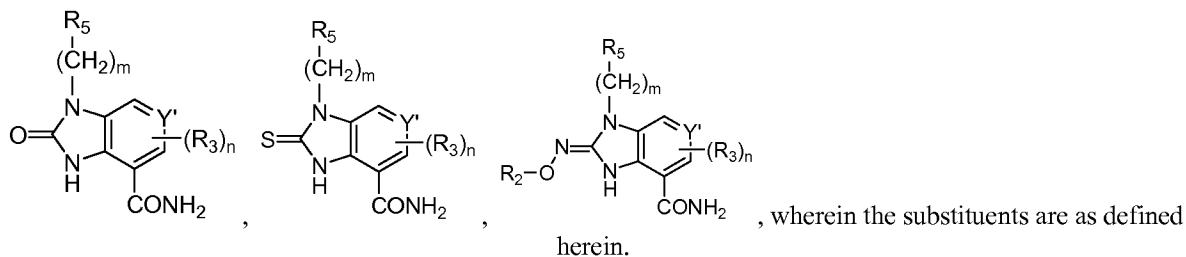
[00158] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIA'-VIC':



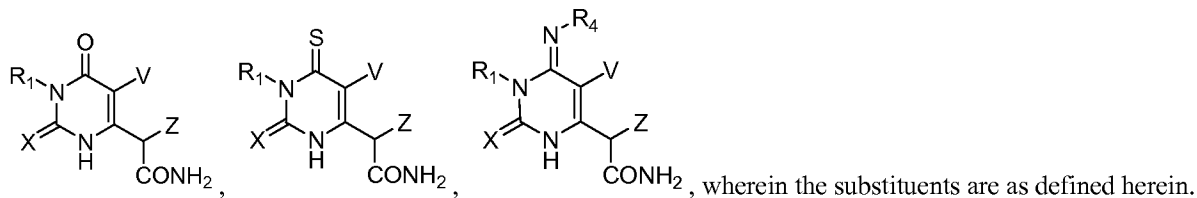
5 [00159] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIA-VIIC:



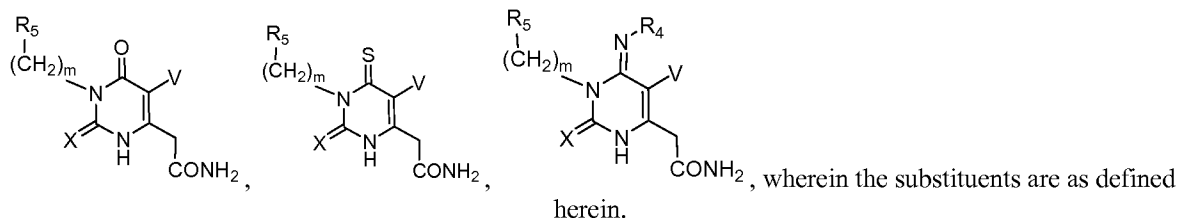
[00160] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIA'-VIIC':



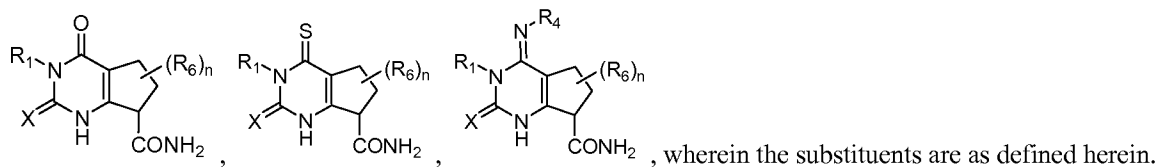
[00161] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIIA-VIIIC:



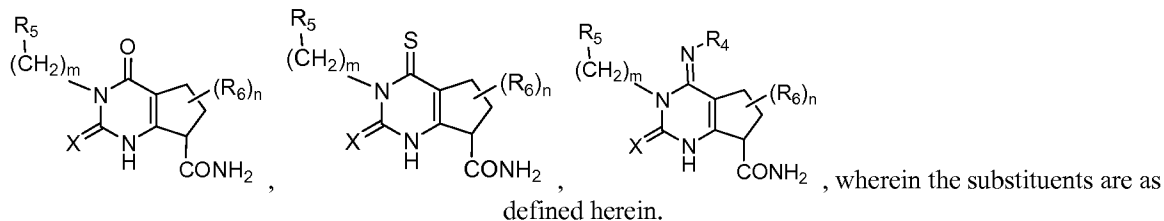
15 [00162] Provided herein are compounds and pharmaceutically acceptable salts of Formulas IXA-IXC:



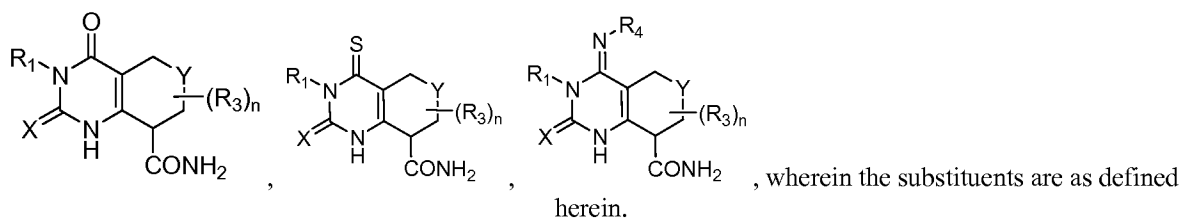
[00163] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XA-XC:



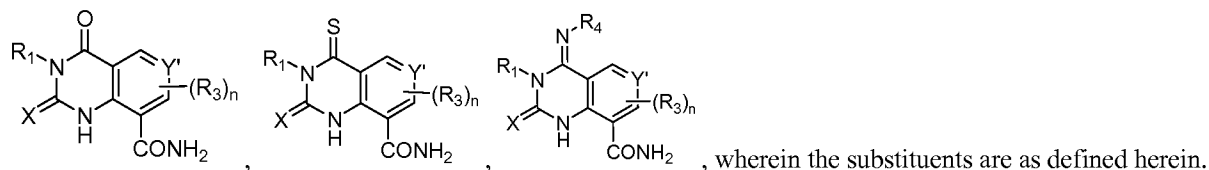
[00164] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XIA-XIC:



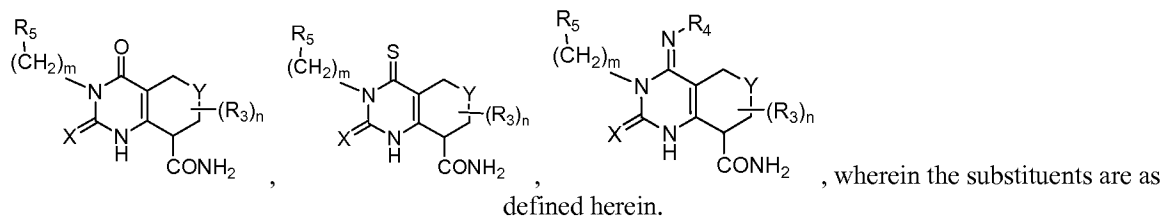
5 [00165] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIA-VIIC:



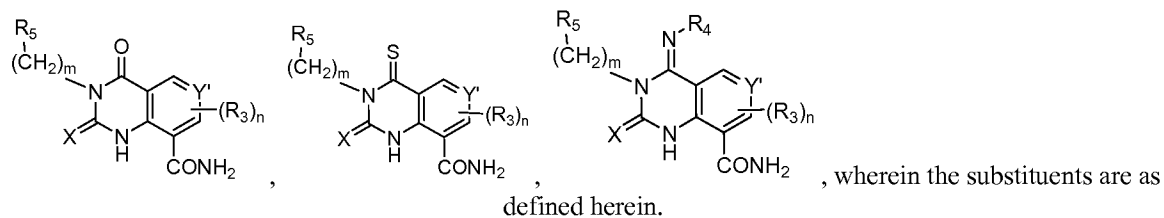
[00166] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIA'-VIIC':



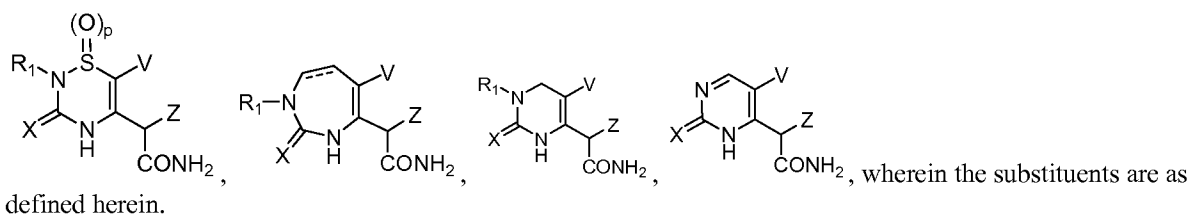
[00167] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIIA-VIIIC:



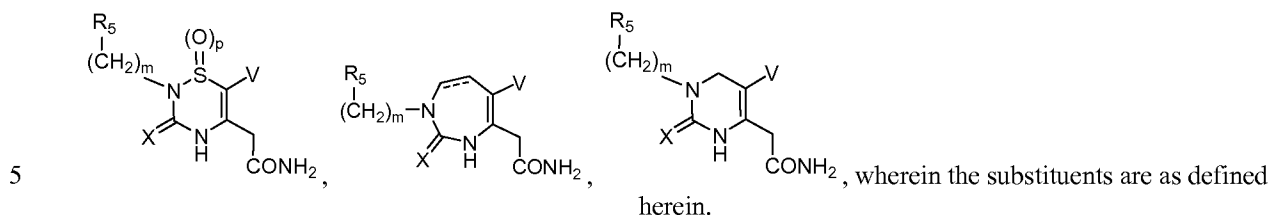
15 [00168] Provided herein are compounds and pharmaceutically acceptable salts of Formulas VIIIA'-VIIIC':



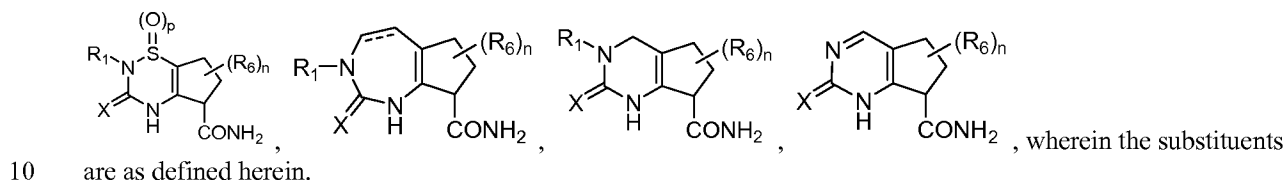
[00169] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XIVA-XIVD:



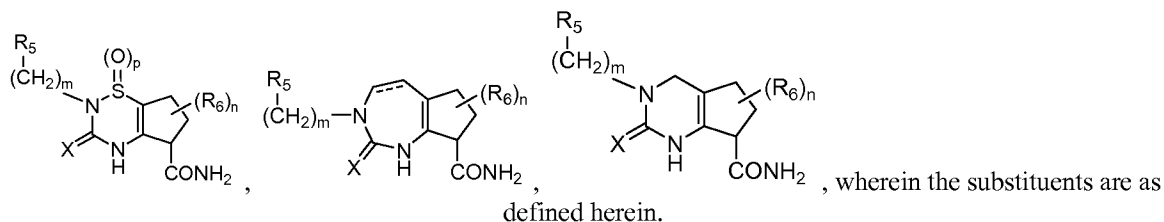
[00170] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVA-XVC:



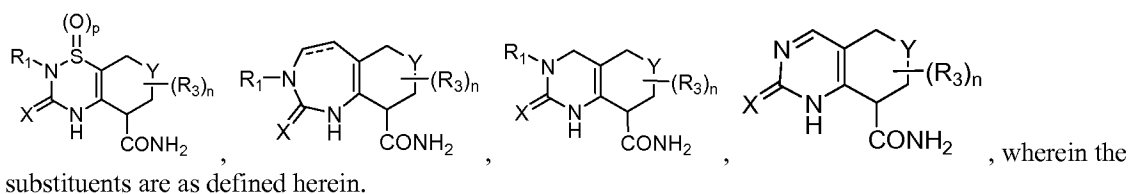
[00171] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVIA-XVID:



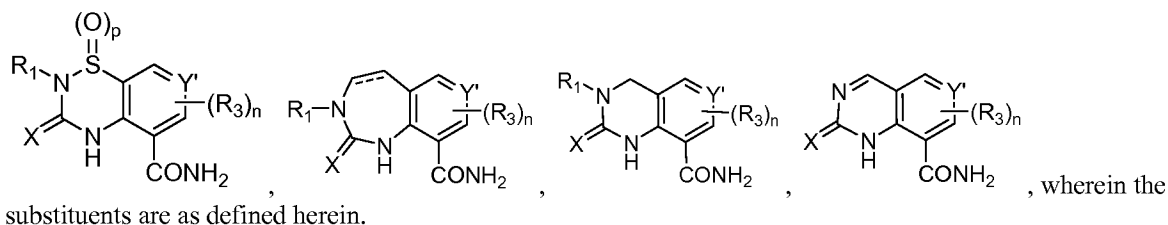
[00172] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVIA-XVIIC:



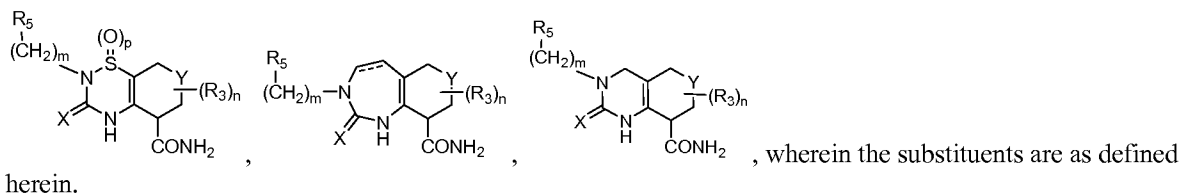
[00173] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVIII A-XVIII D:



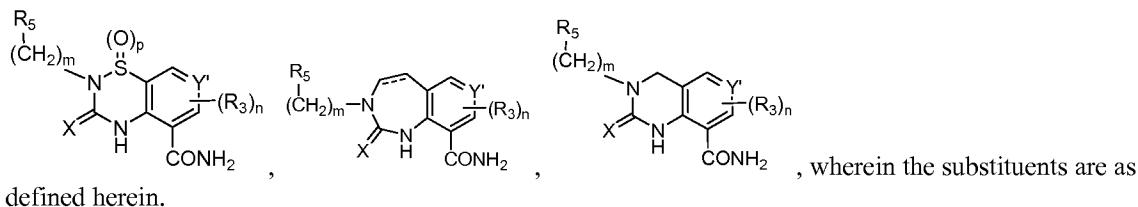
[00174] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XVIII A'-XVIII D':



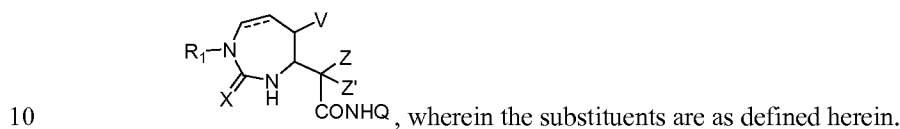
[00175] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XIXA-XIXC:



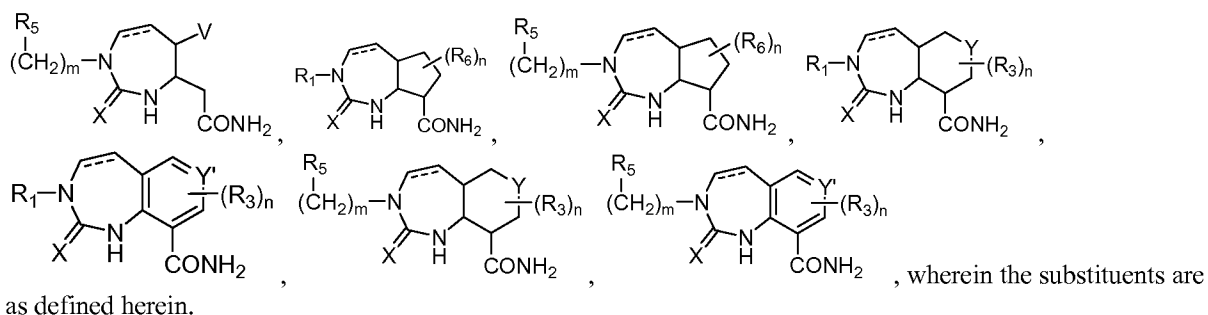
5 [00176] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XIXA'-XIXC':



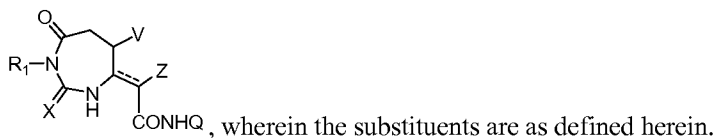
[00177] Provided herein are compounds and pharmaceutically acceptable salts of Formula XX:



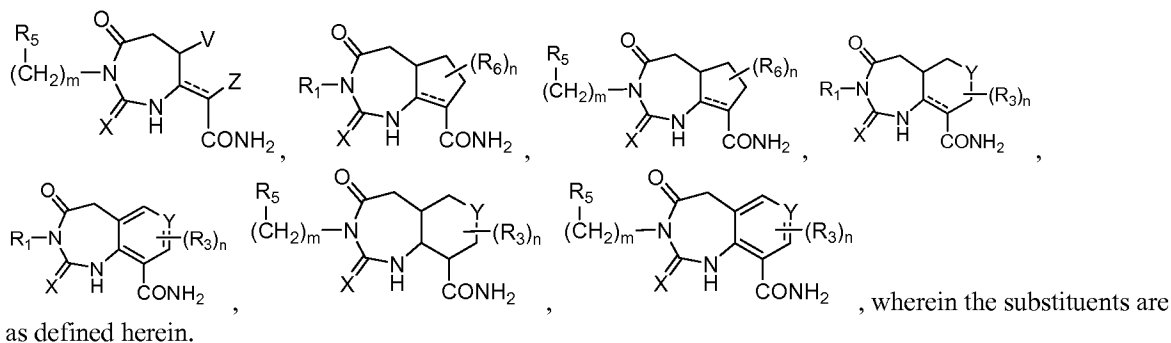
[00178] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XXA-XXG:



[00179] Provided herein are compounds and pharmaceutically acceptable salts of Formula XXI:



[00180] Provided herein are compounds and pharmaceutically acceptable salts of Formulas XXIA-XXIG:



Exemplary Uses

- 5 **[00181]** Provided herein are methods for treating a patient suffering from a sirtuin mediated disorder, comprising administering to said individual an effective amount of a composition comprising a compound of Formulas I-XXI or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof. In some embodiments, the sirtuin-modulating compounds may be useful for a variety of therapeutic applications including, for example, increasing the lifespan of a cell, and
- 10 treating and/or preventing a wide variety of diseases and disorders including, for example, diseases or disorders related to aging or stress (including increasing radiosensitivity and/or chemosensitivity), diabetes, obesity (including stimulation of appetite or weight gain), neurodegenerative diseases, cardiovascular disease, blood clotting disorders, stroke, ischemia, inflammation, cancer (optionally in combination another chemotherapeutic agent), flushing, infections including viral infections (e.g.
- 15 herpes, HIV, adenovirus, and HTLV-1 associated malignant and benign disorders), autoimmune disorders (e.g., systemic lupus erythematosus, scleroderma, and arthritis, in which autoimmune cells should be removed), fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, tumors, leukemias, neoplasms, carcinomas, metabolic diseases, malignant diseases, stimulation of appetite, and/or stimulation of weight gain.
- 20 **[00182]** Compounds of Formulas I-XXI, pharmaceutically acceptable salts, pharmaceutically active metabolites, pharmaceutically acceptable prodrugs, and pharmaceutically acceptable solvates thereof, may modulate the activity of sirtuin enzymes; and, as such, are useful for treating diseases or conditions in which aberrant sirtuin enzyme activity contributes to the pathology and/or symptoms of a disease or condition.
- 25 **[00183]** In certain embodiments, methods for reducing, preventing or treating diseases or disorders using a sirtuin-modulating compound may also comprise increasing the protein level of a sirtuin, such as human SIRT1, SIRT2 and/or SIRT3, or homologs thereof. Increasing protein levels can be achieved by introducing into a cell one or more copies of a nucleic acid that encodes a sirtuin. For example, the level of a sirtuin can be increased in a mammalian cell by introducing into the mammalian cell a nucleic acid encoding the sirtuin, e.g., increasing the level of SIRT1 by introducing a nucleic acid encoding the amino acid sequence set forth in GenBank Accession No. NP__036370 and/or increasing the level of
- 30 SIRT3 by introducing a nucleic acid encoding the amino acid sequence set forth in GenBank Accession No. AAH01042. The nucleic acid may be under the control of a promoter that regulates the expression of the SIRT1 and/or SIRT3 nucleic acid. Alternatively, the nucleic acid may be introduced into the cell at a location in the genome that is downstream of a promoter. Methods for increasing the level of a
- 35 protein using these methods are well known in the art.

[00184] A nucleic acid that is introduced into a cell to increase the protein level of a sirtuin may encode a protein that is at least about 80%, 85%, 90%, 95%, 98%, or 99% identical to the sequence of a sirtuin, e.g., SIRT1 (GenBank Accession No. NP__036370) and/or SIRT3 (GenBank Accession No. AAH01042) protein. For example, the nucleic acid encoding the protein may be at least about 80%, 85%, 90%, 95%, 98%, or 99% identical to a nucleic acid encoding a SIRT1 (e.g. GenBank Accession No. NM__012238) and/or SIRT3 (e.g., GenBank Accession No. BC001042) protein. The nucleic acid may also be a nucleic acid that hybridizes, preferably under stringent hybridization conditions, to a nucleic acid encoding a wild-type sirtuin, e.g., SIRT1 (GenBank Accession No. NM__012238) and/or SIRT3 (e.g., GenBank Accession No. BC001042) protein. Stringent hybridization conditions may include hybridization and a wash in 0.2×SSC at 65°C. When using a nucleic acid that encodes a protein that is different from a wild-type sirtuin protein, such as a protein that is a fragment of a wild-type sirtuin, the protein is preferably biologically active, e.g., is capable of deacetylation. It is only necessary to express in a cell a portion of the sirtuin that is biologically active. For example, a protein that differs from wild-type SIRT1 having GenBank Accession No. NP__036370, preferably contains the core structure thereof. The core structure sometimes refers to amino acids 62-293 of GenBank Accession No. NP__036370, which are encoded by nucleotides 237 to 932 of GenBank Accession No. NM__012238, which encompasses the NAD binding as well as the substrate binding domains. The core domain of SIRT1 may also refer to about amino acids 261 to 447 of GenBank Accession No. NP__036370, which are encoded by nucleotides 834 to 1394 of GenBank Accession No. NM-012238; to about amino acids 242 to 493 of GenBank Accession No. NP__036370, which are encoded by nucleotides 777 to 1532 of GenBank Accession No. NM__012238; or to about amino acids 254 to 495 of GenBank Accession No. NP__036370, which are encoded by nucleotides 813 to 1538 of GenBank Accession No. NM__012238. Whether a protein retains a biological function, e.g., deacetylation capabilities, can be determined according to methods known in the art.

[00185] In certain embodiments, methods for reducing, preventing or treating diseases or disorders using a sirtuin-modulating compound may also comprise decreasing the protein level of a sirtuin, such as human SIRT1, SIRT2 and/or SIRT3, or homologs thereof. Decreasing a sirtuin protein level can be achieved according to methods known in the art. For example, an siRNA, an antisense nucleic acid, or a ribozyme targeted to the sirtuin can be expressed in the cell. A dominant negative sirtuin mutant, e.g., a mutant that is not capable of deacetylating, may also be used. For example, mutant H363Y of SIRT1, described, e.g., in Luo et al. (2001) Cell 107:137 can be used. Alternatively, agents that inhibit transcription can be used.

[00186] Methods for modulating sirtuin protein levels also include methods for modulating the transcription of genes encoding sirtuins, methods for stabilizing/destabilizing the corresponding mRNAs, and other methods known in the art.

[00187] In an exemplary embodiment, a sirtuin-modulating compound may traverse the cytoplasmic membrane of a cell. For example, a compound may have a cell-permeability of at least about 20%, 50%, 75%, 80%, 90% or 95%.

[00188] Sirtuin-modulating compounds described herein may also have one or more of the following characteristics: the compound may be essentially non-toxic to a cell or subject; the sirtuin-modulating

compound may be an organic molecule or a small molecule of 2000 amu or less, 1000 amu or less; a compound may have a half-life under normal atmospheric conditions of at least about 30 days, 60 days, 120 days, 6 months or 1 year; the compound may have a half-life in solution of at least about 30 days, 60 days, 120 days, 6 months or 1 year; a sirtuin-modulating compound may be more stable in solution than resveratrol by at least a factor of about 50%, 2 fold, 5 fold, 10 fold, 30 fold, 50 fold or 100 fold; a sirtuin-modulating compound may promote deacetylation of the DNA repair factor Ku70; a sirtuin-modulating compound may promote deacetylation of RelA/p65; a compound may increase general turnover rates and enhance the sensitivity of cells to TNF-induced apoptosis.

[00189] In certain embodiments, a sirtuin-modulating compound does not have any substantial ability to inhibit a histone deacetylase (HDACs) class I, a HDAC class II, or HDACs I and II, at concentrations (e.g., in vivo) effective for modulating the deacetylase activity of the sirtuin. For instance, in preferred embodiments the sirtuin-modulating compound is a sirtuin-activating compound and is chosen to have an EC₅₀ for activating sirtuin deacetylase activity that is at least 5 fold less than the EC₅₀ for inhibition of an HDAC I and/or HDAC II, and even more preferably at least 10 fold, 100 fold or even 1000 fold less. Methods for assaying HDAC I and/or HDAC II activity are well known in the art and kits to perform such assays may be purchased commercially. See e.g., BioVision, Inc. (Mountain View, Calif.; world wide web at biovision.com) and Thomas Scientific (Swedesboro, N.J.; world wide web at thomasci.com).

[00190] In certain embodiments, a sirtuin-modulating compound does not have any substantial ability to modulate sirtuin homologs. In one embodiment, an activator of a human sirtuin protein may not have any substantial ability to activate a sirtuin protein from lower eukaryotes, particularly yeast or human pathogens, at concentrations (e.g., in vivo) effective for activating the deacetylase activity of human sirtuin. For example, a sirtuin-activating compound may be chosen to have an EC₅₀ for activating a human sirtuin, such as SIRT1 and/or SIRT3, deacetylase activity that is at least 5 fold less than the EC₅₀ for activating a yeast sirtuin, such as Sir2 (such as *Candida*, *S. cerevisiae*, etc.), and even more preferably at least 10 fold, 100 fold or even 1000 fold less. In another embodiment, an inhibitor of a sirtuin protein from lower eukaryotes, particularly yeast or human pathogens, does not have any substantial ability to inhibit a sirtuin protein from humans at concentrations (e.g., in vivo) effective for inhibiting the deacetylase activity of a sirtuin protein from a lower eukaryote. For example, a sirtuin-inhibiting compound may be chosen to have an IC₅₀ for inhibiting a human sirtuin, such as SIRT1 and/or SIRT3, deacetylase activity that is at least 5 fold less than the IC₅₀ for inhibiting a yeast sirtuin, such as Sir2 (such as *Candida*, *S. cerevisiae*, etc.), and even more preferably at least 10 fold, 100 fold or even 1000 fold less.

[00191] In certain embodiments, a sirtuin-modulating compound may have the ability to modulate one or more sirtuin protein homologs, such as, for example, one or more of human SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, or SIRT7. In one embodiment, a sirtuin-modulating compound has the ability to modulate both a SIRT1 and a SIRT3 protein.

[00192] In other embodiments, a SIRT1 modulator does not have any substantial ability to modulate other sirtuin protein homologs, such as, for example, one or more of human SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, or SIRT7, at concentrations (e.g., in vivo) effective for modulating the deacetylase activity of

human SIRT1. For example, a sirtuin-modulating compound may be chosen to have an ED₅₀ for modulating human SIRT1 deacetylase activity that is at least 5 fold less than the ED₅₀ for modulating one or more of human SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, or SIRT7, and even more preferably at least 10 fold, 100 fold or even 1000 fold less. In one embodiment, a SIRT1 modulator does not have any substantial ability to modulate a SIRT3 protein.

[00193] In other embodiments, a SIRT3 modulator does not have any substantial ability to modulate other sirtuin protein homologs, such as, for example, one or more of human SIRT1, SIRT2, SIRT4, SIRT5, SIRT6, or SIRT7, at concentrations (e.g., in vivo) effective for modulating the deacetylase activity of human SIRT3. For example, a sirtuin-modulating compound may be chosen to have an ED₅₀ for modulating human SIRT3 deacetylase activity that is at least 5 fold less than the ED₅₀ for modulating one or more of human SIRT1, SIRT2, SIRT4, SIRT5, SIRT6, or SIRT7, and even more preferably at least 10 fold, 100 fold or even 1000 fold less. In one embodiment, a SIRT3 modulator does not have any substantial ability to modulate a SIRT1 protein.

[00194] In certain embodiments, a sirtuin-modulating compound may have a binding affinity for a sirtuin protein of about 10⁻⁹M, 10⁻¹⁰M, 10⁻¹¹M, 10⁻¹²M or less. A sirtuin-modulating compound may reduce (activator) or increase (inhibitor) the apparent Km of a sirtuin protein for its substrate or NAD⁺ (or other cofactor) by a factor of at least about 2, 3, 4, 5, 10, 20, 30, 50 or 100. In certain embodiments, Km values are determined using the mass spectrometry assay described herein. Preferred activating compounds reduce the Km of a sirtuin for its substrate or cofactor to a greater extent than caused by resveratrol at a similar concentration or reduce the Km of a sirtuin for its substrate or cofactor similar to that caused by resveratrol at a lower concentration. A sirtuin-modulating compound may increase the Vmax of a sirtuin protein by a factor of at least about 2, 3, 4, 5, 10, 20, 30, 50 or 100. A sirtuin-modulating compound may have an ED50 for modulating the deacetylase activity of a SIRT1 and/or SIRT3 protein of less than about 1 nM, less than about 10 nM, less than about 100 nM, less than about 1 μM, less than about 10 μM, less than about 100 μM, or from about 1-10 nM, from about 10-100 nM, from about 0.1-1 μM, from about 1-10 μM or from about 10-100 μM. A sirtuin-modulating compound may modulate the deacetylase activity of a SIRT1 and/or SIRT3 protein by a factor of at least about 5, 10, 20, 30, 50, or 100, as measured in a cellular assay or in a cell based assay. A sirtuin-activating compound may cause at least about 10%, 30%, 50%, 80%, 2 fold, 5 fold, 10 fold, 50 fold or 100 fold greater induction of the deacetylase activity of a sirtuin protein relative to the same concentration of resveratrol. A sirtuin-modulating compound may have an ED₅₀ for modulating SIRT5 that is at least about 10 fold, 20 fold, 30 fold, 50 fold greater than that for modulating SIRT1 and/or SIRT3.

Cancer

[00195] In some embodiments, the sirtuin mediated disorder is cancer, tumors, leukemias, neoplasms, or carcinomas, including but not limited to biliary tract cancer, brain cancer, breast cancer, liver cancer, lung cancer, cervical cancer; choriocarcinoma, melanoma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, endometrial cancer, esophageal cancer, gastric cancer, sarcomas, skin cancer, testicular cancer, thyroid cancer, intraepithelial neoplasms leukemia, myeloid leukemia, glioblastoma, follicular lymphoma, pre-B acute leukemia, chronic lymphocytic B-leukemia, mesothelioma or small cell line cancer. Examples of cancerous disorders include, but are not

limited to, solid tumors, soft tissue tumors, and metastatic lesions. As used herein, the term "cancer" is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. The cancer may be a malignant or non-malignant cancer.

5 [00196] In some embodiments, the methods prevent or treat tumor proliferation and/or metastasis. In some embodiments, the tumor occurs in the brain, breast, lung, ovaries, pancreas, prostate, kidney, colon or rectum. In yet other embodiments, the sirtuin mediated disorder is a proliferative disease selected from psoriasis, restenosis, autoimmune disease, or atherosclerosis. In some embodiments, the cancer cells comprise brain, breast, lung, ovarian, pancreatic, prostate, renal, or colorectal cancer cells.

10 [00197] Examples of tumors and cancers which are p53 dependent include colon cancer, breast cancer, lung cancer, bladder cancer, brain cancer, pancreatic cancer, stomach cancer, esophageal cancer, sarcomas, cervical cancer, liver cancer, lymphomas and neuroblastomas. Metastatic lesions of the aforementioned cancers can also be treated or prevented using a compound identified by the methods described herein.

15 [00198] Provided herein are methods for degrading, inhibiting the growth of or killing cancer cells comprising contacting the cells with an amount of a composition effective to degrade, inhibit the growth of or kill cancer cells, the composition comprising a compound of Formulas I-XXI or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof.

20 [00199] Provided herein are methods of inhibiting tumor size increase, reducing the size of a tumor, reducing tumor proliferation or preventing tumor proliferation in an individual comprising administering to said individual an effective amount of a composition to inhibit tumor size increase, reduce the size of a tumor, reduce tumor proliferation or prevent tumor proliferation, the composition comprising a compound of Formulas I-XXI or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof. In some embodiments the compound of Formulas I-XXI is administered in combination with an additional cancer therapy including, but not limited to surgery, radiation therapy, and administration of at least one chemotherapeutic agent. In some embodiments, the composition is administered before surgery. In other embodiments, the composition is administered after surgery.

25 [00200] In some embodiments, the compound of Formulas I-XXI is administered in combination with an additional cancer therapy. In some embodiments, the additional cancer therapy is selected from surgery, radiation therapy, and administration of at least one chemotherapeutic agent. In various embodiments, the administration of the compound of Formulas I-XXI occurs after surgery. In other embodiments, the administration of the compound of Formulas I-XXI occurs before surgery. Alternatively, cells can be obtained from a subject, treated ex vivo to remove certain undesirable cells, e.g., cancer cells, and administered back to the same or a different subject.

30 [00201] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered to subjects who have recently received or are likely to receive a dose of radiation or toxin. In one embodiment, the dose of radiation or toxin is received as part of a work-related or medical procedure, e.g., working in a nuclear power plant, flying an airplane, an X-ray, CAT scan, or the administration of a radioactive dye for medical imaging; in such an embodiment, the compound is administered as a prophylactic measure. In another embodiment, the radiation or toxin exposure is received unintentionally, e.g., as a result of an industrial accident, habitation in a location of natural

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radiation, terrorist act, or act of war involving radioactive or toxic material. In such a case, the compound is preferably administered as soon as possible after the exposure to inhibit apoptosis and the subsequent development of acute radiation syndrome.

[00202] In certain embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for treating and/or preventing cancer. Calorie restriction by sirtuin regulation has been linked to a reduction in the incidence of age-related disorders including cancer. In other embodiments, sirtuin-modulating compounds that decrease the level and/or activity of a sirtuin protein may be used for treating or preventing cancer. For example, inhibitory compounds may be used to stimulate acetylation of substrates such as p53 and thereby increase apoptosis, as well as to reduce the lifespan of cells and organisms, render them more sensitive to stress, and/or increase the radiosensitivity and/or chemosensitivity of a cell or organism. Exemplary cancers that may be treated using a sirtuin-modulating compound are those of the brain and kidney; hormone-dependent cancers including breast, prostate, testicular, and ovarian cancers; lymphomas, and leukemias. In cancers associated with solid tumors, a modulating compound may be administered directly into the tumor. Cancer of blood cells, e.g., leukemia, can be treated by administering a modulating compound into the blood stream or into the bone marrow. Benign cell growth can also be treated, e.g., warts.

[00203] Chemotherapeutic agents that may be coadministered with modulating compounds described herein as having anti-cancer activity (e.g., compounds that induce apoptosis, compounds that reduce lifespan or compounds that render cells sensitive to stress) include: aminoglutethimide, amsacrine, anastrozole, asparaginase, bcr, bicalutamide, bleomycin, buserelin, busulfan, camptothecin, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, estradiol, estramustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide, testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, and vinorelbine.

[00204] These chemotherapeutic agents may be categorized by their mechanism of action into, for example, following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs (5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine) and purine analogs, folate antagonists and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine(cladribine)); antiproliferative/antimitotic agents including natural products such as vinca alkaloids (vinblastine, vincristine, and vinorelbine), microtubule disruptors such as taxane (paclitaxel, docetaxel), vincristin, vinblastin, nocodazole, epothilones and navelbine, epidipodophyllotoxins(teniposide), DNA damaging agents (actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytoxan, dactinomycin, daunorubicin, docetaxel,

doxorubicin, epirubicin, hexamethylmelamineoxaliplatin, iphosphamide, melphalan, merchloroethamine, mitomycin, mitoxantrone, nitrosourea, paclitaxel, plicamycin, procarbazine, teniposide, triethylenethiophosphoramidate and etoposide (VP16)); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechloroethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and analogs, streptozocin), trazenes--dacarbazine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (letrozole, anastrozole); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, COX-2 inhibitors, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory agents; antisecretory agents (breveldin); immunosuppressives (cyclosporine, tacrolimus (FK-506), sirolimus(rapamycin), azathioprine, mycophenolate mofetil); anti-angiogenic compounds (TNP-470, genistein) and growth factor inhibitors (vascular endothelial growth factor (VEGF) inhibitors, fibroblast growth factor (FGF) inhibitors, epidermal growth factor (EGF) inhibitors); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides; antibodies (trastuzumab); cell cycle inhibitors and differentiation inducers (tretinoin); mTOR inhibitors, topoisomerase inhibitors (doxorubicin (adriamycin), atmsacrine, camptothecin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin, irinotecan (CPT-11) and mitoxantrone, topotecan, irinotecan), corticosteroids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and prednisolone); growth factor signal transduction kinase inhibitors; mitochondrial dysfunction inducers and caspase activators; chromatin disruptors.

[00205] These chemotherapeutic agents may be used by themselves with a sirtuin-modulating compound described herein as inducing cell death or reducing lifespan or increasing sensitivity to stress and/or in combination with other chemotherapeutic agents. Many combinatorial therapies have been developed, including but not limited to those therapeutic agents listed below: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine, Cyclophosphamide, Cisplatin, Etoposide, Cytarabine, Daunorubicin, Lomustine, Carmustine, Procarbazine, Prednisone, Vincristine, Filgrastim, Ifosfamide, Mesna, Mitomycin, Asparaginase, Methotrexate, Fluorouracil, Carboplatin, Paclitax, Epirubicin, Altretamine, Chlorambucil, Mitoxantrone, Leucovorin, Prednisone, Thioguanine, Dexamethasone, Tamoxifen, Leuprolide, Goserelin acetate, Etoposide, Mercaptopurine, Melphalan, Mechlorethamine, Estramustine, Cotrimoxazole, Streptozocin, Hydrocortisone, Topotecan, Vinorelbine, Thiotepa, Flouxymesterone, Idarubicin, Methylprednisolone, and Hydroxyurea.

[00206] In addition to conventional chemotherapeutics, the sirtuin-modulating compounds described herein as capable of inducing cell death or reducing lifespan can also be used with antisense RNA, RNAi or other

polynucleotides to inhibit the expression of the cellular components that contribute to unwanted cellular proliferation that are targets of conventional chemotherapy. Such targets are, merely to illustrate, growth factors, growth factor receptors, cell cycle regulatory proteins, transcription factors, or signal transduction kinases.

- 5 [00207] Combination therapies comprising sirtuin-modulating compounds and a conventional chemotherapeutic agent may be advantageous over combination therapies known in the art because the combination allows the conventional chemotherapeutic agent to exert greater effect at lower dosage.

Aged Skin

- 10 [00208] Signs of aged skin include, e.g., wrinkles, lines, sagging, freckles, tanned skin, discoloration, hyperpigmentation, age spots, e.g., "liver spots", thinning of the skin, cataracts, epidermal hyperplasia, skin elastosis, degradation of extracellular matrix, or precancerous or cancerous skin growths (actinic keratoses, solar keratoses).

- 15 [00209] In one embodiment, the invention provides a method extending the lifespan of a cell, extending the proliferative capacity of a cell, slowing ageing of a cell, promoting the survival of a cell, delaying cellular senescence in a cell, mimicking the effects of calorie restriction, increasing the resistance of a cell to stress, or preventing apoptosis of a cell, by contacting the cell with a sirtuin-modulating compound of the invention that increases the level and/or activity of a sirtuin protein. In an exemplary embodiment, the methods comprise contacting the cell with a sirtuin-activating compound.

- 20 [00210] In one embodiment, the invention may be used to increase the amount of time that cells, particularly primary cells (i.e., cells obtained from an organism, e.g., a human), may be kept alive in a cell culture. Embryonic stem (ES) cells and pluripotent cells, and cells differentiated therefrom, may also be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein to keep the cells, or progeny thereof, in culture for longer periods of time. Such cells can also be used for transplantation into a subject, e.g., after ex vivo modification.

- 25 [00211] In one embodiment, cells that are intended to be preserved for long periods of time may be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. The cells may be in suspension (e.g., blood cells, serum, biological growth media, etc.) or in tissues or organs. For example, blood collected from an individual for purposes of transfusion may be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein to preserve the blood cells for longer periods of time. Additionally, blood to be used for forensic purposes may also be preserved using a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. Other cells that may be treated to extend their lifespan or protect against apoptosis include cells for consumption, e.g., cells from non-human mammals (such as meat) or plant cells (such as vegetables).

- 35 [00212] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be applied during developmental and growth phases in mammals, plants, insects or microorganisms, in order to, e.g., alter, retard or accelerate the developmental and/or growth process.

- 40 [00213] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to treat cells useful for transplantation or cell therapy, including, for example, solid tissue grafts, organ transplants, cell suspensions, stem cells, bone marrow cells, etc. The cells or tissue

may be an autograft, an allograft, a syngraft or a xenograft. The cells or tissue may be treated with the sirtuin-modulating compound prior to administration/implantation, concurrently with administration/implantation, and/or post administration/implantation into a subject. The cells or tissue may be treated prior to removal of the cells from the donor individual, ex vivo after removal of the cells or tissue from the donor individual, or post implantation into the recipient. For example, the donor or recipient individual may be treated systemically with a sirtuin-modulating compound or may have a subset of cells/tissue treated locally with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. In certain embodiments, the cells or tissue (or donor/recipient individuals) may additionally be treated with another therapeutic agent useful for prolonging graft survival, such as, for example, an immunosuppressive agent, a cytokine, an angiogenic factor, etc.

[00214] In yet other embodiments, cells may be treated with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein in vivo, e.g., to increase their lifespan or prevent apoptosis. For example, skin can be protected from aging (e.g., developing wrinkles, loss of elasticity, etc.) by treating skin or epithelial cells with a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. In an exemplary embodiment, skin is contacted with a pharmaceutical or cosmetic composition comprising a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. Exemplary skin afflictions or skin conditions that may be treated in accordance with the methods described herein include disorders or diseases associated with or caused by inflammation, sun damage or natural aging. For example, the compositions find utility in the prevention or treatment of contact dermatitis (including irritant contact dermatitis and allergic contact dermatitis), atopic dermatitis (also known as allergic eczema), actinic keratosis, keratinization disorders (including eczema), epidermolysis bullosa diseases (including penfigus), exfoliative dermatitis, seborrheic dermatitis, erythemas (including erythema multiforme and erythema nodosum), damage caused by the sun or other light sources, discoid lupus erythematosus, dermatomyositis, psoriasis, skin cancer and the effects of natural aging. In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for the treatment of wounds and/or burns to promote healing, including, for example, first-, second- or third-degree burns and/or a thermal, chemical or electrical burns.

[00215] In another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used for treating or preventing a disease or condition induced or exacerbated by cellular senescence in a subject; methods for decreasing the rate of senescence of a subject, e.g., after onset of senescence; methods for extending the lifespan of a subject; methods for treating or preventing a disease or condition relating to lifespan; methods for treating or preventing a disease or condition relating to the proliferative capacity of cells; and methods for treating or preventing a disease or condition resulting from cell damage or death. In certain embodiments, the method does not act by decreasing the rate of occurrence of diseases that shorten the lifespan of a subject. In certain embodiments, a method does not act by reducing the lethality caused by a disease, such as cancer.

[00216] In yet another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered to a subject in order to generally increase the lifespan of its cells and to protect its cells against stress and/or against apoptosis. It is believed that treating a subject with a

compound described herein is similar to subjecting the subject to hormesis, i.e., mild stress that is beneficial to organisms and may extend their lifespan.

Cardiovascular Diseases

5 [00217] In one embodiment, the invention provides a method for treating and/or preventing a cardiovascular disease by administering to a subject in need thereof a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein.

such as a stroke, heart disease, heart failure, arthritis, and high blood pressure

10 [00218] Cardiovascular diseases that can be treated or prevented using the sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein include cardiomyopathy or myocarditis; such as idiopathic cardiomyopathy, metabolic cardiomyopathy, alcoholic cardiomyopathy, drug-induced cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy. Also treatable or preventable using compounds and methods described herein are atheromatous disorders of the major blood vessels (macrovascular disease) such as the aorta, the coronary arteries, the carotid arteries, the
15 cerebrovascular arteries, the renal arteries, the iliac arteries, the femoral arteries, and the popliteal arteries. Other vascular diseases that can be treated or prevented include those related to platelet aggregation, the retinal arterioles, the glomerular arterioles, the vasa nervorum, cardiac arterioles, and associated capillary beds of the eye, the kidney, the heart, and the central and peripheral nervous systems. The sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein
20 may also be used for increasing HDL levels in plasma of an individual. Yet other disorders that may be treated with sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein include restenosis, e.g., following coronary intervention, and disorders relating to an abnormal level of high density and low density cholesterol.

[00219] In one embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin
25 protein may be administered as part of a combination therapeutic with another cardiovascular agent including, for example, an anti-arrhythmic agent, an antihypertensive agent, a calcium channel blocker, a cardioplegic solution, a cardiotonic agent, a fibrinolytic agent, a sclerosing solution, a vasoconstrictor agent, a vasodilator agent, a nitric oxide donor, a potassium channel blocker, a sodium channel blocker, statins, or a natriuretic agent.

30 [00220] In one embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered as part of a combination therapeutic with an anti-arrhythmia agent. Anti-arrhythmia agents are often organized into four main groups according to their mechanism of action: type I, sodium channel blockade; type II, beta-adrenergic blockade; type III, repolarization
35 prolongation; and type IV, calcium channel blockade. Type I anti-arrhythmic agents include lidocaine, moricizine, mexiletine, tocainide, procainamide, encainide, flecanide, tocainide, phenytoin, propafenone, quinidine, disopyramide, and flecainide. Type II anti-arrhythmic agents include propranolol and esmolol. Type III includes agents that act by prolonging the duration of the action potential, such as amiodarone, artilide, bretylium, clofilium, isobutilide, sotalol, azimilide, dofetilide, dronedarone, ersentilide, ibutilide, tedisamil, and trecetilide. Type IV anti-arrhythmic agents include
40 verapamil, diltiazem, digitalis, adenosine, nickel chloride, and magnesium ions.

[00221] In another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered as part of a combination therapeutic with another cardiovascular agent. Examples of cardiovascular agents include vasodilators, for example, hydralazine; angiotensin converting enzyme inhibitors, for example, captopril; anti-anginal agents, for example, isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate; anti-arrhythmic agents, for example, quinidine, procainamide and lignocaine; cardioglycosides, for example, digoxin and digitoxin; calcium antagonists, for example, verapamil and nifedipine; diuretics, such as thiazides and related compounds, for example, bendroflumethiazide, chlorothiazide, chlorothalidone, hydrochlorothiazide and other diuretics, for example, furosemide and triamterene, and sedatives, for example, nitrazepam, flurazepam and diazepam.

[00222] Other exemplary cardiovascular agents include, for example, a cyclooxygenase inhibitor such as aspirin or indomethacin, a platelet aggregation inhibitor such as clopidogrel, ticlopidine or aspirin, fibrinogen antagonists or a diuretic such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorthiazide, trichloromethiazide, polythiazide or benzthiazide as well as ethacrynic acid trierythrin, chlorthalidone, furosemide, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds, angiotensin converting enzyme inhibitors such as captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazapril, delapril, pentopril, quinapril, ramipril, lisinopril, and salts of such compounds, angiotensin II antagonists such as losartan, irbesartan or valsartan, thrombolytic agents such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (APSAC, Eminase, Beecham Laboratories), or animal salivary gland plasminogen activators, calcium channel blocking agents such as verapamil, nifedipine or diltiazem, thromboxane receptor antagonists such as ifetroban, prostacyclin mimetics, or phosphodiesterase inhibitors. Such combination products if formulated as a fixed dose employ the compounds of this invention within the dose range described above and the other pharmaceutically active agent within its approved dose range.

[00223] Yet other exemplary cardiovascular agents include, for example, vasodilators, e.g., bencyclane, cinnarizine, citicoline, cyclandelate, cyclonicate, ebumamonine, phenoxethyl, flunarizine, ibudilast, ifenprodil, lomerizine, naphthol, nikamate, nosergoline, nimodipine, papaverine, pentifylline, nifedipine, vincamin, vinpocetine, vichizyl, pentoxifylline, prostacyclin derivatives (such as prostaglandin E1 and prostaglandin I2), an endothelin receptor blocking drug (such as bosentan), diltiazem, nicorandil, and nitroglycerin.

[00224] Examples of the cerebral protecting drug include radical scavengers (such as edaravone, vitamin E, and vitamin C), glutamate antagonists, AMPA antagonists, kainate antagonists, NMDA antagonists, GABA agonists, growth factors, opioid antagonists, phosphatidylcholine precursors, serotonin agonists, $\text{Na}^+/\text{Ca}^{2+}$ channel inhibitory drugs, and K^+ channel opening drugs.

[00225] Examples of the brain metabolic stimulants include amantadine, tiapride, and gamma-aminobutyric acid.

[00226] Examples of the anticoagulant include heparins (such as heparin sodium, heparin potassium, dalteparin sodium, dalteparin calcium, heparin calcium, pamaparin sodium, reviparin sodium, and danaparoid sodium), warfarin, enoxaparin, argatroban, batroxobin, and sodium citrate.

[00227] Examples of the antiplatelet drug include ticlopidine hydrochloride, dipyridamole, cilostazol, ethyl icosapentate, sarpogrelate hydrochloride, dilazep hydrochloride, trapidil, a nonsteroidal antiinflammatory agent (such as aspirin), beraprost sodium, iloprost, and indobufene.

[00228] Examples of the thrombolytic drug include urokinase, tissue-type plasminogen activators (such as alteplase, tisokinase, nateplase, pamiteplase, monteplase, and rateplase), and nasaruplase.

[00229] Examples of the antihypertensive drug include angiotensin converting enzyme inhibitors (such as captopril, alacepril, lisinopril, imidapril, quinapril, temocapril, delapril, benazepril, cilazapril, trandolapril, enalapril, ceronapril, fosinopril, imadapril, mobertpril, perindopril, ramipril, spirapril, and randolapril), angiotensin II antagonists (such as losartan, candesartan, valsartan, eprosartan, and irbesartan), calcium channel blocking drugs (such as aranidipine, efonidipine, nicardipine, bamidipine, benidipine, manidipine, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, amlodipine, diltiazem, bepridil, clentiazem, phendilin, galopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, cilnidipine, elgodipine, isradipine, lacidipine, lercanidipine, nimodipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, and perhexiline), β -adrenaline receptor blocking drugs (propranolol, pindolol, indenolol, carteolol, bunitrolol, atenolol, acebutolol, metoprolol, timolol, nipradilol, penbutolol, nadolol, tilisolol, carvedilol, bisoprolol, betaxolol, celiprolol, bopindolol, bevantolol, labetalol, alprenolol, amosulalol, arotinolol, befunolol, bucumolol, bufetolol, buferalol, buprandolol, butylidine, butofilolol, carazolol, cetamolol, cloranolol, dilevalol, epanolol, levobunolol, mepindolol, metipranolol, moprolol, nadoxolol, nevibolol, oxprenolol, practol, pronetalol, sotalol, sufinalol, talindolol, tertalol, toliprolol, xybenolol, and esmolol), cc-receptor blocking drugs (such as amosulalol, prazosin, terazosin, doxazosin, bunazosin, urapidil, phentolamine, arotinolol, dapiprazole, fenspiride, indoramin, labetalol, naftopidil, nicergoline, tamsulosin, tolazoline, trimazosin, and yohimbine), sympathetic nerve inhibitors (such as clonidine, guanfacine, guanabenz, methyl dopa, and reserpine), hydralazine, todrilazine, budralazine, and cadralazine.

[00230] Examples of the anti anginal drug include nitrate drugs (such as amyl nitrite, nitroglycerin, and isosorbide), β -adrenaline receptor blocking drugs (such as propranolol, pindolol, indenolol, carteolol, bunitrolol, atenolol, acebutolol, metoprolol, timolol, nipradilol, penbutolol, nadolol, tilisolol, carvedilol, bisoprolol, betaxolol, celiprolol, bopindolol, bevantolol, labetalol, alprenolol, amosulalol, arotinolol, befunolol, bucumolol, bufetolol, buferalol, buprandolol, butylidine, butofilolol, carazolol, cetamolol, cloranolol, dilevalol, epanolol, levobunolol, mepindolol, metipranolol, moprolol, nadoxolol, nevibolol, oxprenolol, practol, pronetalol, sotalol, sufinalol, talindolol, tertalol, toliprolol, and xybenolol), calcium channel blocking drugs (such as aranidipine, efonidipine, nicardipine, bamidipine, benidipine, manidipine, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, amlodipine, diltiazem, bepridil, clentiazem, phendiline, galopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, cilnidipine, elgodipine, isradipine, lacidipine, lercanidipine, nimodipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, and perhexiline) trimetazidine, dipyridamole, etafenone, dilazep, trapidil, nicorandil, enoxaparin, and aspirin.

[00231] Examples of the diuretic include thiazide diuretics (such as hydrochlorothiazide, methyclothiazide, trichlormethiazide, benzylhydrochlorothiazide, and penflutizide), loop diuretics (such as furosemide, etacrynic acid, bumetanide, piretanide, azosemide, and torasemide), K⁺ sparing diuretics (spironolactone, triamterene, and potassium canrenoate), osmotic diuretics (such as isosorbide, D-mannitol, and glycerin), nonthiazide diuretics (such as meticrane, tripamide, chlorthalidone, and mefruside), and acetazolamide.

[00232] Examples of the cardiotonic include digitalis formulations (such as digitoxin, digoxin, methyl digoxin, deslanoside, vesnarinone, lanatoside C, and proscillaridin), xanthine formulations (such as aminophylline, choline theophylline, diprophylline, and proxiphylline), catecholamine formulations (such as dopamine, dobutamine, and docarpamine), PDE III inhibitors (such as amrinone, olprinone, and milrinone), denopamine, ubidecarenone, pimobendan, levosimendan, aminoethylsulfonic acid, vesnarinone, carperitide, and colforsin daropate.

[00233] Examples of the antiarrhythmic drug include ajmaline, pirlmenol, procainamide, cibenzoline, disopyramide, quinidine, aprindine, mexiletine, lidocaine, phenyloin, pilsicainide, propafenone, flecainide, atenolol, acebutolol, sotalol, propranolol, metoprolol, pindolol, amiodarone, nifekalant, diltiazem, bepridil, and verapamil.

[00234] Examples of the antihyperlipidemic drug include atorvastatin, simvastatin, pravastatin sodium, fluvastatin sodium, clinofibrate, clofibrate, simfibrate, fenofibrate, bezafibrate, colestimide, and colestyramine.

[00235] Examples of the immunosuppressant include azathioprine, mizoribine, cyclosporine, tacrolimus, gusperimus, and methotrexate.

Blood Coagulation Disorders

[00236] In other aspects, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used to treat or prevent blood coagulation disorders (or hemostatic disorders). As used interchangeably herein, the terms "hemostasis", "blood coagulation," and "blood clotting" refer to the control of bleeding, including the physiological properties of vasoconstriction and coagulation. Further, the formation of blood clots does not only limit bleeding in case of an injury (hemostasis), but may lead to serious organ damage and death in the context of atherosclerotic diseases by occlusion of an important artery or vein. Thrombosis is thus blood clot formation at the wrong time and place.

[00237] Accordingly, the present invention provides anticoagulation and antithrombotic treatments aiming at inhibiting the formation of blood clots in order to prevent or treat blood coagulation disorders, such as myocardial infarction, stroke, loss of a limb by peripheral artery disease or pulmonary embolism.

[00238] As used interchangeably herein, "modulating or modulation of hemostasis" and "regulating or regulation of hemostasis" includes the induction (e.g., stimulation or increase) of hemostasis, as well as the inhibition (e.g., reduction or decrease) of hemostasis.

[00239] In one aspect, the invention provides a method for reducing or inhibiting hemostasis in a subject by administering a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. The compositions and methods disclosed herein are useful for the treatment or prevention of thrombotic disorders. Examples of thrombotic disorders include, but are not limited to, thromboembolism, deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, miscarriage, thrombophilia

associated with anti-thrombin III deficiency, protein C deficiency, protein S deficiency, resistance to activated protein C, dysfibrinogenemia, fibrinolytic disorders, homocystinuria, pregnancy, inflammatory disorders, myeloproliferative disorders, arteriosclerosis, angina, e.g., unstable angina, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, cancer metastasis, sickle cell disease, glomerular nephritis, and drug induced thrombocytopenia (including, for example, heparin induced thrombocytopenia). In addition, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered to prevent thrombotic events or to prevent re-occlusion during or after therapeutic clot lysis or procedures such as angioplasty or surgery.

[00240] In another embodiment, a combination drug regimen may include drugs or compounds for the treatment or prevention of blood coagulation disorders or secondary conditions associated with these conditions. Thus, a combination drug regimen may include one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein and one or more anti-coagulation or anti-thrombosis agents. For example, one or more sirtuin-modulating compounds can be combined with an effective amount of one or more of: aspirin, heparin, and oral Warfarin that inhibits Vit K-dependent factors, low molecular weight heparins that inhibit factors X and II, thrombin inhibitors, inhibitors of platelet GP IIb/IIIa receptors, inhibitors of tissue factor (TF), inhibitors of human von Willebrand factor, inhibitors of one or more factors involved in hemostasis (in particular in the coagulation cascade). In addition, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be combined with thrombolytic agents, such as t-PA, streptokinase, reptilase, TNK-t-PA, and staphylokinase.

Neuronal Diseases/Disorders

[00241] In certain aspects, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used to treat patients suffering from neurodegenerative diseases, and traumatic or mechanical injury to the central nervous system (CNS), spinal cord or peripheral nervous system (PNS). Neurodegenerative disease typically involves reductions in the mass and volume of the human brain, which may be due to the atrophy and/or death of brain cells, which are far more profound than those in a healthy person that are attributable to aging. Neurodegenerative diseases can evolve gradually, after a long period of normal brain function, due to progressive degeneration (e.g., nerve cell dysfunction and death) of specific brain regions. Alternatively, neurodegenerative diseases can have a quick onset, such as those associated with trauma or toxins. The actual onset of brain degeneration may precede clinical expression by many years. Examples of neurodegenerative diseases include, but are not limited to, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), diffuse Lewy body disease, chorea-acanthocytosis, primary lateral sclerosis, ocular diseases (ocular neuritis), chemotherapy-induced neuropathies (e.g., from vincristine, paclitaxel, bortezomib), Creutzfeldt-Jakob disease, retinitis pigmentosa, diabetes-induced neuropathies, cerebellar degeneration and Friedreich's ataxia. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used to treat these disorders and others as described below.

[00242] In another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used to treat or prevent any disease or disorder involving axonopathy. Distal

axonopathy is a type of peripheral neuropathy that results from some metabolic or toxic derangement of peripheral nervous system (PNS) neurons. It is the most common response of nerves to metabolic or toxic disturbances, and as such may be caused by metabolic diseases such as diabetes, renal failure, deficiency syndromes such as malnutrition and alcoholism, or the effects of toxins or drugs.

5 [00243] In an exemplary embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used to treat or prevent multiple sclerosis (MS), including relapsing MS and monosymptomatic MS, and other demyelinating conditions, such as, for example, chronic inflammatory demyelinating polyneuropathy (CIDP), or symptoms associated therewith.

10 [00244] In yet another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used to treat trauma to the nerves, including, trauma due to disease, injury (including surgical intervention), or environmental trauma (e.g., neurotoxins, alcoholism, etc.). They may also be useful to prevent, treat, and alleviate symptoms of various PNS disorders, such as: Leprosy, Charcot-Marie-Tooth disease, Guillain-Barre syndrome, Brachial Plexus Neuropathies.

15 [00245] In another embodiment, a sirtuin activating compound may be used to treat or prevent chemotherapeutic induced neuropathy. Chemotherapy drugs can damage any part of the nervous system. The sirtuin modulating compounds may be administered prior to administration of the chemotherapeutic agent, concurrently with administration of the chemotherapeutic drug, and/or after initiation of administration of the chemotherapeutic drug. If the sirtuin activating compound is administered after the initiation of administration of the chemotherapeutic drug, it is desirable that the sirtuin activating compound be
20 administered prior to, or at the first signs, of chemotherapeutic induced neuropathy.

[00246] The chemotherapy drugs which are most commonly associated with neuropathy, are the Vinca alkaloids (anti-cancer drugs originally derived from a member of the periwinkle--the Vinca plant genus) and a platinum-containing drug called Cisplatin. The Vinca alkaloids include the drugs vinblastine, vincristine and vindesine. Many combination chemotherapy treatments for lymphoma for example
25 CHOP and CVP contain vincristine, which is the drug known to cause this problem most frequently. Indeed, it is the risk of neuropathy that limits the dose of vincristine that can be administered.

[00247] In another embodiment, a sirtuin activating compound may be used to treat or prevent a polyglutamine disease. There are a number of disorders whose pathologies have been attributed, at least in part, to polyglutamine-based aggregation. These disorders include, for example, Huntington's disease,
30 Spinalbulbar Muscular Atrophy (SBMA or Kennedy's Disease), Dentatorubropallidoluysian Atrophy (DRPLA), Spinocerebellar Ataxia 1 (SCA1), Spinocerebellar Ataxia 2 (SCA2), Machado-Joseph Disease (MJD; SCA3), Spinocerebellar Ataxia 6 (SCA6), Spinocerebellar Ataxia 7 (SCA7), and Spinocerebellar Ataxia 12 (SCA12). A variety of cell free assays, cell based assays, and organismal assays are available for evaluating polyglutamine aggregation, e.g., Huntingtin polyglutamine
35 aggregation.

[00248] Many transcription factors have also been found in neuronal inclusions in different diseases. It is possible that these transcription factors interact with the polyglutamine-containing proteins and then become trapped in the neuronal inclusions. This in turn might keep the transcription factors from turning genes on and off as needed by the cell. Another observation is hypoacetylation of histones in
40 affected cells. This has led to the hypothesis that Class I/II Histone Deacetylase (HDAC I/II) inhibitors,

which are known to increase histone acetylation, may be a novel therapy for polyglutamine diseases (U.S. patent application Ser. No. 10/476,627; "Method of treating neurodegenerative, psychiatric, and other disorders with deacetylase inhibitors").

[00249] In yet another embodiment, the invention provides a method for treating or preventing neuropathy

related to ischemic injuries or diseases, such as, for example, coronary heart disease (including congestive heart failure and myocardial infarctions), stroke, emphysema, hemorrhagic shock, peripheral vascular disease (upper and lower extremities) and transplant related injuries.

[00250] In certain embodiments, the invention provides a method to treat a central nervous system cell to prevent damage in response to a decrease in blood flow to the cell.

[00251] Another aspect encompasses administering a sirtuin activating compound to a subject to treat a central nervous system ischemic condition. A number of central nervous system ischemic conditions may be treated by the sirtuin activating compounds described herein. In one embodiment, the ischemic condition is a stroke that results in any type of ischemic central nervous system damage, such as apoptotic or necrotic cell death, cytotoxic edema or central nervous system tissue anoxia.

[00252] In another embodiment, the ischemic condition may result from a disorder that occurs in a part of the subject's body outside of the central nervous system, but yet still causes a reduction in blood flow to the central nervous system. These disorders may include, but are not limited to a peripheral vascular disorder, a venous thrombosis, a pulmonary embolus, arrhythmia (e.g. atrial fibrillation), a myocardial infarction, a transient ischemic attack, unstable angina, or sickle cell anemia. Moreover, the central nervous system ischemic condition may occur as result of the subject undergoing a surgical procedure.

[00253] In one embodiment, the ischemic condition results from a vaso-occlusion. The vaso-occlusion may be any type of occlusion, but is typically a cerebral thrombosis or an embolism. In a further embodiment, the ischemic condition may result from a hemorrhage. The hemorrhage may be any type of hemorrhage, but is generally a cerebral hemorrhage or a subarachnoid hemorrhage. In still another embodiment, the ischemic condition may result from the narrowing of a vessel. Generally speaking, the vessel may narrow as a result of a vasoconstriction such as occurs during vasospasms, or due to arteriosclerosis. In yet another embodiment, the ischemic condition results from an injury to the brain or spinal cord.

[00254] In yet another aspect, a sirtuin activating compound may be administered to reduce infarct size of the ischemic core following a central nervous system ischemic condition. Moreover, a sirtuin activating compound may also be beneficially administered to reduce the size of the ischemic penumbra or transitional zone following a central nervous system ischemic condition.

[00255] In one embodiment, a combination drug regimen may include drugs or compounds for the treatment or prevention of neurodegenerative disorders or secondary conditions associated with these conditions.

Thus, a combination drug regimen may include one or more sirtuin activators and one or more anti-neurodegeneration agents. For example, one or more sirtuin-activating compounds can be combined with an effective amount of one or more of: L-DOPA; a dopamine agonist; an adenosine A_{2A} receptor antagonist; a COMT inhibitor; a MAO inhibitor; an N-NOS inhibitor; a sodium channel antagonist; a selective N-methyl D-aspartate (NMDA) receptor antagonist or modulator; an AMPA/kainate receptor antagonist; a calcium channel antagonist; a potassium channel opener; a GABA-A receptor agonist; an

acetyl-cholinesterase inhibitor; a matrix metalloprotease inhibitor; a PARP inhibitor; an inhibitor of p38 MAP kinase or c-jun-N-terminal kinases; TPA; NDA antagonists; beta-interferons; growth factors; glutamate inhibitors; and/or as part of a cell therapy.

[00256] In an exemplary embodiment, a combination therapy for treating or preventing MS comprises a therapeutically effective amount of one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein and one or more of Avonex® (interferon beta-1a), Tysabri® (natalizumab), or Fumaderm® (BG-12/Oral Fumarate).

[00257] In another embodiment, a combination therapy for treating or preventing diabetic neuropathy or conditions associated therewith comprises a therapeutically effective amount of one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein and one or more of tricyclic antidepressants (TCAs) (including, for example, imipramine, amitriptyline, desipramine and nortriptyline), serotonin reuptake inhibitors (SSRIs) (including, for example, fluoxetine, paroxetine, sertralene, and citalopram) and antiepileptic drugs (AEDs) (including, for example, gabapentin, carbamazepine, and topiramate).

[00258] In another embodiment, the invention provides a method for treating or preventing a polyglutamine disease using a combination comprising at least one sirtuin activating compound and at least one HDAC I/II inhibitor. Examples of HDAC I/II inhibitors include hydroxamic acids, cyclic peptides, benzamides, short-chain fatty acids, and depudecin.

Weight Control

[00259] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for treating or preventing weight gain or obesity in a subject. For example, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used, for example, to treat or prevent hereditary obesity, dietary obesity, hormone related obesity, obesity related to the administration of medication, to reduce the weight of a subject, or to reduce or prevent weight gain in a subject. A subject in need of such a treatment may be a subject who is obese, likely to become obese, overweight, or likely to become overweight. Subjects who are likely to become obese or overweight can be identified, for example, based on family history, genetics, diet, activity level, medication intake, or various combinations thereof.

[00260] In yet other embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered to subjects suffering from a variety of other diseases and conditions that may be treated or prevented by promoting weight loss in the subject. Such diseases include, for example, high blood pressure, hypertension, high blood cholesterol, dyslipidemia, type 2 diabetes, insulin resistance, glucose intolerance, hyperinsulinemia, coronary heart disease, angina pectoris, congestive heart failure, stroke, gallstones, cholecystitis and cholelithiasis, gout, osteoarthritis, obstructive sleep apnea and respiratory problems, some types of cancer (such as endometrial, breast, prostate, and colon), complications of pregnancy, poor female reproductive health (such as menstrual irregularities, infertility, irregular ovulation), bladder control problems (such as stress incontinence); uric acid nephrolithiasis; psychological disorders (such as depression, eating disorders, distorted body image, and low self esteem).

[00261] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for inhibiting adipogenesis or fat cell differentiation, whether in vitro or in vivo. In particular, high circulating levels of insulin and/or insulin like growth factor (IGF) 1 will be prevented from recruiting preadipocytes to differentiate into adipocytes. Such methods may be used for treating or preventing obesity.

[00262] In other embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for reducing appetite and/or increasing satiety, thereby causing weight loss or avoidance of weight gain. A subject in need of such a treatment may be a subject who is overweight, obese or a subject likely to become overweight or obese. The method may comprise administering daily or, every other day, or once a week, a dose, e.g., in the form of a pill, to a subject. The dose may be an "appetite reducing dose."

[00263] In other embodiments, a sirtuin-modulating compound that decreases the level and/or activity of a sirtuin protein may be used to stimulate appetite and/or weight gain. A method may comprise administering to a subject, such as a subject in need thereof, a pharmaceutically effective amount of a sirtuin-modulating agent that decreases the level and/or activity of a sirtuin protein, such as SIRT1 and/or SIRT3. A subject in need of such a treatment may be a subject who has cachexia or may be likely to develop cachexia. A combination of agents may also be administered. A method may further comprise monitoring in the subject the state of the disease or of activation of sirtuins, for example, in adipose tissue.

[00264] Methods for stimulating fat accumulation in cells may be used in vitro, to establish cell models of weight gain, which may be used, e.g., for identifying other drugs that prevent weight gain.

[00265] Also provided are methods for modulating adipogenesis or fat cell differentiation, whether in vitro or in vivo. In particular, high circulating levels of insulin and/or insulin like growth factor (IGF) 1 will be prevented from recruiting preadipocytes to differentiate into adipocytes. Such methods may be used to modulate obesity. A method for stimulating adipogenesis may comprise contacting a cell with a sirtuin-modulating agent that decreases the level and/or activity of a sirtuin protein.

[00266] In another embodiment, the invention provides methods of decreasing fat or lipid metabolism in a subject by administering a sirtuin-modulating compound that decreases the level and/or activity of a sirtuin protein. The method includes administering to a subject an amount of a sirtuin-modulating compound, e.g., in an amount effective to decrease mobilization of fat to the blood from WAT cells and/or to decrease fat burning by BAT cells.

[00267] Methods for promoting appetite and/or weight gain may include, for example, prior identifying a subject as being in need of decreased fat or lipid metabolism, e.g., by weighing the subject, determining the BMI of the subject, or evaluating fat content of the subject or sirtuin activity in cells of the subject. The method may also include monitoring the subject, e.g., during and/or after administration of a sirtuin-modulating compound. The administering can include one or more dosages, e.g., delivered in boluses or continuously. Monitoring can include evaluating a hormone or a metabolite. Exemplary hormones include leptin, adiponectin, resistin, and insulin. Exemplary metabolites include triglycerides, cholesterol, and fatty acids.

[00268] In one embodiment, a sirtuin-modulating compound that decreases the level and/or activity of a sirtuin protein may be used to modulate (e.g., increase) the amount of subcutaneous fat in a tissue, e.g., in facial tissue or in other surface-associated tissue of the neck, hand, leg, or lips. The sirtuin-modulating compound may be used to increase the rigidity, water retention, or support properties of the tissue. For example, the sirtuin-modulating compound can be applied topically, e.g., in association with another agent, e.g., for surface-associated tissue treatment. The sirtuin-modulating compound may also be injected subcutaneously, e.g., within the region where an alteration in subcutaneous fat is desired.

[00269] A method for modulating weight may further comprise monitoring the weight of the subject and/or the level of modulation of sirtuins, for example, in adipose tissue.

[00270] In an exemplary embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as a combination therapy for treating or preventing weight gain or obesity. For example, one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered in combination with one or more anti-obesity agents.

Exemplary anti-obesity agents include, for example, phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A agonist, a monoamine reuptake inhibitor (such as sibutramine), a sympathomimetic agent, a serotonergic agent (such as dexfenfluramine or fenfluramine), a dopamine agonist (such as bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, the OB protein (leptin), a leptin analog, a leptin receptor agonist, a galanin antagonist or a GI lipase inhibitor or decreaser (such as orlistat). Other anorectic agents include bombesin agonists, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the glucagon-like peptide-1 receptor such as Exendin and ciliary neurotrophic factors such as Axokine.

[00271] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered to reduce drug-induced weight gain. For example, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered as a combination therapy with medications that may stimulate appetite or cause weight gain, in particular, weight gain due to factors other than water retention. Examples of medications that may cause weight gain, include for example, diabetes treatments, including, for example, sulfonylureas (such as glipizide and glyburide), thiazolidinediones (such as pioglitazone and rosiglitazone), meglitinides, nateglinide, repaglinide, sulphonylurea medicines, and insulin; anti-depressants, including, for example, tricyclic antidepressants (such as amitriptyline and imipramine), irreversible monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), bupropion, paroxetine, and mirtazapine; steroids, such as, for example, prednisone; hormone therapy; lithium carbonate; valproic acid; carbamazepine; chlorpromazine; thiothixene; beta blockers (such as propranolol); alpha blockers (such as clonidine, prazosin and terazosin); and contraceptives including oral contraceptives (birth control pills) or other contraceptives containing estrogen and/or progesterone (Depo-Provera, Norplant, Ortho), testosterone or Megestrol. In another exemplary embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as part of a smoking cessation program to prevent weight gain or reduce weight already gained.

Metabolic Disorders/Diabetes

[00272] Insulin dependent diabetes mellitus (Type 1 diabetes) is an autoimmune disease, where insulinitis leads to the destruction of pancreatic β -cells. At the time of clinical onset of type 1 diabetes mellitus, significant number of insulin producing β -cells are destroyed and only 15% to 40% are still capable of insulin production (McCulloch et al. (1991) Diabetes 40:673-679). β -cell failure results in a life long dependence on daily insulin injections and exposure to the acute and late complication of the disease.

[00273] Type 2 diabetes mellitus is a metabolic disease of impaired glucose homeostasis characterized by hyperglycemia, or high blood sugar, as a result of defective insulin action which manifests as insulin resistance, defective insulin secretion, or both. A patient with Type 2 diabetes mellitus has abnormal carbohydrate, lipid, and protein metabolism associated with insulin resistance and/or impaired insulin secretion. The disease leads to pancreatic beta cell destruction and eventually absolute insulin deficiency. Without insulin, high glucose levels remain in the blood. The long term effects of high blood glucose include blindness, renal failure, and poor blood circulation to these areas, which can lead to foot and ankle amputations. Early detection is critical in preventing patients from reaching this severity. The majority of patients with diabetes have the non-insulin dependent form of diabetes, currently referred to as Type 2 diabetes mellitus.

[00274] This disclosure also includes methods of treating disorders related to or resulting from diabetes, for example end organ damage, diabetic gastroparesis, diabetic neuropathy, cardiac dysrhythmia, etc.

[00275] The compounds described herein can be used to modulate a fat cell, e.g., an adipocyte, e.g., differentiation of the adipocyte. For example, a compound described herein can be administered in an amount effective to prevent fat accumulation in a normal or a pathological state. Disorders relating to adipocytes include obesity. In particular, obesity can lead to type II diabetes in successive phases. Clinically, these phases can be characterized as normal glucose tolerance, impaired glucose tolerance, hyperinsulinemic diabetes, and hypoinsulinemic diabetes. Such a progressive impairment of glucose storage correlates with a rise in basal glycemia.

[00276] The compounds described herein can be used to treat or prevent other metabolic disorders too, e.g., a metabolic syndrome. Metabolic syndrome (e.g., Syndrome X) is characterized by a group of metabolic risk factors in one person. They include: central obesity (excessive fat tissue in and around the abdomen), atherogenic dyslipidemia (blood fat disorders--mainly high triglycerides and low HDL cholesterol--that foster plaque buildups in artery walls); insulin resistance or glucose intolerance (the body can't properly use insulin or blood sugar); prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor [-1] in the blood); raised blood pressure (i.e., hypertension) (130/85 mmHg or higher); and proinflammatory state (e.g., elevated high-sensitivity C-reactive protein in the blood). The underlying causes of this syndrome can include overweight/obesity, physical inactivity and genetic factors. People with metabolic syndrome are at increased risk of coronary heart disease, other diseases related to plaque buildups in artery walls (e.g., stroke and peripheral vascular disease) and type 2 diabetes. Metabolic syndrome is closely associated with a generalized metabolic disorder called insulin resistance, in which the body is unable to insulin efficiently.

[00277] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for treating or preventing a metabolic disorder, such as insulin-resistance, a pre-

diabetic state, type II diabetes, and/or complications thereof. Administration of a sirtuin-modulating compounds that increases the level and/or activity of a sirtuin protein may increase insulin sensitivity and/or decrease insulin levels in a subject. A subject in need of such a treatment may be a subject who has insulin resistance or other precursor symptom of type II diabetes, who has type II diabetes, or who is likely to develop any of these conditions. For example, the subject may be a subject having insulin resistance, e.g., having high circulating levels of insulin and/or associated conditions, such as hyperlipidemia, dyslipogenesis, hypercholesterolemia, impaired glucose tolerance, high blood glucose sugar level, other manifestations of syndrome X, hypertension, atherosclerosis and lipodystrophy.

In an exemplary embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as a combination therapy for treating or preventing a metabolic disorder. For example, one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered in combination with one or more anti-diabetic agents. Exemplary anti-diabetic agents include, for example, an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase I B inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a peroxisome proliferator-activated receptor- γ , (PPAR- γ) ligand such as troglitazone, rosiglitazone, pioglitazone or GW-1929, a sulfonylurea, glipazide, glyburide, or chlorpropamide wherein the amounts of the first and second compounds result in a therapeutic effect. Other anti-diabetic agents include a glucosidase inhibitor, a glucagon-like peptide-1 (GLP-1), insulin, a PPAR α/γ dual agonist, a meglitimide and an α P2 inhibitor. In an exemplary embodiment, an anti-diabetic agent may be a dipeptidyl peptidase IV (DP-IV or DPP-IV) inhibitor, such as, for example LAF237 from Novartis (NVP DPP728; 1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) or MK-04301 from Merck (see e.g., Hughes et al., Biochemistry 38: 11597-603 (1999)).

Inflammatory Diseases

[00278] In other aspects, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used to treat or prevent a disease or disorder associated with inflammation. Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered prior to the onset of, at, or after the initiation of inflammation. When used prophylactically, the compounds are preferably provided in advance of any inflammatory response or symptom. Administration of the compounds may prevent or attenuate inflammatory responses or symptoms.

[00279] Exemplary inflammatory conditions include, for example, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, diabetes (e.g., insulin dependent diabetes mellitus or juvenile onset diabetes), menstrual cramps, cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, mucous colitis, ulcerative colitis, gastritis, esophagitis, pancreatitis, peritonitis, Alzheimer's disease, shock, ankylosing spondylitis, gastritis, conjunctivitis, pancreatis (acute or chronic), multiple organ injury syndrome (e.g., secondary to septicemia or trauma), myocardial infarction, atherosclerosis, stroke, reperfusion injury (e.g., due to cardiopulmonary bypass or kidney dialysis), acute glomerulonephritis, vasculitis, thermal injury (i.e., sunburn), necrotizing enterocolitis, granulocyte transfusion associated syndrome, and/or Sjogren's syndrome. Exemplary inflammatory conditions of the skin include, for example, eczema, atopic

dermatitis, contact dermatitis, urticaria, scleroderma, psoriasis, and dermatosis with acute inflammatory components.

[00280] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to treat or prevent allergies and respiratory conditions, including asthma, bronchitis, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, and any chronic obstructive pulmonary disease (COPD). The compounds may be used to treat chronic hepatitis infection, including hepatitis B and hepatitis C.

[00281] Additionally, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to treat autoimmune diseases and/or inflammation associated with autoimmune diseases such as organ-tissue autoimmune diseases (e.g., Raynaud's syndrome), scleroderma, myasthenia gravis, transplant rejection, endotoxin shock, sepsis, psoriasis, eczema, dermatitis, multiple sclerosis, autoimmune thyroiditis, uveitis, systemic lupus erythematosus, Addison's disease, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), and Grave's disease.

[00282] In certain embodiments, one or more sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be taken alone or in combination with other compounds useful for treating or preventing inflammation. Exemplary anti-inflammatory agents include, for example, steroids (e.g., cortisol, cortisone, fludrocortisone, prednisone, 6a-methylprednisone, triamcinolone, betamethasone or dexamethasone), nonsteroidal antiinflammatory drugs (NSAIDS (e.g., aspirin, acetaminophen, tolmetin, ibuprofen, mefenamic acid, piroxicam, nabumetone, rofecoxib, celecoxib, etodolac or nimesulide). In another embodiment, the other therapeutic agent is an antibiotic (e.g., vancomycin, penicillin, amoxicillin, ampicillin, cefotaxime, ceftriaxone, cefixime, rifampin, metronidazole, doxycycline or streptomycin). In another embodiment, the other therapeutic agent is a PDE4 inhibitor (e.g., roflumilast or rolipram). In another embodiment, the other therapeutic agent is an antihistamine (e.g., cyclizine, hydroxyzine, promethazine or diphenhydramine). In another embodiment, the other therapeutic agent is an anti-malarial (e.g., artemisinin, artemether, artesunate, chloroquine phosphate, mefloquine hydrochloride, doxycycline hyclate, proguanil hydrochloride, atovaquone or halofantrine). In one embodiment, the other therapeutic agent is drotrecogin alfa.

[00283] In an exemplary embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered with a selective COX-2 inhibitor for treating or preventing inflammation. Exemplary selective COX-2 inhibitors include, for example, deracoxib, parecoxib, celecoxib, valdecoxib, rofecoxib, etoricoxib, lumiracoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, tert-butyl 1-benzyl-4-[(4-oxopiperidin-1-yl)sulfonyl]piperidine-4-carboxylate, 4-[5-(phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, salts and prodrugs thereof.

Flushing

[00284] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for reducing the incidence or severity of flushing and/or hot flashes which are symptoms of a disorder. For instance, the subject method includes the use of sirtuin-modulating

compounds that increase the level and/or activity of a sirtuin protein, alone or in combination with other agents, for reducing incidence or severity of flushing and/or hot flashes in cancer patients. In other embodiments, the method provides for the use of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein to reduce the incidence or severity of flushing and/or hot flashes in menopausal and post-menopausal woman.

[00285] In another aspect, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used as a therapy for reducing the incidence or severity of flushing and/or hot flashes which are side-effects of another drug therapy, e.g., drug-induced flushing. In certain embodiments, a method for treating and/or preventing drug-induced flushing comprises administering to a patient in need thereof a formulation comprising at least one flushing inducing compound and at least one sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein. In other embodiments, a method for treating drug induced flushing comprises separately administering one or more compounds that induce flushing and one or more sirtuin-modulating compounds, e.g., wherein the sirtuin-modulating compound and flushing inducing agent have not been formulated in the same compositions. When using separate formulations, the sirtuin-modulating compound may be administered (1) at the same as administration of the flushing inducing agent, (2) intermittently with the flushing inducing agent, (3) staggered relative to administration of the flushing inducing agent, (4) prior to administration of the flushing inducing agent, (5) subsequent to administration of the flushing inducing agent, and (6) various combination thereof. Exemplary flushing inducing agents include, for example, niacin, faloixifene, antidepressants, anti-psychotics, chemotherapeutics, calcium channel blockers, and antibiotics.

[00286] In one embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to reduce flushing side effects of a vasodilator or an antilipemic agent (including anticholesteremic agents and lipotropic agents). In an exemplary embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be used to reduce flushing associated with the administration of niacin.

[00287] In another representative embodiment, the method involves the use of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein to reduce flushing side effects of raloxifene. Raloxifene acts like estrogen in certain places in the body, but is not a hormone. It helps prevent osteoporosis in women who have reached menopause. A common side effect of raloxifene is hot flashes (sweating and flushing).

[00288] In another representative embodiment, the method involves the use of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein to reduce flushing side effects of antidepressants or anti-psychotic agent. For instance, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used in conjunction (administered separately or together) with a serotonin reuptake inhibitor, a 5HT2 receptor antagonist, an anticonvulsant, a norepinephrine reuptake inhibitor, an α -adrenoreceptor antagonist, an NK-3 antagonist, an NK-1 receptor antagonist, a PDE4 inhibitor, an Neuropeptide Y5 Receptor Antagonists, a D4 receptor antagonist, a 5HT1A receptor antagonist, a 5HT1D receptor antagonist, a CRF antagonist, a monoamine oxidase inhibitor, or a sedative-hypnotic drug.

[00289] In certain embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used as part of a treatment with a serotonin reuptake inhibitor (SRI) to reduce flushing. In certain preferred embodiments, the SRI is a selective serotonin reuptake inhibitor (SSRI), such as a fluoxetine (fluoxetine, norfluoxetine) or a nefazodonoid (nefazodone, hydroxynefazodone, oxonefazodone).

[00290] In still another representative embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to reduce flushing side effects of chemotherapeutic agents, such as cyclophosphamide, tamoxifen.

[00291] In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to reduce flushing side effects of calcium channel blockers, such as amlodipine.

In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used to reduce flushing side effects of antibiotics. For example, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be used in combination with levofloxacin.

Ocular Disorders

[00292] One aspect of the present invention is a method for inhibiting, reducing or otherwise treating vision impairment by administering to a patient a therapeutic dosage of sirtuin modulator selected from a compound disclosed herein, or a pharmaceutically acceptable salt, prodrug or a metabolic derivative thereof.

[00293] In certain aspects of the invention, the vision impairment is caused by damage to the optic nerve or central nervous system. In particular embodiments, optic nerve damage is caused by high intraocular pressure, such as that created by glaucoma. In other particular embodiments, optic nerve damage is caused by swelling of the nerve, which is often associated with an infection or an immune (e.g., autoimmune) response such as in optic neuritis.

[00294] Glaucoma describes a group of disorders which are associated with a visual field defect, cupping of the optic disc, and optic nerve damage. These are commonly referred to as glaucomatous optic neuropathies. Most glaucomas are usually, but not always, associated with a rise in intraocular pressure. Exemplary forms of glaucoma include Glaucoma and Penetrating Keratoplasty, Acute Angle Closure, Chronic Angle Closure, Chronic Open Angle, Angle Recession, Aphakic and Pseudophakic, Drug-Induced, Hyphema, Intraocular Tumors, Juvenile, Lens-Particle, Low Tension, Malignant, Neovascular, Phacolytic, Phacomorphic, Pigmentary, Plateau Iris, Primary Congenital, Primary Open Angle, Pseudoexfoliation, Secondary Congenital, Adult Suspect, Unilateral, Uveitic, Ocular Hypertension, Ocular Hypotony, Posner-Schlossman Syndrome and Scleral Expansion Procedure in Ocular Hypertension & Primary Open-angle Glaucoma.

[00295] Optic neuritis (ON) is inflammation of the optic nerve and causes acute loss of vision. It is highly associated with multiple sclerosis (MS) as 15-25% of MS patients initially present with ON, and 50-75% of ON patients are diagnosed with MS. ON is also associated with infection (e.g., viral infection, meningitis, syphilis), inflammation (e.g., from a vaccine), infiltration and ischemia.

[00296] Another condition leading to optic nerve damage is anterior ischemic optic neuropathy (AION). There are two types of AION. Arteritic AION is due to giant cell arteritis (vasculitis) and leads to acute vision loss. Non-arteritic AION encompasses all cases of ischemic optic neuropathy other than those due to

giant cell arteritis. The pathophysiology of AION is unclear although it appears to incorporate both inflammatory and ischemic mechanisms.

[00297] Other damage to the optic nerve is typically associated with demyelination, inflammation, ischemia, toxins, or trauma to the optic nerve. Exemplary conditions where the optic nerve is damaged include Demyelinating Optic Neuropathy (Optic Neuritis, Retrobulbar Optic Neuritis), Optic Nerve Sheath Meningioma, Adult Optic Neuritis, Childhood Optic Neuritis, Anterior Ischemic Optic Neuropathy, Posterior Ischemic Optic Neuropathy, Compressive Optic Neuropathy, Papilledema, Pseudopapilledema and Toxic/Nutritional Optic Neuropathy.

[00298] Other neurological conditions associated with vision loss, albeit not directly associated with damage to the optic nerve, include Amblyopia, Bells Palsy, Chronic Progressive External Ophthalmoplegia, Multiple Sclerosis, Pseudotumor Cerebri and Trigeminal Neuralgia.

[00299] In certain aspects of the invention, the vision impairment is caused by retinal damage. In particular embodiments, retinal damage is caused by disturbances in blood flow to the eye (e.g., arteriosclerosis, vasculitis). In particular embodiments, retinal damage is caused by disruption of the macula (e.g., exudative or non-exudative macular degeneration).

[00300] Other exemplary diseases include ocular bacterial infections (e.g. conjunctivitis, keratitis, tuberculosis, syphilis, gonorrhea), viral infections (e.g. Ocular Herpes Simplex Virus, Varicella Zoster Virus, Cytomegalovirus retinitis, Human Immunodeficiency Virus (HIV)) as well as progressive outer retinal necrosis secondary to HIV or other HIV-associated and other immunodeficiency-associated ocular diseases. In addition, ocular diseases include fungal infections (e.g. Candida choroiditis, histoplasmosis), protozoal infections (e.g. toxoplasmosis) and others such as ocular toxocariasis and sarcoidosis.

[00301] One aspect of the invention is a method for inhibiting, reducing or treating vision impairment in a subject undergoing treatment with a chemotherapeutic drug (e.g., a neurotoxic drug, a drug that raises intraocular pressure such as a steroid), by administering to the subject in need of such treatment a therapeutic dosage of a sirtuin modulator disclosed herein.

[00302] Another aspect of the invention is a method for inhibiting, reducing or treating vision impairment in a subject undergoing surgery, including ocular or other surgeries performed in the prone position such as spinal cord surgery, by administering to the subject in need of such treatment a therapeutic dosage of a sirtuin modulator disclosed herein. Ocular surgeries include cataract, iridotomy and lens replacements. Another aspect of the invention is the treatment, including inhibition and prophylactic treatment, of age related ocular diseases include cataracts, dry eye, retinal damage and the like, by administering to the subject in need of such treatment a therapeutic dosage of a sirtuin modulator disclosed herein.

[00303] The macula is responsible for our acute central vision and composed of light-sensing cells (cones) while the underlying retinal pigment epithelium (RPE) and choroid nourish and help remove waste materials. The RPE nourishes the cones with the vitamin A substrate for the photosensitive pigments and digests the cones shed outer tips. RPE is exposed to high levels of UV radiation, and secretes factors that inhibit angiogenesis. The choroid contains a dense vascular network that provides nutrients and removes the waste materials.

[00304] Macular pigment, one of the protective factors that prevent sunlight from damaging the retina, is formed by the accumulation of nutritionally derived carotenoids, such as lutein, the fatty yellow pigment that serves as a delivery vehicle for other important nutrients and zeaxanthin. Antioxidants such as vitamins C and E, beta-carotene and lutein, as well as zinc, selenium and copper, are all found in the healthy macula. In addition to providing nourishment, these antioxidants protect against free radical damage that initiates macular degeneration.

[00305] Another aspect of the invention is the prevention or treatment of damage to the eye caused by stress, chemical insult or radiation, by administering to the subject in need of such treatment a therapeutic dosage of a sirtuin modulator disclosed herein. Radiation or electromagnetic damage to the eye can include that caused by CRT's or exposure to sunlight or UV.

[00306] In one embodiment, a combination drug regimen may include drugs or compounds for the treatment or prevention of ocular disorders or secondary conditions associated with these conditions. Thus, a combination drug regimen may include one or more sirtuin activators and one or more therapeutic agents for the treatment of an ocular disorder. For example, one or more sirtuin-activating compounds can be combined with an effective amount of one or more of: an agent that reduces intraocular pressure, an agent for treating glaucoma, an agent for treating optic neuritis, an agent for treating CMV Retinopathy, an agent for treating multiple sclerosis, and/or an antibiotic, etc.

[00307] In one embodiment, a sirtuin modulator can be administered in conjunction with a therapy for reducing intraocular pressure. One group of therapies involves blocking aqueous production. A second group of therapies for reducing intraocular pressure involve reducing vitreous volume. A third group of therapies involve facilitating aqueous outflow from the eye.

[00308] Exemplary therapeutic agents for reducing intraocular pressure include ALPHAGAN® P (Allergan) (brimonidine tartrate ophthalmic solution), AZOPT® (Alcon) (brinzolamide ophthalmic suspension), BETAGAN® (Allergan) (levobunolol hydrochloride ophthalmic solution, USP), BETIMOL® (Vistakon) (timolol ophthalmic solution), BETOPTIC S® (Alcon) (betaxolol HCl), BRIMONIDINE TARTRATE (Bausch & Lomb), CARTEOLOL HYDROCHLORIDE (Bausch & Lomb), COSOPT® (Merck) (dorzolamide hydrochloride-timolol maleate ophthalmic solution), LUMIGAN® (Allergan) (bimatoprost ophthalmic solution), OPTIPRANOLOL® (Bausch & Lomb) (metipranolol ophthalmic solution), TIMOLOL GFS (Falcon) (timolol maleate ophthalmic gel forming solution), TIMOPTIC® (Merck) (timolol maleate ophthalmic solution), TRAVATAN® (Alcon) (travoprost ophthalmic solution), TRUSOPT® (Merck) (dorzolamide hydrochloride ophthalmic solution) and XALATAN® (Pharmacia & Upjohn) (latanoprost ophthalmic solution).

[00309] In one embodiment, a sirtuin modulator can be administered in conjunction with a therapy for treating and/or preventing glaucoma. An example of a glaucoma drug is DARANIDE®.

[00310] In one embodiment, a sirtuin modulator can be administered in conjunction with a therapy for treating and/or preventing optic neuritis. Examples of drugs for optic neuritis include DECADRON® Phosphate Injection (Merck) (Dexamethasone Sodium Phosphate), DEPO-MEDROL® (Pharmacia & Upjohn)(methylprednisolone acetate), HYDROCORTONE® Tablets (Merck) (Hydrocortisone), ORAPRED® (Biomarin) (prednisolone sodium phosphate oral solution) and PEDIAPRED® (Celltech) (prednisolone sodium phosphate, USP).

[00311] In one embodiment, a sirtuin modulator can be administered in conjunction with a therapy for treating and/or preventing CMV Retinopathy. Treatments for CMV retinopathy include CYTOVENE® (ganciclovir capsules) and VALCYTE® (Roche Laboratories) (valganciclovir hydrochloride tablets).

[00312] In one embodiment, a sirtuin modulator can be administered in conjunction with a therapy for treating and/or preventing multiple sclerosis. Examples of such drugs include DANTRIUM® (Procter & Gamble Pharmaceuticals) (dantrolene sodium), NOVANTRONE® (Serono) (mitoxantrone), AVONEX® (Biogen Idec) (Interferon beta-1a), BETASERON® (Berlex) (Interferon beta-1b), COPAXONE® (Teva Neuroscience) (glatiramer acetate injection) and REBIF® (Pfizer) (interferon beta-1a).

[00313] In addition, macrolide and/or mycophenolic acid, which has multiple activities, can be co-administered with a sirtuin modulator. Macrolide antibiotics include tacrolimus, cyclosporine, sirolimus, everolimus, ascomycin, erythromycin, azithromycin, clarithromycin, clindamycin, lincomycin, dirithromycin, josamycin, spiramycin, diacetyl-midecamycin, tylosin, roxithromycin, ABT-773, telithromycin, leucomycins, and lincosamide.

Mitochondrial-Associated Diseases and Disorders

[00314] In certain embodiments, the invention provides methods for treating diseases or disorders that would benefit from increased mitochondrial activity. The methods involve administering to a subject in need thereof a therapeutically effective amount of a sirtuin activating compound. Increased mitochondrial activity refers to increasing activity of the mitochondria while maintaining the overall numbers of mitochondria (e.g., mitochondrial mass), increasing the numbers of mitochondria thereby increasing mitochondrial activity (e.g., by stimulating mitochondrial biogenesis), or combinations thereof. In certain embodiments, diseases and disorders that would benefit from increased mitochondrial activity include diseases or disorders associated with mitochondrial dysfunction.

[00315] In certain embodiments, methods for treating diseases or disorders that would benefit from increased mitochondrial activity may comprise identifying a subject suffering from a mitochondrial dysfunction. Methods for diagnosing a mitochondrial dysfunction may involve molecular genetic, pathologic and/or biochemical analysis are summarized in Cohen and Gold, Cleveland Clinic Journal of Medicine, 68: 625-642 (2001). One method for diagnosing a mitochondrial dysfunction is the Thor-Byrne-ier scale (see e.g., Cohen and Gold, supra; Collin S. et al., Eur Neurol. 36: 260-267 (1996)). Other methods for determining mitochondrial number and function include, for example, enzymatic assays (e.g., a mitochondrial enzyme or an ATP biosynthesis factor such as an ETC enzyme or a Krebs cycle enzyme), determination of mitochondrial mass, mitochondrial volume, and/or mitochondrial number, quantification of mitochondrial DNA, monitoring intracellular calcium homeostasis and/or cellular responses to perturbations of this homeostasis, evaluation of response to an apoptogenic stimulus, determination of free radical production.

[00316] Diseases and disorders associated with mitochondrial dysfunction include diseases and disorders in which deficits in mitochondrial respiratory chain activity contribute to the development of pathophysiology of such diseases or disorders in a mammal. This includes 1) congenital genetic deficiencies in activity of one or more components of the mitochondrial respiratory chain; and 2) acquired deficiencies in the activity of one or more components of the mitochondrial respiratory chain,

wherein such deficiencies are caused by a) oxidative damage during aging; b) elevated intracellular calcium; c) exposure of affected cells to nitric oxide; d) hypoxia or ischemia; e) microtubule-associated deficits in axonal transport of mitochondria, or f) expression of mitochondrial uncoupling proteins.

[00317] Diseases or disorders that would-benefit from increased mitochondrial activity generally include for example, diseases in which free radical mediated oxidative injury leads to tissue degeneration, diseases in which cells inappropriately undergo apoptosis, and diseases in which cells fail to undergo apoptosis. Exemplary diseases or disorders that would benefit from increased mitochondrial activity include, for example, AD (Alzheimer's Disease), ADPD (Alzheimer's Disease and Parkinson's Disease), AMDF (Ataxia, Myoclonus and Deafness), auto-immune disease, cancer, CIPO (Chronic Intestinal Pseudoobstruction with myopathy and Ophthalmoplegia), congenital muscular dystrophy, CPEO (Chronic Progressive External Ophthalmoplegia), DEAF (Maternally inherited DEAFness or aminoglycoside-induced DEAFness), DEMCHO (Dementia and Chorea), diabetes mellitus (Type I or Type II), DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness), DMDF (Diabetes Mellitus and Deafness), dystonia, Exercise Intolerance, ESOC (Epilepsy, Strokes, Optic atrophy, and Cognitive decline), FBSN (Familial Bilateral Striatal Necrosis), FICP (Fatal Infantile Cardiomyopathy Plus, a MELAS-associated cardiomyopathy), GER (Gastrointestinal Reflux), HD (Huntington's Disease), KSS (Kearns Sayre Syndrome), "later-onset" myopathy, LDYT (Leber's hereditary optic neuropathy and DYsTonias), Leigh's Syndrome, LHON (Leber Hereditary Optic Neuropathy), L IMM (Lethal Infantile Mitochondrial Myopathy), MDM (Myopathy and Diabetes Mellitus), MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes), MEPR (Myoclonic Epilepsy and Psychomotor Regression), MERME (MERRF/MELAS overlap disease), MERRF (Myoclonic Epilepsy and Ragged Red Muscle Fibers), MHCM (Maternally Inherited Hypertrophic CardioMyopathy), MICM (Maternally Inherited Cardiomyopathy), MILS (Maternally Inherited Leigh Syndrome), Mitochondrial Encephalocardiomyopathy, Mitochondrial Encephalomyopathy, MM (Mitochondrial Myopathy), MMC (Maternal Myopathy and Cardiomyopathy), MNGIE (Myopathy and external ophthalmoplegia, Neuropathy, Gastro-Intestinal, Encephalopathy), Multisystem Mitochondrial Disorder (myopathy, encephalopathy, blindness, hearing loss, peripheral neuropathy), NARP (Neurogenic muscle weakness, Ataxia, and Retinitis Pigmentosa; alternate phenotype at this locus is reported as Leigh Disease), PD (Parkinson's Disease), Pearson's Syndrome, PEM (Progressive Encephalopathy), PEO (Progressive External Ophthalmoplegia), PME (Progressive Myoclonus Epilepsy), PMPS (Pearson Marrow-Pancreas Syndrome), psoriasis, RTT (Rett Syndrome), schizophrenia, SIDS (Sudden Infant Death Syndrome), SNHL (Sensorineural Hearing Loss), Varied Familial Presentation (clinical manifestations range from spastic paraparesis to multisystem progressive disorder & fatal cardiomyopathy to truncal ataxia, dysarthria, severe hearing loss, mental regression, ptosis, ophthalmoparesis, distal cyclones, and diabetes mellitus), or Wolfram syndrome.

[00318] Other diseases and disorders that would benefit from increased mitochondrial activity include, for example, Friedreich's ataxia and other ataxias, amyotrophic lateral sclerosis (ALS) and other motor neuron diseases, macular degeneration, epilepsy, Alpers syndrome, Multiple mitochondrial DNA deletion syndrome, MtDNA depletion syndrome, Complex I deficiency, Complex II (SDH) deficiency,

Complex III deficiency, Cytochrome c oxidase (COX, Complex IV) deficiency, Complex V deficiency, Adenine Nucleotide Translocator (ANT) deficiency, Pyruvate dehydrogenase (PDH) deficiency, Ethylmalonic aciduria with lactic acidemia, 3-Methyl glutaconic aciduria with lactic acidemia, Refractory epilepsy with declines during infection, Asperger syndrome with declines during infection, Autism with declines during infection, Attention deficit hyperactivity disorder (ADHD), Cerebral palsy with declines during infection, Dyslexia with declines during infection, materially inherited thrombocytopenia and leukemia syndrome, MARIAHS syndrome (Mitochondrial ataxia, recurrent infections, aphasia, hypouricemia/hypomyelination, seizures, and dicarboxylic aciduria), ND6 dystonia, Cyclic vomiting syndrome with declines during infection, 3-Hydroxy isobutyric aciduria with lactic acidemia, Diabetes mellitus with lactic acidemia, Uridine responsive neurologic syndrome (URNS), Dilated cardiomyopathy, Splenic Lymphoma, and Renal Tubular Acidosis/Diabetes/Ataxia syndrome.

[00319] In other embodiments, the invention provides methods for treating a subject suffering from mitochondrial disorders arising from, but not limited to, post-traumatic head injury and cerebral edema, stroke (invention methods useful for preventing or preventing reperfusion injury), Lewy body dementia, hepatorenal syndrome, acute liver failure, NASH (non-alcoholic steatohepatitis), Anti-metastasis/prodifferentiation therapy of cancer, idiopathic congestive heart failure, atrial fibrillation (non-valvular), Wolff-Parkinson-White Syndrome, idiopathic heart block, prevention of reperfusion injury in acute myocardial infarctions, familial migraines, irritable bowel syndrome, secondary prevention of non-Q wave myocardial infarctions, Premenstrual syndrome, Prevention of renal failure in hepatorenal syndrome, anti-phospholipid antibody syndrome, eclampsia/pre-eclampsia, oopause infertility, ischemic heart disease/angina, and Shy-Drager and unclassified dysautonomia syndromes.

[00320] In still another embodiment, there are provided methods for the treatment of mitochondrial disorders associated with pharmacological drug-related side effects. Types of pharmaceutical agents that are associated with mitochondrial disorders include reverse transcriptase inhibitors, protease inhibitors, inhibitors of DHOD, and the like. Examples of reverse transcriptase inhibitors include, for example, Azidothymidine (AZT), Stavudine (D4T), Zalcitabine (ddC), Didanosine (DDI), Fluoriodoauracil (FIAU), Lamivudine (3TC), Abacavir and the like. Examples of protease inhibitors include, for example, Ritonavir, Indinavir, Saquinavir, Nelfinavir and the like. Examples of inhibitors of dihydroorotate dehydrogenase (DHOD) include, for example, Leflunomide, Brequinar, and the like.

[00321] Common symptoms of mitochondrial diseases include cardiomyopathy, muscle weakness and atrophy, developmental delays (involving motor, language, cognitive or executive function), ataxia, epilepsy, renal tubular acidosis, peripheral neuropathy, optic neuropathy, autonomic neuropathy, neurogenic bowel dysfunction, sensorineural deafness, neurogenic bladder dysfunction, dilating cardiomyopathy, migraine, hepatic failure, lactic acidemia, and diabetes mellitus.

[00322] In certain embodiments, the invention provides methods for treating a disease or disorder that would benefit from increased mitochondrial activity that involves administering to a subject in need thereof one or more sirtuin activating compounds in combination with another therapeutic agent such as, for example, an agent useful for treating mitochondrial dysfunction (such as antioxidants, vitamins, or respiratory chain cofactors), an agent useful for reducing a symptom associated with a disease or disorder involving mitochondrial dysfunction (such as, an anti-seizure agent, an agent useful for

alleviating neuropathic pain, an agent for treating cardiac dysfunction), a cardiovascular agent (as described further below), a chemotherapeutic agent (as described further below), or an anti-neurodegeneration agent (as described further below). In an exemplary embodiment, the invention provides methods for treating a disease or disorder that would benefit from increased mitochondrial activity that involves administering to a subject in need thereof one or more sirtuin activating compounds in combination with one or more of the following: coenzyme Q₁₀, L-carnitine, thiamine, riboflavin, niacinamide, folate, vitamin E, selenium, lipoic acid, or prednisone. Compositions comprising such combinations are also provided herein.

[00323] In exemplary embodiments, the invention provides methods for treating diseases or disorders that would benefit from increased mitochondrial activity by administering to a subject a therapeutically effective amount of a sirtuin activating disorders (e.g., Friedreich's Ataxia, muscular dystrophy, multiple sclerosis, etc.), disorders of neuronal instability (e.g., seizure disorders, migraine, etc.), developmental delay, neurodegenerative disorders (e.g., Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, etc.), ischemia, renal tubular acidosis, age-related neurodegeneration and cognitive decline, chemotherapy fatigue, age-related or chemotherapy-induced menopause or irregularities of menstrual cycling or ovulation, mitochondrial myopathies, mitochondrial damage (e.g., calcium accumulation, excitotoxicity, nitric oxide exposure, hypoxia, etc.), and mitochondrial deregulation.

[00324] Delays in neurological or neuropsychological development are often found in children with mitochondrial diseases. Disorders characterized by developmental delay include Rett's Syndrome, pervasive developmental delay (or PDD-NOS "pervasive developmental delay not otherwise specified" to distinguish it from specific subcategories like autism), autism, Asperger's Syndrome, and Attention Deficit/Hyperactivity Disorder (ADHD), which is becoming recognized as a delay or lag in development of neural circuitry underlying executive functions. In certain embodiments, sirtuin activating compounds may be useful for treating treating patients with neurodevelopmental delays (e.g., involving motor, language, executive function, and cognitive skills), or other delays or arrests of neurological and neuropsychological development in the nervous system and somatic development in non-neural tissues like muscle and endocrine glands.

[00325] The two most significant severe neurodegenerative diseases associated with aging, Alzheimer's Disease (AD) and Parkinson's Disease (PD), both involve mitochondrial dysfunction in their pathogenesis. Huntington's Disease also involves mitochondrial dysfunction in affected brain regions, with cooperative interactions of excitotoxic stimulation and mitochondrial dysfunction contributing to neuronal degeneration. In certain embodiments, sirtuin activating compounds may be useful for treating and attenuating progression of age-related neurodegenerative diseases including AD and PD.

[00326] One of the major genetic defects in patients with Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease) is mutation or deficiency in Copper-Zinc Superoxide Dismutase (SOD 1), an antioxidant enzyme. Mitochondria both produce and are primary targets for reactive oxygen species. Inefficient transfer of electrons to oxygen in mitochondria is the most significant physiological source of free radicals in mammalian systems. Deficiencies in antioxidants or antioxidant enzymes can result in or exacerbate mitochondrial degeneration. In certain embodiments, sirtuin activating compounds may be useful for treating ALS, for reversing or slowing the progression of clinical symptoms.

[00327] Oxygen deficiency results in both direct inhibition of mitochondrial respiratory chain activity by depriving cells of a terminal electron acceptor for Cytochrome c reoxidation at Complex IV, and indirectly, especially in the nervous system, via secondary post-anoxic excitotoxicity and nitric oxide formation. In conditions like cerebral anoxia, angina or sickle cell anemia crises, tissues are relatively hypoxic. In such cases, compounds that increase mitochondrial activity provide protection of affected tissues from deleterious effects of hypoxia, attenuate secondary delayed cell death, and accelerate recovery from hypoxic tissue stress and injury. In certain embodiments, sirtuin activating compounds may be useful for preventing delayed cell death (apoptosis in regions like the hippocampus or cortex occurring about 2 to 5 days after an episode of cerebral ischemia) after ischemic or hypoxic insult to the brain.

[00328] Acidosis due to renal dysfunction is often observed in patients with mitochondrial disease, whether the underlying respiratory chain dysfunction is congenital or induced by ischemia or cytotoxic agents like cisplatin. Renal tubular acidosis often requires administration of exogenous sodium bicarbonate to maintain blood and tissue pH. In certain embodiments, sirtuin activating compounds may be useful for treating renal tubular acidosis and other forms of renal dysfunction caused by mitochondrial respiratory chain deficits.

[00329] During normal aging, there is a progressive decline in mitochondrial respiratory chain function. Beginning about age 40, there is an exponential rise in accumulation of mitochondrial DNA defects in humans, and a concurrent decline in nuclear-regulated elements of mitochondrial respiratory activity. Many mitochondrial DNA lesions have a selection advantage during mitochondrial turnover, especially in postmitotic cells. Mitochondrial failure contributes to most degenerative diseases (especially neurodegeneration) that accompany aging. Congenital mitochondrial diseases often involve early-onset neurodegeneration similar in fundamental mechanism to disorders that occur during aging of people born with normal mitochondria. In certain embodiments, sirtuin activating compounds may be useful for treating or attenuating cognitive decline and other degenerative consequences of aging.

[00330] Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in cells subjected to oxidative stress or cancer chemotherapy agents like cisplatin due to both greater vulnerability and less efficient repair of mitochondrial DNA. Although mitochondrial DNA may be more sensitive to damage than nuclear DNA, it is relatively resistant, in some situations, to mutagenesis by chemical carcinogens. This is because mitochondria respond to some types of mitochondrial DNA damage by destroying their defective genomes rather than attempting to repair them. This results in global mitochondrial dysfunction for a period after cytotoxic chemotherapy. Clinical use of chemotherapy agents like cisplatin, mitomycin, and cytoxan is often accompanied by debilitating "chemotherapy fatigue", prolonged periods of weakness and exercise intolerance which may persist even after recovery from hematologic and gastrointestinal toxicities of such agents. In certain embodiments, sirtuin activating compounds may be useful for treatment and prevention of side effects of cancer chemotherapy related to mitochondrial dysfunction.

[00331] A crucial function of the ovary is to maintain integrity of the mitochondrial genome in oocytes, since mitochondria passed onto a fetus are all derived from those present in oocytes at the time of conception. Deletions in mitochondrial DNA become detectable around the age of menopause, and are also

associated with abnormal menstrual cycles. Since cells cannot directly detect and respond to defects in mitochondrial DNA, but can only detect secondary effects that affect the cytoplasm, like impaired respiration, redox status, or deficits in pyrimidine synthesis, such products of mitochondrial function participate as a signal for oocyte selection and follicular atresia, ultimately triggering menopause when maintenance of mitochondrial genomic fidelity and functional activity can no longer be guaranteed. This is analogous to apoptosis in cells with DNA damage, which undergo an active process of cellular suicide when genomic fidelity can no longer be achieved by repair processes. Women with mitochondrial cytopathies affecting the gonads often undergo premature menopause or display primary cycling abnormalities. Appropriate support of mitochondrial function or compensation for mitochondrial dysfunction therefore is useful for protecting against age-related or chemotherapy-induced menopause or irregularities of menstrual cycling or ovulation. In certain embodiments, sirtuin activating compounds may be useful for treating and preventing amenorrhea, irregular ovulation, menopause, or secondary consequences of menopause.

[00332] In certain embodiments, sirtuin modulating compounds may be useful for treatment mitochondrial myopathies. Mitochondrial myopathies range from mild, slowly progressive weakness of the extraocular muscles to severe, fatal infantile myopathies and multisystem encephalomyopathies. Some syndromes have been defined, with some overlap between them. Established syndromes affecting muscle include progressive external ophthalmoplegia, the Kearns-Sayre syndrome (with ophthalmoplegia, pigmentary retinopathy, cardiac conduction defects, cerebellar ataxia, and sensorineural deafness), the MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), the MERFF syndrome (myoclonic epilepsy and ragged red fibers), limb-girdle distribution weakness, and infantile myopathy (benign or severe and fatal). Muscle biopsy specimens stained with modified Gomori's trichrome stain show ragged red fibers due to excessive accumulation of mitochondria. Biochemical defects in substrate transport and utilization, the Krebs cycle, oxidative phosphorylation, or the respiratory chain are detectable. Numerous mitochondrial DNA point mutations and deletions have been described, transmitted in a maternal, nonmendelian inheritance pattern. Mutations in nuclear-encoded mitochondrial enzymes occur.

[00333] In certain embodiments, sirtuin activating compounds may be useful for treating patients suffering from toxic damage to mitochondria, such as, toxic damage due to calcium accumulation, excitotoxicity, nitric oxide exposure, drug induced toxic damage, or hypoxia.

[00334] In certain embodiments, sirtuin activating compounds may be useful for treating diseases or disorders associated with mitochondrial deregulation.

[00335] Transcription of mitochondrial DNA encoding respiratory chain components requires nuclear factors. In neuronal axons, mitochondria must shuttle back and forth to the nucleus in order to maintain respiratory chain activity. If axonal transport is impaired by hypoxia or by drugs like taxol which affect microtubule stability, mitochondria distant from the nucleus undergo loss of cytochrome oxidase activity. Accordingly, treatment with a sirtuin activating compound may be useful for promoting nuclear-mitochondrial interactions.

Mitochondria are the primary source of free radicals and reactive oxygen species, due to spillover from the mitochondrial respiratory chain, especially when defects in one or more respiratory chain components impairs

orderly transfer of electrons from metabolic intermediates to molecular oxygen. To reduce oxidative damage, cells can compensate by expressing mitochondrial uncoupling proteins (UCP), of which several have been identified. UCP-2 is transcribed in response to oxidative damage, inflammatory cytokines, or excess lipid loads, e.g. fatty liver and steatohepatitis. UCPs reduce spillover of reactive oxygen species from mitochondria by discharging proton gradients across the mitochondrial inner membrane, in effect wasting energy produced by metabolism and rendering cells vulnerable to energy stress as a trade-off for reduced oxidative injury.

Muscle Performance

[00336] In other embodiments, the invention provides methods for enhancing muscle performance by administering a therapeutically effective amount of a sirtuin activating compound. For example, sirtuin activating compounds may be useful for improving physical endurance (e.g., ability to perform a physical task such as exercise, physical labor, sports activities, etc.), inhibiting or retarding physical fatigues, enhancing blood oxygen levels, enhancing energy in healthy individuals, enhance working capacity and endurance, reducing muscle fatigue, reducing stress, enhancing cardiac and cardiovascular function, improving sexual ability, increasing muscle ATP levels, and/or reducing lactic acid in blood. In certain embodiments, the methods involve administering an amount of a sirtuin activating compound that increase mitochondrial activity, increase mitochondrial biogenesis, and/or increase mitochondrial mass. Aside from muscle performance during endurance exercise, free radicals and oxidative stress parameters are affected in pathophysiological states.

[00337] In certain embodiments, the invention provides novel dietary compositions comprising sirtuin modulators, a method for their preparation, and a method of using the compositions for improvement of sports performance. Accordingly, provided are therapeutic compositions, foods and beverages that have actions of improving physical endurance and/or inhibiting physical fatigues for those people involved in broadly-defined exercises including sports requiring endurance and labors requiring repeated muscle exertions. Such dietary compositions may additionally comprise electrolytes, caffeine, vitamins, carbohydrates, etc.

Autoimmune Diseases

[00338] It is well-known that apoptosis plays a role in AIDS pathogenesis in the immune system. However, HIV-1 also induces neurological disease. There are four main peripheral neuropathies associated with HIV, namely sensory neuropathy, AIDP/CIPD, drug-induced neuropathy and CMV-related.

[00339] The most common type of neuropathy associated with AIDS is distal symmetrical polyneuropathy (DSPN). This syndrome is a result of nerve degeneration and is characterized by numbness and a sensation of pins and needles. Treatment with tricyclic antidepressants relieves symptoms but does not affect the underlying nerve damage.

[00340] A less frequent, but more severe type of neuropathy is known as acute or chronic inflammatory demyelinating polyneuropathy (AIDP/CIDP). In AIDP/CIDP there is damage to the fatty membrane covering the nerve impulses. This kind of neuropathy involves inflammation and resembles the muscle deterioration often identified with long-term use of AZT.

[00341] CMV causes several neurological syndromes in AIDS, including encephalitis, myelitis, and polyradiculopathy.

Other Uses

[00342] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for treating or preventing viral infections (such as infections by influenza, herpes or papilloma virus) or as antifungal agents. In certain embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as part of a combination drug therapy with another therapeutic agent for the treatment of viral diseases, including, for example, acyclovir, ganciclovir and zidovudine. In another embodiment, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be administered as part of a combination drug therapy with another anti-fungal agent including, for example, topical anti-fungals such as ciclopirox, clotrimazole, econazole, miconazole, nystatin, oxiconazole, terconazole, and tolnaftate, or systemic anti-fungal such as fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral), and miconazole (Monistat I.V.).

[00343] Subjects that may be treated as described herein include eukaryotes, such as mammals, e.g., humans, ovines, bovines, equines, porcines, canines, felines, non-human primate, mice, and rats. Cells that may be treated include eukaryotic cells, e.g., from a subject described above, or plant cells, yeast cells and prokaryotic cells, e.g., bacterial cells. For example, modulating compounds may be administered to farm animals to improve their ability to withstand farming conditions longer.

[00344] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used to increase lifespan, stress resistance, and resistance to apoptosis in plants. In one embodiment, a compound is applied to plants, e.g., on a periodic basis, or to fungi. In another embodiment, plants are genetically modified to produce a compound. In another embodiment, plants and fruits are treated with a compound prior to picking and shipping to increase resistance to damage during shipping. Plant seeds may also be contacted with compounds described herein, e.g., to preserve them.

[00345] In other embodiments, sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may be used for modulating lifespan in yeast cells. Situations in which it may be desirable to extend the lifespan of yeast cells include any process in which yeast is used, e.g., the making of beer, yogurt, and bakery items, e.g., bread. Use of yeast having an extended lifespan can result in using less yeast or in having the yeast be active for longer periods of time. Yeast or other mammalian cells used for recombinantly producing proteins may also be treated as described herein.

[00346] Sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used to increase lifespan, stress resistance and resistance to apoptosis in insects. In this embodiment, compounds would be applied to useful insects, e.g., bees and other insects that are involved in pollination of plants. In a specific embodiment, a compound would be applied to bees involved in the production of honey. Generally, the methods described herein may be applied to any organism, e.g., eukaryote, that may have commercial importance. For example, they can be applied to fish (aquaculture) and birds (e.g., chicken and fowl).

[00347] Higher doses of sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein may also be used as a pesticide by interfering with the regulation of silenced genes and the regulation of apoptosis during development. In this embodiment, a compound may be applied to plants using a method known in the art that ensures the compound is bio-available to insect larvae, and not to plants.

[00348] At least in view of the link between reproduction and longevity (Longo and Finch, Science, 2002), sirtuin-modulating compounds that increase the level and/or activity of a sirtuin protein can be applied to affect the reproduction of organisms such as insects, animals and microorganisms.

5 *Synthetic Procedures*

[00349] In another aspect, methods for synthesizing the compounds described herein are provided. In some embodiments, the compounds described herein can be prepared by the methods described below. The procedures and examples below are intended to illustrate those methods. Neither the procedures nor the examples should be construed as limiting the invention in any way. Compounds described herein may also be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in combination with methods described herein. In additions, solvents, temperatures and other reaction conditions presented herein may vary according to the practice and knowledge of those of skill in the art.

[00350] The starting materials used for the synthesis of the compounds as described herein can be obtained from commercial sources, such as Aldrich Chemical Co. (Milwaukee, Wis.), Sigma Chemical Co. (St. Louis, Mo.), or the starting materials can be synthesized. The compounds described herein, and other related compounds having different substituents can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999) (all of which are incorporated by reference in their entirety). General methods for the preparation of compounds as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein. As a guide the following synthetic methods may be utilized.

Formation of Covalent Linkages by Reaction of an Electrophile with a Nucleophile

[00351] The compounds described herein can be modified using various electrophiles or nucleophiles to form new functional groups or substituents. The table below entitled "Examples of Covalent Linkages and Precursors Thereof" lists selected examples of covalent linkages and precursor functional groups which yield and can be used as guidance toward the variety of electrophiles and nucleophiles combinations available. Precursor functional groups are shown as electrophilic groups and nucleophilic groups.

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	Amines/anilines
Carboxamides	Acyl azides	Amines/anilines
Carboxamides	Acyl halides	Amines/anilines
Esters	Acyl halides	Alcohols/phenols
Esters	Acyl nitriles	Alcohols/phenols
Carboxamides	Acyl nitriles	Amines/anilines
Imines	Aldehydes	Amines/anilines
Hydrazones	Aldehydes or ketones	Hydrazines
Oximes	Aldehydes or ketones	Hydroxylamines
Alkyl amines	Alkyl halides	Amines/anilines
Esters	Alkyl halides	Carboxylic acids
Thioethers	Alkyl halides	Thiols

Ethers	Alkyl halides	Alcohols/phenols
Thioethers	Alkyl sulfonates	Thiols
Esters	Alkyl sulfonates	Carboxylic acids
Ethers	Alkyl sulfonates	Alcohols/phenols
Esters	Anhydrides	Alcohols/phenols
Carboxamides	Anhydrides	Amines/anilines
Thiophenols	Aryl halides	Thiols
Aryl amines	Aryl halides	Amines
Thioethers	Aziridines	Thiols
Boronate esters	Boronates	Glycols
Carboxamides	Carboxylic acids	Amines/anilines
Esters	Carboxylic acids	Alcohols
Hydrazines	Hydrazides	Carboxylic acids
N-acylureas or Anhydrides	Carbodiimides	Carboxylic acids
Esters	Diazoalkanes	Carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	Haloacetamides	Thiols
Ammotriazines	Halotriazines	Amines/anilines
Triazinyl ethers	Halotriazines	Alcohols/phenols
Amidines	Imido esters	Amines/anilines
Ureas	Isocyanates	Amines/anilines
Urethanes	Isocyanates	Alcohols/phenols
Thioureas	Isothiocyanates	Amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	Phosphoramidites	Alcohols
Silyl ethers	Silyl halides	Alcohols
Alkyl amines	Sulfonate esters	Amines/anilines
Thioethers	Sulfonate esters	Thiols
Esters	Sulfonate esters	Carboxylic acids
Ethers	Sulfonate esters	Alcohols
Sulfonamides	Sulfonyl halides	Amines/anilines
Sulfonate esters	Sulfonyl halides	Phenols/alcohols

Examples of Covalent Linkages and Precursors Thereof

Use of Protecting Groups

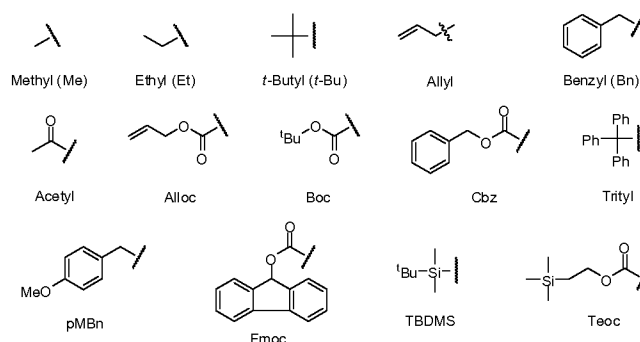
[00352] In the reactions described, it may be necessary to protect reactive functional groups, for example

hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid
 5 their unwanted participation in the reactions. Protecting groups are used to block some or all reactive
 moieties and prevent such groups from participating in chemical reactions until the protective group is
 removed. Protected derivatives are useful in the preparation of the compounds described herein or in
 themselves may be active as inhibitors. It is preferred that each protective group be removable by a
 different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the
 10 requirement of differential removal. Protective groups can be removed by acid, base, and
 hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyl dimethylsilyl are acid labile
 and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups
 protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base
 labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as,
 15 but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups
 such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically
 removable.

[00353] Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester compounds as exemplified herein, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

[00354] Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which the compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

[00355] Protecting or blocking groups may be selected from:



[00356] Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, *Protective Groups*, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference in their entirety.

Further Forms of the Compounds

Isomers

[00357] The compounds described herein may exist as geometric isomers. The compounds described herein may possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, compounds may exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein.

[00358] The compounds described herein may possess one or more chiral centers and each center may exist in the R or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion may also be useful for the applications described herein.

[00359] In some embodiments, the compounds described herein can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to

form a pair of diastereoisomeric compounds or complexes, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds described herein, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The single enantiomer of high optical purity (ee>90%) is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981, herein incorporated by reference in its entirety.

Labeled compounds

[00360] It should be understood that the compounds described herein include their isotopically-labeled equivalents, including their use for treating disorders. For example, the invention provides for methods of treating diseases, by administering isotopically-labeled forms of the described herein. The isotopically-labeled compounds can be administered as pharmaceutical compositions. Thus, the compounds described herein also include their isotopically-labeled isomers, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, pharmaceutically acceptable salts, esters, prodrugs, solvate, hydrates or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^3H and carbon-14, i. e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i. e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds, pharmaceutically acceptable salts, esters, prodrugs, solvates, hydrates or derivatives thereof can generally be prepared by carrying out procedures described herein, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[00361] The compounds described herein may be labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00362] The compounds described herein may also exist as their pharmaceutically acceptable salts, which may also be useful for treating disorders. For example, the invention provides for methods of treating

diseases, by administering pharmaceutically acceptable salts of the compounds described herein. The pharmaceutically acceptable salts can be administered as pharmaceutical compositions.

[00363] Thus, the compounds described herein can be prepared as pharmaceutically acceptable salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, for example an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Base addition salts can also be prepared by reacting the free acid form of the compounds described herein with a pharmaceutically acceptable inorganic or organic base, including, but not limited to organic bases such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like and inorganic bases such as aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. In addition, the salt forms of the disclosed compounds can be prepared using salts of the starting materials or intermediates.

[00364] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, Q-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

Solvates

[00365] The compounds described herein may also exist in various solvated forms, which may also be useful for treating disorders. For example, the invention provides for methods of treating diseases, by administering solvates of the compounds described herein. The solvates can be administered as pharmaceutical compositions. Preferably the solvates are pharmaceutically acceptable solvates.

[00366] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Polymorphs

[00367] The compounds described herein may also exist in various polymorphic states, all of which are herein contemplated, and which may also be useful for treating disorders. For example, the invention provides for methods of treating diseases, by administering polymorphs of the compounds described herein. The various polymorphs can be administered as pharmaceutical compositions.

5 [00368] Thus, the compounds described herein include all their crystalline forms, known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of the compound. Polymorphs may have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, solvates and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage
10 temperature may cause a single crystal form to dominate.

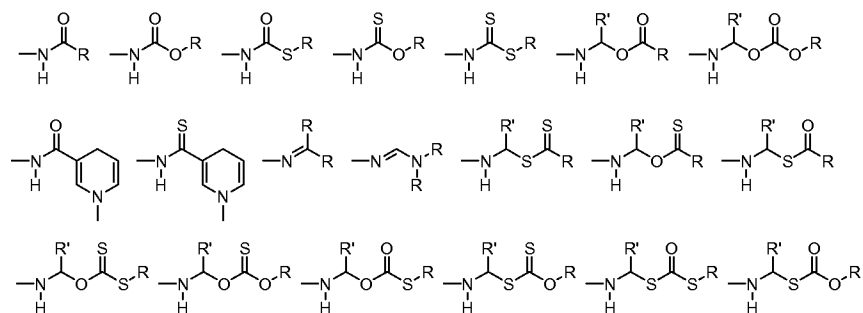
Prodrugs

15 [00369] The compounds described herein may also exist in prodrug form, which may also be useful for treating disorders. For example, the invention provides for methods of treating diseases, by administering prodrugs of the compounds described herein. The prodrugs can be administered as pharmaceutical compositions.

[00370] Prodrugs are generally drug precursors that, following administration to a subject and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by
20 a metabolic pathway. Some prodrugs have a chemical group present on the prodrug that renders it less active and/or confers solubility or some other property to the drug. Once the chemical group has been cleaved and/or modified from the prodrug the active drug is generated. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have
25 improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be the compound as described herein which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide
30 (polyamino acid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

[00371] Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. The design of prodrugs to date has been to increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent. See, e.g.,
35 Fedorak et al., *Am. J. Physiol.*, 269:G210-218 (1995); McLoed et al., *Gastroenterol*, 106:405-413 (1994); Hochhaus et al., *Biomed. Chrom.*, 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics*, 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula et al., *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, all incorporated herein in their
40 entirety.

[00372] Pharmaceutically acceptable prodrugs of the compounds described herein include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, metal salts and sulfonate esters. Various forms of prodrugs are well known in the art. See for example *Design of Prodrugs*, Bundgaard, A. Ed., Elsevier, 1985 and *Method in Enzymology*, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in *A Textbook of Drug Design and Development*, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., *Advanced Drug Delivery Review*, **1992**, 8, 1-38, each of which is incorporated herein by reference. The prodrugs described herein include, but are not limited to, the following groups and combinations of these groups; amine derived prodrugs:



Hydroxy prodrugs include, but are not limited to acyloxyalkyl esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters and disulfide containing esters.

[00373] In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed.

[00374] Prodrug derivatives of compounds described herein can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*, (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). By way of example only, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent, such as, but not limited to, 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like. Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth herein are included within the scope of the claims. Indeed, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00375] Compounds described herein having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug*

Delivery Reviews 1996, 19, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups.

[00376] Derivatization of hydroxy groups as (acyloxy) methyl and (acyloxy) ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities. Phosphate ester functionalities may also be used as prodrug moieties.

[00377] Sites on the aromatic ring portions of the compounds described herein may be susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, can reduce, minimize or eliminate this metabolic pathway.

Pharmaceutical compositions

[00378] The present invention can be administered alone or as a pharmaceutical composition, thus the invention further provides pharmaceutical compositions and methods of making said pharmaceutical composition. In some embodiments, the pharmaceutical compositions comprise an effective amount of the compounds of Formulas I-XXI, or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof. The pharmaceutical composition may comprise of admixing at least one active ingredient, or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, together with one or more carriers, excipients, buffers, adjuvants, stabilizers, or other materials well known to those skilled in the art and optionally other therapeutic agents. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy.

[00379] Examples of excipients that may be used in conjunction with the present invention include, but are not limited to water, saline, dextrose, glycerol or ethanol. The injectable compositions may also optionally comprise minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

[00380] Example of pharmaceutically acceptable carriers that may optionally be used include, but are not limited to aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[00381] In some embodiments the pharmaceutical compositions are for the treatment of disorders. In some embodiments the pharmaceutical compositions are for the treatment of disorders in a mammal. In some embodiments the pharmaceutical compositions are for the treatment of cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, etc.

Sirtuin Mediated Disorders

[00382] Described herein are compounds, pharmaceutical compositions and methods for treating a patient suffering from a histone deacetylase mediated disorder by administering an effective amount of

a compound of Formulas I-XXI, or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, alone or in combination with one or more additional active ingredients.

[00383] In some embodiments, a compound of Formulas I-XXI is used in the treatment of an inflammatory disease including, but not limited to, asthma, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, psoriasis, sarcoidosis, and rheumatoid arthritis.

[00384] In some embodiments, a compound of Formulas I-XXI is used in the treatment of an infection including, but not limited to, malaria, protozoal infections, EBV, HIV, hepatitis B and C, KSHV, toxoplasmosis and coccidiosis.

[00385] In some embodiments, a compound of Formulas I-XXI is used in the treatment of an autoimmune disorder including, but not limited to, conditions treatable by immune modulation, rheumatoid arthritis, autoimmune diabetes, lupus, multiple sclerosis, and allergies.

[00386] In some embodiments, a compound of Formulas I-XXI is used in the treatment of a neurological disorder including, but not limited to, Huntington's disease, epilepsy, neuropathic pain, depression, and bipolar disorders.

[00387] In some embodiments, a compound of Formulas I-XXI is used in the treatment of a proliferative disorder including, but not limited to, psoriasis, restenosis, autoimmune disease, proliferative responses associated with organ transplantation, and atherosclerosis.

[00388] In some embodiments, a compound of Formulas I-XXI is used in the treatment of a fibrogenic disorder including, but not limited to, scleroderma, keloid formation, pulmonary fibrosis and liver cirrhosis.

[00389] In some embodiments, a compound of Formulas I-XXI is used in the treatment of a cardiac disorder including, but not limited to, cardiovascular conditions, cardiac hypertrophy, idiopathic cardiomyopathies, and heart failure.

[00390] In some embodiments, a compound of Formulas I-XXI is used in the treatment of a hyperproliferative disorder including, but not limited to, hematologic and nonhematologic cancers, cancerous and precancerous skin lesions, leukemias, hyperplasias, fibrosis, angiogenesis, psoriasis, atherosclerosis, and smooth muscle proliferation in the blood vessels.

[00391] In some embodiments, a compound of Formulas I-XXI is used in the treatment of a metabolic disease including, but not limited to, genetic related metabolic disorders, cystic fibrosis, peroxisome biogenesis disorder, alpha-1 anti-trypsin, adrenoleukodystrophy, and spinal muscular atrophy.

[00392] In some embodiments, a compound of Formulas I-XXI is used in the treatment of a malignant disease including, but not limited to, malignant fibrous histiocytoma, malignant mesothelioma, and malignant thymoma.

[00393] In some embodiments, the compounds Formulas I-XXI are used in wound healing including, but not limited to, healing of wounds associated with radiation therapy.

[00394] In some embodiments, a compound of Formulas I-XXI is used in the treatment of a stroke, ischemia, cancer, tumors, leukemias, neoplasms, or carcinomas, including but not limited to cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, leukemia, myeloid leukemia, glioblastoma, follicular lymphoma, pre-B acute leukemia, chronic lymphocytic B-leukemia, mesothelioma or small cell lung cancer. Additional

cancers to be treated with the methods and compounds of Formulas I-XI include hematologic and non-hematologic cancers. Hematologic cancer includes multiple myeloma, leukemias, and lymphomas, acute leukemia, acute lymphocytic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL), chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). Lymphoma further includes Hodgkin's lymphoma and non-Hodgkin's lymphoma, cutaneous t-cell lymphoma (CTCL) and mantle cell lymphoma (MCL). Non-hematologic cancer includes brain cancer, cancers of the head and neck, lung cancer, breast cancer, cancers of the reproductive system, cancers of the gastro-intestinal system, pancreatic cancer, and cancers of the urinary system, cancer of the upper digestive tract or colorectal cancer, bladder cancer or renal cell carcinoma, and prostate cancer.

[00395] In some embodiments, the cancers to treat with the methods and compositions described herein include cancers that are epithelial malignancies (having epithelial origin), and particularly any cancers (tumors) that express EGFR. Non-limiting examples of premalignant or precancerous cancers/tumors having epithelial origin include actinic keratoses, arsenic keratoses, xeroderma pigmentosum, Bowen's disease, leukoplakias, metaplasias, dysplasias and papillomas of mucous membranes, e.g. of the mouth, tongue, pharynx and larynx, precancerous changes of the bronchial mucous membrane such as metaplasias and dysplasias (especially frequent in heavy smokers and people who work with asbestos and/or uranium), dysplasias and leukoplakias of the cervix uteri, vulval dystrophy, precancerous changes of the bladder, e.g. metaplasias and dysplasias, papillomas of the bladder as well as polyps of the intestinal tract. Non-limiting examples of semi-malignant or malignant cancers/tumors of the epithelial origin are breast cancer, skin cancer (e.g., basal cell carcinomas), bladder cancer (e.g., superficial bladder carcinomas), colon cancer, gastro-intestinal (GI) cancer, prostate cancer, uterine cancer, cervical cancer, ovarian cancer, esophageal cancer, stomach cancer, laryngeal cancer and lung cancer.

[00396] Additional types of cancers which may be treated using the compounds and methods described herein include: cancers of oral cavity and pharynx, cancers of the respiratory system, cancers of bones and joints, cancers of soft tissue, skin cancers, cancers of the genital system, cancers of the eye and orbit, cancers of the nervous system, cancers of the lymphatic system, and cancers of the endocrine system. These cancers further include cancer of the tongue, mouth, pharynx, or other oral cavity; esophageal cancer, stomach cancer, or cancer of the small intestine; colon cancer or rectal, anal, or anorectal cancer; cancer of the liver, intrahepatic bile duct, gallbladder, pancreas, or other biliary or digestive organs; laryngeal, bronchial, and other cancers of the respiratory organs; heart cancer, melanoma, basal cell carcinoma, squamous cell carcinoma, other non-epithelial skin cancer; uterine or cervical cancer; uterine corpus cancer; ovarian, vulvar, vaginal, or other female genital cancer; prostate, testicular, penile or other male genital cancer; urinary bladder cancer; cancer of the kidney; renal, pelvic, or urethral cancer or other cancer of the genito-urinary organs; thyroid cancer or other endocrine cancer; chronic lymphocytic leukemia; and cutaneous T-cell lymphoma, both granulocytic and monocytic.

[00397] Yet other types of cancers which may be treated using the compounds and methods described herein include: adenocarcinoma, angiosarcoma, astrocytoma, acoustic neuroma, anaplastic astrocytoma, basal cell carcinoma, blastoglioma, chondrosarcoma, choriocarcinoma, chordoma, craniopharyngioma,

cutaneous melanoma, cystadenocarcinoma, endotheliosarcoma, embryonal carcinoma, ependymoma, Ewing's tumor, epithelial carcinoma, fibrosarcoma, gastric cancer, genitourinary tract cancers, glioblastoma multiforme, hemangioblastoma, hepatocellular carcinoma, hepatoma, Kaposi's sarcoma, large cell carcinoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, medullary thyroid carcinoma, medulloblastoma, meningioma mesothelioma, myelomas, myxosarcoma neuroblastoma, neurofibrosarcoma, oligodendroglioma, osteogenic sarcoma, epithelial ovarian cancer, papillary carcinoma, papillary adenocarcinomas, parathyroid tumors, pheochromocytoma, pinealoma, plasmacytomas, retinoblastoma, rhabdomyosarcoma, sebaceous gland carcinoma, seminoma, skin cancers, melanoma, small cell lung carcinoma, squamous cell carcinoma, sweat gland carcinoma, synovioma, thyroid cancer, uveal melanoma, and Wilm's tumor.

Abnormal cell growth

[00398] Also described herein are compounds, pharmaceutical compositions and methods for inhibiting abnormal cell growth. In some embodiments, the abnormal cell growth occurs in a mammal. Methods for inhibiting abnormal cell growth comprise administering an effective amount of a compound of Formulas I-XXI, or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein abnormal cell growth is inhibited. Methods for inhibiting abnormal cell growth in a mammal comprise administering to the mammal an amount of the compound of Formula I-XXI, pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein the amounts of the compound, pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, is effective in inhibiting abnormal cell growth in the mammal.

[00399] In some embodiments, the methods comprise administering an effective amount of a compound of Formulas I-XXI, pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, in combination with an amount of a chemotherapeutic, wherein the amounts of the compound, or pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, and of the chemotherapeutic are together effective in inhibiting abnormal cell growth. Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the invention. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

[00400] Also described are methods for inhibiting abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound of Formulas I-XXI, pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, in combination with radiation therapy, wherein the amounts of the compound, pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, is in combination with the radiation therapy effective in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of a compound of Formulas I-XXI in this combination therapy can be determined as described herein.

[00401] The invention also relates to a method of and to a pharmaceutical composition of inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of Formulas I-XXI, pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, or an isotopically-labeled derivative thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

[00402] Anti-angiogenesis agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with the compound of the present invention and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREXTM (alecoxib), valdecoxib, and rofecoxib. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (i. e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-11, MMP-12, andMMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, and RS 13-0830.

Modes of Administration

[00403] Described herein are compounds of Formula I-XXI or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. Also described, are pharmaceutical compositions comprising a compound of Formulas I-XXI or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. The compounds and compositions described herein may be administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice.

[00404] Administration of the compounds and compositions described herein can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical, intrapulmonary, rectal administration, by implant, by a vascular stent impregnated with the compound, and other suitable methods commonly known in the art. For example, compounds described herein can be administered locally to the area in need of treatment. This may be achieved by, for example, but not limited to, local infusion during surgery, topical application, e.g., cream, ointment, injection, catheter, or implant, said implant made, e.g., out of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. The administration can also be by direct injection at the site (or former site) of a tumor or neoplastic or pre-neoplastic tissue. Those of ordinary skill in the art are familiar with formulation and administration techniques that can be employed with the compounds and methods of the invention, e.g., as discussed in Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington's, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

[00405] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, intramedullary, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intratracheal, subcuticular, intraarticular, subarachnoid, and intrastemal), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal,

sublingual, intranasal, intraocular, and vaginal) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the compound of the
5 subject invention or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

10 **[00406]** Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

15 **[00407]** Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders (e.g., povidone, gelatin,
20 hydroxypropylmethyl cellulose), inert diluents, preservative, disintegrant (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient
25 therein. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable
30 liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to
35 characterize different combinations of active compound doses.

[00408] Pharmaceutical preparations may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory
40 agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in

unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[00409] Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, biocide, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes or other microparticulate systems may be used to target the compound to blood components or one or more organs. The concentration of the active ingredient in the solution may vary widely. Typically, the concentration of the active ingredient in the solution is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions

[00410] Pharmaceutical preparations may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00411] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[00412] Pharmaceutical preparations may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[00413] Pharmaceutical preparations may be administered topically, that is by non-systemic administration. This includes the application of the compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such the compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[00414] Pharmaceutical preparations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, suspensions, powders, solutions, spray, aerosol, oil, and drops suitable for administration to the eye, ear or nose. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active ingredients and optionally one

or more excipients or diluents. The amount of active ingredient present in the topical formulation may vary widely. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

[00415] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[00416] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient.

[00417] Pharmaceutical preparations for administration by inhalation are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray.

Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, pharmaceutical preparations may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[00418] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Formulations

[00419] The compounds or compositions described herein can be delivered in a vesicle, *e.g.*, a liposome (see, for example, Langer, *Science* 1990, 249, 1527-1533; Treat et al., *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Bernstein and Fidler, Ed., Liss, N.Y., pp. 353-365, 1989). The compounds and pharmaceutical compositions described herein can also be delivered in a controlled release system. In one embodiment, a pump may be used (see, Sefton, 1987, *CRC Crit. Rev. Biomed. Eng.* 14:201; Buchwald et al. *Surgery*, 1980 88, 507; Saudek et al. *N. Engl. J. Med.* 1989, 321, (574). Additionally, a controlled release system can be placed in proximity of the therapeutic target. (See, Goodson, *Medical Applications of Controlled Release*, 1984, Vol. 2, pp. 115-138). The pharmaceutical compositions described herein can also contain the active ingredient in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents,

flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, such as microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be un-coated or coated by known techniques to mask the taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, or cellulose acetate butyrate may be employed as appropriate. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[00420] Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

[00421] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisole or alpha-tocopherol.

[00422] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening,

flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[00423] Pharmaceutical compositions may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening agents, flavoring agents, preservatives and antioxidants.

[00424] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

[00425] Pharmaceutical compositions may be in the form of a sterile injectable aqueous solution. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion. The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00426] Pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the inhibitors with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

[00427] For topical use, creams, ointments, jellies, solutions or suspensions, *etc.*, containing the compound or composition of the invention can be used. As used herein, topical application can include mouth washes and gargles.

[00428] Pharmaceutical compositions may be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

Doses

[00429] In one embodiment, suitable dosages are total daily dosage of between about 25 to 4000 mg/m². They can be administered in various cycles: once daily at a dose of about 200 to 600 mg; twice daily at a dose of about 200 to 400 mg; twice daily at a dose of about 200 to 400 mg intermittently (e.g. three, four, or five days per week); three times daily at a dose of about 100 to 250 mg; daily dose is 200 mg, which can be administered once-daily, twice-daily, or three-times daily; daily dose is 300 mg, which can be administered once-daily or twice-daily; daily dose is 400 mg, which can be administered once-daily or twice-daily.

[00430] In one embodiment, the compound is administered systemically to attain a blood level from about 0.01 μ M to about 10 μ M. In additional or further embodiments, the therapeutic composition is administered at a sufficient dosage to attain a blood level of from about 0.05 μ M to about 10 μ M. In additional or further embodiments, the blood level of is from about 0.1 μ M to about 7 μ M. In other embodiments, the compound is administered systemically to attain a blood level from about 0.01 μ M to about 10 μ M. In additional or further embodiments, the therapeutic composition is administered at a sufficient dosage to attain a blood level from about 0.05 μ M to about 10 μ M. In additional or further embodiments, the blood level is from about 0.1 μ M to about 7 μ M.

[00431] In one embodiment, the total dosage range is about 0.01 mg to about 5 mg per kg body weight per day. In additional or further embodiments, a total dosage will range from about 0.1 mg to about 4 mg per kg body weight per day. In additional or further embodiments, a total dosage range from about 0.1 mg to about 1 mg per kg body weight per day.

[00432] The compounds described herein can also be administered in combination with at least one second chemotherapeutic compound (e.g. pharmaceuticals, small-molecule compounds, antibodies and fragments thereof, immune system modulating proteins, antibiotics, or other biologic therapy), radiotherapy, or surgery. Such co-administration is believed to increase efficacy, provide synergistic effect, and/or provide increased therapeutic value to each agent, compound, or additional treatment (e.g. radiotherapy or surgery).

[00433] In one embodiment, the compound described herein is administered with a second chemotherapeutic compound. The co-administered compounds can be administered in a variety of cycles: the compound can be administered continuously, daily, every other day, every third day, once a week, twice a week, three times a week, bi-weekly, or monthly, while the second chemotherapeutic agent is administered continuously, daily, one day a week, two days a week, three days a week, four days a week, five days a week, six days a week, bi-weekly, or monthly. The compound and the second chemotherapeutic compound or cancer can be administered in, but are not limited to, any combination of the aforementioned cycles. In one non-limiting example, the compound is administered three times a week for the first two weeks followed by no administration for four weeks, and the second chemotherapeutic

compound is administered continuously over the same six week period. In yet another non-limiting example, the compound is administered once a week for six weeks, and the second chemotherapeutic compound is administered every other day over the same six week period. In yet another non-limiting example, the compound is administered the first two days of a week, and the second chemotherapeutic compound is administered continuously for all seven days of the same week.

[00434] In addition to the administration of the compounds in cycles, the cycles themselves may consist of varying schedules. In one embodiment, a cycle is administered weekly. In additional embodiments, a cycle is administered for one week with one, two, three, four, six, or eight weeks off before repeating the cycle. In further embodiments, a cycle is administered for two weeks with one, two, three, four, six, or eight weeks off before repeating the cycle. In still further embodiments, the cycle is administered for three, four, five, or six weeks, with one, two, three, four, six, or eight weeks off before repeating the cycle.

[00435] When a compound is administered with an additional treatment such as radiotherapy, the radiotherapy can be administered at 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 14 days, 21 days, or 28 days after administration of at least one cycle of a compound. In additional embodiments, the radiotherapy can be administered in any variation of timing with any variation of the aforementioned cycles for a compound. Additional schedules for co-administration of radiotherapy with cycles of a compound will be known in the art, can be further determined by appropriate testing, clinical trials, or can be determined by qualified medical professionals.

[00436] When a compound is administered with an additional treatment such as surgery, the compound is administered 1, 2, 3, 4, 5, 6, 7, 14, 21, or 28 days prior to surgery. In additional embodiments, at least one cycle of the compound is administered 1, 2, 3, 4, 5, 6, 7, 14, 21, or 28 days after surgery. Additional variations of administering compound cycles in anticipation of surgery, or after the occurrence of surgery, will be known in the art, can be further determined by appropriate testing and/or clinical trials, or can be determined by assessment of qualified medical professionals.

[00437] In addition to the aforementioned examples and embodiments of dosages, cycles, and schedules of cycles, numerous permutations of the aforementioned dosages, cycles, and schedules of cycles for the co-administration of a compound with a second chemotherapeutic compound, radiotherapy, or surgery are contemplated herein and can be administered according to the patient, type of cancer, and/or appropriate treatment schedule as determined by qualified medical professionals.

Dosage Forms

[00438] The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, cachet, pill, lozenge, powder or granule, sustained release formulations, solution, liquid, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment, cream, lotions, sprays, foams, gel or paste, or for rectal or vaginal administration as a suppository or pessary. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and the compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

[00439] Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[00440] Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch or other cellulosic material, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Other reagents such as an inhibitor, surfactant or solubilizer, plasticizer, stabilizer, viscosity increasing agent, or film forming agent may also be added. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

[00441] Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Ester, Pa., 18th Edition (1990).

Combination Therapies

[00442] In certain embodiments, the sirtuin-modulating compounds described herein may be taken alone or in combination with other compounds. In one embodiment, a mixture of two or more sirtuin-modulating compounds may be administered to a subject in need thereof. In another embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered with one or more of the following compounds: resveratrol, butein, fisetin, piceatannol, or quercetin. In an exemplary embodiment, a sirtuin-modulating compound that increases the level and/or activity of a sirtuin protein may be administered in combination with nicotinic acid. In another embodiment, a sirtuin-modulating compound that decreases the level and/or activity of a sirtuin protein may be administered with one or more of the following compounds: nicotinamide (NAM), suranim; NF023 (a G-protein antagonist); NF279 (a purinergic receptor antagonist); Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid); (-)-epigallocatechin (hydroxy on sites 3,5,7,3',4',5'); (-)-epigallocatechin gallate (Hydroxy sites 5,7,3',4',5' and gallate ester on 3); cyanidin chloride (3,5,7,3',4'-pentahydroxyflavylium chloride); delphinidin chloride (3,5,7,3',4',5'-hexahydroxyflavylium chloride); myricetin (cannabiscetin; 3,5,7,3',4',5'-hexahydroxyflavone); 3,7,3',4',5'-pentahydroxyflavone; gossypetin (3,5,7,8,3',4'-hexahydroxyflavone), sirtinol; and splitomicin (see e.g., Howitz et al. (2003) Nature 425:191; Grozinger et al. (2001) J. Biol. Chem. 276:38837; Dedalov et al. (2001) PNAS 98:15113; and Hirao et al. (2003) J. Biol. Chem 278:52773).

[00443] In yet another embodiment, one or more sirtuin-modulating compounds may be administered with one or more therapeutic agents for the treatment or prevention of various diseases, including, for example,

cancer, diabetes, neurodegenerative diseases, cardiovascular disease, blood clotting, inflammation, flushing, obesity, ageing, stress, etc. In various embodiments, combination therapies comprising a sirtuin-modulating compound may refer to (1) pharmaceutical compositions that comprise one or more sirtuin-modulating compounds in combination with one or more therapeutic agents (e.g., one or more therapeutic agents described herein); and (2) co-administration of one or more sirtuin-modulating compounds with one or more therapeutic agents wherein the sirtuin-modulating compound and therapeutic agent have not been formulated in the same compositions (but may be present within the same kit or package, such as a blister pack or other multi-chamber package; connected, separately sealed containers (e.g., foil pouches) that can be separated by the user; or a kit where the sirtuin modulating compound(s) and other therapeutic agent(s) are in separate vessels). When using separate formulations, the sirtuin-modulating compound may be administered at the same, intermittent, staggered, prior to, subsequent to, or combinations thereof, with the administration of another therapeutic agent.

[00444] In certain embodiments, the compounds described herein, their pharmaceutically acceptable salts, prodrug, solvates, polymorphs, tautomers or isomers may also be administered in combination with another cancer therapy or therapies. These additional cancer therapies can be, for example, surgery, radiation therapy, administration of chemotherapeutic agents and combinations of any two or all of these methods. Combination treatments may occur sequentially or concurrently and the combination therapies may be neoadjuvant therapies or adjuvant therapies

[00445] In some embodiments, the compounds described herein can be administered with an additional therapeutic agent. In these embodiments, the compound described herein can be in a fixed combination with the additional therapeutic agent or a non-fixed combination with the additional therapeutic agent.

[00446] By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds described herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the compound. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of another therapeutic agent, the overall therapeutic benefit to the patient is enhanced. Or, by way of example only, the benefit experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[00447] Other therapies include, but are not limited to administration of other therapeutic agents, radiation therapy or both. In the instances where the compounds described herein are administered with other therapeutic agents, the compounds described herein need not be administered in the same pharmaceutical composition as other therapeutic agents, and may, because of different physical and chemical characteristics, be administered by a different route. For example, the compounds/compositions may be administered orally to generate and maintain good blood levels thereof, while the other therapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same

pharmaceutical composition, is within the knowledge of the skilled clinician with the teachings described herein. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician. The particular choice of compound (and where appropriate, other therapeutic agent and/or radiation) will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

[00448] The compounds and compositions described herein (and where appropriate chemotherapeutic agent and/or radiation) may be administered concurrently (*e.g.*, simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (*i.e.*, within a single treatment protocol) with the compound/composition.

[00449] In combinational applications and uses, the compound/composition and the chemotherapeutic agent and/or radiation need not be administered simultaneously or essentially simultaneously, and the initial order of administration of the compound/composition, and the chemotherapeutic agent and/or radiation, may not be important. Thus, the compounds/compositions of the invention may be administered first followed by the administration of the chemotherapeutic agent and/or radiation; or the chemotherapeutic agent and/or radiation may be administered first followed by the administration of the compounds/compositions of the invention. This alternate administration may be repeated during a single treatment protocol. With the teachings described herein, the determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, would be within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient. For example, the chemotherapeutic agent and/or radiation may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of the compounds/compositions of the invention followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete. Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of the compound/composition for treatment according to the individual patient's needs, as the treatment proceeds. The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, *e.g.*, CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

[00450] In some embodiments, a composition described herein is administered before the administration of one or more chemotherapeutic agents. As non-limiting examples of this embodiment of the invention, the chemotherapeutic agent can be administered hours (*e.g.* one, five, ten, etc.) or days (*e.g.*, one, two, three, etc.) after administration of the composition described herein. In some embodiments, the

subsequent administration is shortly after (*e.g.*, within an hour) administration of the compound described herein.

[00451] Specific, non-limiting examples of possible combination therapies include use of the compounds of the invention with agents found in the following pharmacotherapeutic classifications as indicated below.

These lists should not be construed to be closed, but should instead serve as illustrative examples common to the relevant therapeutic area at present. Moreover, combination regimens may include a variety of routes of administration and should include oral, intravenous, intraocular, subcutaneous, dermal, and inhaled topical.

[00452] In some embodiments, therapeutic agents may include chemotherapeutic agents, but are not limited to, anticancer agents, alkylating agents, cytotoxic agents, antimetabolic agents, hormonal agents, plant-derived agents, and biologic agents.

[00453] Examples of anti-tumor substances, for example those selected from, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred anti-metabolites disclosed in European Patent Application No. 239362 such as N- (5- [N- (3, 4-dihydro-2-methyl-4- oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example, interferon; and anti-hormones, for example anti- estrogens such as NolvadexTM (tamoxifen) or, for example anti-androgens such as CasodexTM (4'-cyano-3- (4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'- (trifluoromethyl) propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of treatment.

[00454] Alkylating agents are polyfunctional compounds that have the ability to substitute alkyl groups for hydrogen ions. Examples of alkylating agents include, but are not limited to, bischloroethylamines (nitrogen mustards, *e.g.* chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard), aziridines (*e.g.* thiotepa), alkyl alkane sulfonates (*e.g.* busulfan), nitrosoureas (*e.g.* carmustine, lomustine, streptozocin), nonclassic alkylating agents (altretamine, dacarbazine, and procarbazine), platinum compounds (carboplatin and cisplatin). These compounds react with phosphate, amino, hydroxyl, sulfhydryl, carboxyl, and imidazole groups. Under physiological conditions, these drugs ionize and produce positively charged ion that attach to susceptible nucleic acids and proteins, leading to cell cycle arrest and/or cell death. Combination therapy including a sirtuin modulator and an alkylating agent may have therapeutic synergistic effects on cancer and reduce side effects associated with these chemotherapeutic agents.

[00455] Cytotoxic agents are a group of drugs that produced in a manner similar to antibiotics as a modification of natural products. Examples of cytotoxic agents include, but are not limited to, anthracyclines (*e.g.* doxorubicin, daunorubicin, epirubicin, idarubicin and anthracenedione), mitomycin C, bleomycin, dactinomycin, plicatamycin. These cytotoxic agents interfere with cell growth by targeting different cellular components. For example, anthracyclines are generally believed to interfere with the action of DNA topoisomerase II in the regions of transcriptionally active DNA, which leads to DNA strand scissions. Bleomycin is generally believed to chelate iron and forms an activated complex, which then

binds to bases of DNA, causing strand scissions and cell death. Combination therapy including a sirtuin modulator and a cytotoxic agent may have therapeutic synergistic effects on cancer and reduce side effects associated with these chemotherapeutic agents.

[00456] Antimetabolic agents are a group of drugs that interfere with metabolic processes vital to the physiology and proliferation of cancer cells. Actively proliferating cancer cells require continuous synthesis of large quantities of nucleic acids, proteins, lipids, and other vital cellular constituents. Many of the antimetabolites inhibit the synthesis of purine or pyrimidine nucleosides or inhibit the enzymes of DNA replication. Some antimetabolites also interfere with the synthesis of ribonucleosides and RNA and/or amino acid metabolism and protein synthesis as well. By interfering with the synthesis of vital cellular constituents, antimetabolites can delay or arrest the growth of cancer cells. Examples of antimetabolic agents include, but are not limited to, fluorouracil (5-FU), floxuridine (5-FUdR), methotrexate, leucovorin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, and gemcitabine. Combination therapy including a sirtuin modulator and an antimetabolic agent may have therapeutic synergistic effects on cancer and reduce side effects associated with these chemotherapeutic agents.

[00457] Hormonal agents are a group of drug that regulate the growth and development of their target organs. Most of the hormonal agents are sex steroids and their derivatives and analogs thereof, such as estrogens, androgens, and progestins. These hormonal agents may serve as antagonists of receptors for the sex steroids to down regulate receptor expression and transcription of vital genes. Examples of such hormonal agents are synthetic estrogens (e.g. diethylstilbestrol), antiestrogens (e.g. tamoxifen, toremifene, fluoxymesterol and raloxifene), antiandrogens (bicalutamide, nilutamide, flutamide), aromatase inhibitors (e.g., aminoglutethimide, anastrozole and tetrazole), ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone. Combination therapy including a sirtuin modulator and a hormonal agent may have therapeutic synergistic effects on cancer and reduce side effects associated with these chemotherapeutic agents.

[00458] Plant-derived agents are a group of drugs that are derived from plants or modified based on the molecular structure of the agents. Examples of plant-derived agents include, but are not limited to, vinca alkaloids (e.g., vincristine, vinblastine, vindesine, vinzolidine and vinorelbine), podophyllotoxins (e.g., etoposide (VP-16) and teniposide (VM-26)), taxanes (e.g., paclitaxel and docetaxel). These plant-derived agents generally act as antimitotic agents that bind to tubulin and inhibit mitosis. Podophyllotoxins such as etoposide are believed to interfere with DNA synthesis by interacting with topoisomerase II, leading to DNA strand scission. Combination therapy including a sirtuin modulator and a plant-derived agent may have therapeutic synergistic effects on cancer and reduce side effects associated with these chemotherapeutic agents.

[00459] Biologic agents are a group of biomolecules that elicit cancer/tumor regression when used alone or in combination with chemotherapy and/or radiotherapy. Examples of biologic agents include, but are not limited to, immuno-modulating proteins such as cytokines, monoclonal antibodies against tumor antigens, tumor suppressor genes, and cancer vaccines. Combination therapy including a sirtuin modulator and a biologic agent may have therapeutic synergistic effects on cancer, enhance the patient's

immune responses to tumorigenic signals, and reduce potential side effects associated with this chemotherapeutic agent.

[00460] For the treatment of oncologic diseases, proliferative disorders, and cancers, compounds according to the present invention may be administered with an agent selected from the group comprising: aromatase inhibitors, antiestrogen, anti-androgen, corticosteroids, gonadorelin agonists, topoisomerase 1 and 2 inhibitors, microtubule active agents, alkylating agents, nitrosoureas, antineoplastic antimetabolites, platinum containing compounds, lipid or protein kinase targeting agents, IMiDs, protein or lipid phosphatase targeting agents, anti-angiogenic agents, Akt inhibitors, IGF-I inhibitors, FGF3 modulators, mTOR inhibitors, Smac mimetics, HDAC inhibitors, other sirtuin modulators, agents that induce cell differentiation, bradykinin 1 receptor antagonists, angiotensin II antagonists, cyclooxygenase inhibitors, heparanase inhibitors, lymphokine inhibitors, cytokine inhibitors, IKK inhibitors, P38MAPK inhibitors, HSP90 inhibitors, multikinase inhibitors, bisphosphonates, rapamycin derivatives, anti-apoptotic pathway inhibitors, apoptotic pathway agonists, PPAR agonists, inhibitors of Ras isoforms, telomerase inhibitors, protease inhibitors, metalloproteinase inhibitors, aminopeptidase inhibitors, dacarbazine (DTIC), actinomycins C₂, C₃, D, and F₁, cyclophosphamide, melphalan, estramustine, maytansinol, rifamycin, streptovaricin, doxorubicin, daunorubicin, epirubicin, idarubicin, detorubicin, carminomycin, idarubicin, epirubicin, esorubicin, mitoxantrone, bleomycins A, A₂, and B, camptothecin, Irinotecan®, Topotecan®, 9-aminocamptothecin, 10,11 -methylenedioxcamptothecin, 9-nitrocamptothecin, bortezomib, temozolomide, TAS103, NPI0052, combretastatin, combretastatin A-2, combretastatin A-4, calicheamicins, neocarzinostats, epothilones A B, C, and semi-synthetic variants, Herceptin®, Rituxan®, CD40 antibodies, asparaginase, interleukins, interferons, leuprolide, and pegaspargase, 5-fluorouracil, fluorodeoxyuridine, ptorafur, 5'-deoxyfluorouridine, UFT, MITC, S-1 capecitabine, diethylstilbestrol, tamoxifen, toremefine, tolumudex, thymitaq, flutamide, fluoxymesterone, bicalutamide, finasteride, estradiol, trioxifene, dexamethasone, leuproelin acetate, estramustine, droloxifene, medroxyprogesterone, megestrol acetate, aminoglutethimide, testolactone, testosterone, diethylstilbestrol, hydroxyprogesterone, mitomycins A, B and C, porfiromycin, cisplatin, carboplatin, oxaliplatin, tetraplatin, platinum-DACH, ormaplatin, thalidomide, lenalidomide, CI-973, telomestatin, CHIR258, Rad 001, SAHA, Tubacin, 17-AAG, sorafenib, JM-216, podophyllotoxin, epipodophyllotoxin, etoposide, teniposide, Tarceva®, Iressa®, Imatinib®, Miltefosine®, Perifosine®, aminopterin, methotrexate, methopterin, dichloro-methotrexate, 6-mercaptopurine, thioguanine, azattuoprine, allopurinol, cladribine, fludarabine, pentostatin, 2-chloroadenosine, deoxycytidine, cytosine arabinoside, cytarabine, azacitidine, 5-azacytosine, gencitabine, 5-azacytosine-arabinoside, vincristine, vinblastine, vinorelbine, leurosine, leurosidine and vindesine, paclitaxel, taxotere and docetaxel.

[00461] Cytokines possess profound immunomodulatory activity. Some cytokines such as interleukin-2 (IL-2, aldesleukin) and interferon have demonstrated antitumor activity and have been approved for the treatment of patients with metastatic renal cell carcinoma and metastatic malignant melanoma. IL-2 is a T-cell growth factor that is central to T-cell-mediated immune responses. The selective antitumor effects of IL-2 on some patients are believed to be the result of a cell-mediated immune response that discriminate between self and nonself. Examples of interleukins that may be used in conjunction with a

sirtuin modulator include, but are not limited to, interleukin 2 (IL-2), and interleukin 4 (IL-4), interleukin 12 (IL-12).

[00462] Interferons include more than 23 related subtypes with overlapping activities, all of the IFN subtypes within the scope of the present invention. IFN has demonstrated activity against many solid and hematologic malignancies, the later appearing to be particularly sensitive.

[00463] Other cytokines that may be used in conjunction with a sirtuin modulator include those cytokines that exert profound effects on hematopoiesis and immune functions. Examples of such cytokines include, but are not limited to erythropoietin, granulocyte-CSF (filgrastin), and granulocyte, macrophage-CSF (sargramostim). These cytokines may be used in conjunction with a sirtuin modulator to reduce chemotherapy-induced myelopoietic toxicity.

[00464] Other immuno-modulating agents other than cytokines may also be used in conjunction with a sirtuin modulator to inhibit abnormal cell growth. Examples of such immuno-modulating agents include, but are not limited to bacillus Calmette-Guerin, levamisole, and octreotide, a long-acting octapeptide that mimics the effects of the naturally occurring hormone somatostatin.

[00465] Monoclonal antibodies against tumor antigens are antibodies elicited against antigens expressed by tumors, preferably tumor-specific antigens. For example, monoclonal antibody HERCEPTIN® (Trastuzumab) is raised against human epidermal growth factor receptor2 (HER2) that is overexpressed in some breast tumors including metastatic breast cancer. Overexpression of HER2 protein is associated with more aggressive disease and poorer prognosis in the clinic. HERCEPTIN® is used as a single agent for the treatment of patients with metastatic breast cancer whose tumors over express the HER2 protein. Combination therapy including a sirtuin modulator and HERCEPTIN® may have therapeutic synergistic effects on tumors, especially on metastatic cancers.

[00466] Another example of monoclonal antibodies against tumor antigens is RITUXAN® (Rituximab) that is raised against CD20 on lymphoma cells and selectively deplete normal and malignant CD20⁺pre-B and mature B cells. RITUXAN® is used as single agent for the treatment of patients with relapsed or refractory low-grade or follicular, CD20⁺, B cell non-Hodgkin's lymphoma. Combination therapy including a sirtuin modulator and RITUXAN® may have therapeutic synergistic effects not only on lymphoma, but also on other forms or types of malignant tumors.

[00467] Tumor suppressor genes are genes that function to inhibit the cell growth and division cycles, thus preventing the development of neoplasia. Mutations in tumor suppressor genes cause the cell to ignore one or more of the components of the network of inhibitory signals, overcoming the cell cycle check points and resulting in a higher rate of controlled cell growth-cancer. Examples of the tumor suppressor genes include, but are not limited to, DPC-4, NF-1, NF-2, RB, p53, WT1, BRCA1 and BRCA2.

[00468] DPC-4 is involved in pancreatic cancer and participates in a cytoplasmic pathway that inhibits cell division. NF-1 codes for a protein that inhibits Ras, a cytoplasmic inhibitory protein. NF-1 is involved in neurofibroma and pheochromocytomas of the nervous system and myeloid leukemia. NF-2 encodes a nuclear protein that is involved in meningioma, schwannoma, and ependymoma of the nervous system. RB codes for the pRB protein, a nuclear protein that is a major inhibitor of cell cycle. RB is involved in retinoblastoma as well as bone, bladder, small cell lung and breast cancer. P53 codes for p53 protein that regulates cell division and can induce apoptosis. Mutation and/or inaction of p53 is found in a wide

ranges of cancers. WT1 is involved in Wilms tumor of the kidneys. BRCA1 is involved in breast and ovarian cancer, and BRCA2 is involved in breast cancer. The tumor suppressor gene can be transferred into the tumor cells where it exerts its tumor suppressing functions. Combination therapy including a sirtuin modulator and a tumor suppressor may have therapeutic synergistic effects on patients suffering from various forms of cancers.

[00469] Cancer vaccines are a group of agents that induce the body's specific immune response to tumors. Most of cancer vaccines under research and development and clinical trials are tumor-associated antigens (TAAs). TAA are structures (i.e. proteins, enzymes or carbohydrates) which are present on tumor cells and relatively absent or diminished on normal cells. By virtue of being fairly unique to the tumor cell, TAAs provide targets for the immune system to recognize and cause their destruction. Example of TAAs include, but are not limited to gangliosides (GM2), prostate specific antigen (PSA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) (produced by colon cancers and other adenocarcinomas, e.g. breast, lung, gastric, and pancreas cancer s), melanoma associated antigens (MART-1, gp 100, MAGE 1,3 tyrosinase), papillomavirus E6 and E7 fragments, whole cells or portions/lysates of autologous tumor cells and allogeneic tumor cells.

[00470] An additional component may be used in the combination to augment the immune response to TAAs. Examples of adjuvants include, but are not limited to, bacillus Calmette-Guerin (BCG), endotoxin lipopolysaccharides, keyhole limpet hemocyanin (GKLH), interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF) and cytoxan, a chemotherapeutic agent which is believed to reduce tumor-induced suppression when given in low doses.

[00471] For the treatment of inflammatory diseases and pain, compounds according to the present invention may be administered with an agent selected from the group comprising: corticosteroids, non-steroidal anti-inflammatories, muscle relaxants and combinations thereof with other agents, anesthetics and combinations thereof with other agents, expectorants and combinations thereof with other agents, antidepressants, anticonvulsants and combinations thereof; antihypertensives, opioids, topical cannabinoids, and other agents, such as capsaicin.

[00472] For the treatment of inflammatory diseases and pain, compounds according to the present invention may be administered with an agent selected from the group comprising: betamethasone dipropionate (augmented and nonaugmented), betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream (Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%)), guaifenesin, guaifenesin/ketoprofen/cyclobenzaprine, amitriptyline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisooxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamezipine, zonisamide, mexiletine, gabapentin/clonidine, gabapentin/carbamazepine, carbamazepine/cyclobenzaprine, antihypertensives

including clonidine, codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil; CB1/CB2 ligands, acetaminophen, infliximab) nitric oxide synthase inhibitors, particularly inhibitors of inducible nitric oxide synthase; and other agents, such as capsaicin.

5 [00473] For the treatment of ophthalmologic disorders and diseases of the eye, compounds according to the present invention may be administered with an agent selected from the group comprising: beta-blockers, carbonic anhydrase inhibitors, α - and β -adrenergic antagonists including α -adrenergic antagonists, α 2 agonists, miotics, prostaglandin analogs, corticosteroids, immunosuppressant agents, timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol, brinzolamide, dorzolamide, nipradilol, iopidine, 10 brimonidine, pilocarpine, epinephrine, latanoprost, travoprost, bimatoprost, unoprostone, dexamethasone, prednisone, methylprednisolone, azathioprine, cyclosporine, and immunoglobulins.

[00474] For the treatment of autoimmune disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: corticosteroids, immunosuppressants, prostaglandin analogs and antimetabolites, dexamethasone, prednisone, methylprednisolone, 15 azathioprine, cyclosporine, immunoglobulins, latanoprost, travoprost, bimatoprost, unoprostone, infliximab, rituximab and methotrexate.

[00475] For the treatment of metabolic disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: insulin, insulin derivatives and mimetics, insulin secretagogues, insulin sensitizers, biguanide agents, alpha-glucosidase inhibitors, 20 insulinotropic sulfonylurea receptor ligands, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors, GLP-1 (glucagon like peptide-1), GLP-1 analogs, DPPIV (dipeptidyl peptidase IV) inhibitors, RXR ligands sodium-dependent glucose co-transporter inhibitors, glycogen phosphorylase A inhibitors, an AGE breaker, PPAR modulators, non-glitazone type PPARS agonist, tformin, Glipizide, glyburide, Amaryl, meglitinides, nateglinide, repaglinide, PT- 25 112, SB-517955, SB4195052, SB-216763, NN-57-05441, NN-57-05445, GW-0791, AGN-¹⁹4²⁰4, T-1095, BAY R3401, acarbose Exendin-4, DPP728, LAF237, vildagliptin, MK-0431, saxagliptin, GSK23A, pioglitazone, rosiglitazone, (R)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzene-sulfonyl}2,3-dihydro-1H-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, and GI-262570.

30 [00476] For the combinational treatment and uses described herein, the administration of the compound/composition with a therapeutic agent, surgery, and/or radiation therapy may cause one or more undesirable side effects from the combination treatment. Such side effects may include, for example, nausea, vomiting, immunosuppression and susceptibility to infections, anemia and pain. It is, therefore, beneficial to the patient that these side effects are mitigated or abrogated. Additional 35 therapeutic agents for treatment of these side effects may be administered along with the combination treatment.

[00477] In some embodiments, the combination treatments with the invention described herein can be administered with a therapeutic agent specific for the treatment of side effects. In these embodiments, the combination treatments with the invention described herein can be fixed with the additional

therapeutic agent specific for the treatment of side effects or non-fixed with the additional therapeutic agent for treatment of side effects.

[00478] In applications with administration of the therapeutic agent for treatment of side effects with the combination treatments as described, the therapeutic agent for treatment of side effects may be administered concurrently (*e.g.*, simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature and onset of the side effect, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (*i.e.*, within a single treatment protocol) with the compound/composition. For a non-limiting example, an anti-nausea drug may be prophylactically administered prior to combination treatment with the compound and radiation therapy. For another non-limiting example, an agent for rescuing immuno-suppressive side effects is administered to the patient subsequent to the combination treatment of compound and another chemotherapeutic agent. The routes of administration for the therapeutic agent for side effects can also differ than the administration of the combination treatment. The determination of the mode of administration for treatment of side effects and the advisability of administration, where possible, in the same pharmaceutical composition, is within the knowledge of the skilled clinician with the teachings described herein. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician. The particular choice of therapeutic agent for treatment of side effects will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol.

[00479] In some embodiments, therapeutic agents specific for treating side effects may be administered before the administration of the combination treatment described. In other embodiments, therapeutic agents specific for treating side effects may be administered simultaneously with the administration of the combination treatment described. In another embodiment, therapeutic agents specific for treating side effects may be administered after the administration of the combination treatment described.

[00480] In some embodiments, therapeutic agents specific for treating side effects may include, but are not limited to, anti-emetic agents, immuno-restorative agents, antibiotic agents, anemia treatment agents, and analgesic agents for treatment of pain and inflammation.

[00481] Anti-emetic agents are a group of drugs effective for treatment of nausea and emesis (vomiting). Cancer therapies frequently cause urges to vomit and/or nausea. Many anti-emetic drugs target the 5-HT₃ serotonin receptor which is involved in transmitting signals for emesis sensations. These 5-HT₃ antagonists include, but are not limited to, dolasetron (Anzemet®), granisetron (Kytril®), ondansetron (Zofran®), palonosetron and tropisetron. Other anti-emetic agents include, but are not limited to, the dopamine receptor antagonists such as chlorpromazine, domperidone, droperidol, haloperidol, metaclopramide, promethazine, and prochlorperazine; antihistamines such as cyclizine, diphenhydramine, dimenhydrinate, meclizine, promethazine, and hydroxyzine; lorazepam, scopolamine, dexamethasone, emetrol®, propofol, and trimethobenzamide. Administration of these anti-emetic agents in addition to the above described combination treatment will manage the potential nausea and emesis side effects caused by the combination treatment.

[00482] Immuno-restorative agents are a group of drugs that counter the immuno-suppressive effects of many cancer therapies. The therapies often cause myelosuppression, a substantial decrease in the production of leukocytes (white blood cells). The decreases subject the patient to a higher risk of infections. Neutropenia is a condition where the concentration of neutrophils, the major leukocyte, is severely depressed. Immuno-restorative agents are synthetic analogs of the hormone, granulocyte colony stimulating factor (G-CSF), and act by stimulating neutrophil production in the bone marrow. These include, but are not limited to, filgrastim (Neupogen®), PEG-filgrastim (Neulasta®) and lenograstim. Administration of these immuno-restorative agents in addition to the above described combination treatment will manage the potential myelosuppression effects caused by the combination treatment.

[00483] Antibiotic agents are a group of drugs that have anti-bacterial, anti-fungal, and anti-parasite properties. Antibiotics inhibit growth or causes death of the infectious microorganisms by various mechanisms such as inhibiting cell wall production, preventing DNA replication, or deterring cell proliferation. Potentially lethal infections occur from the myelosuppression side effects due to cancer therapies. The infections can lead to sepsis where fever, widespread inflammation, and organ dysfunction arise. Antibiotics manage and abolish infection and sepsis and include, but are not limited to, amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, tobramycin, loracarbef, ertapenem, cilastatin, meropenem, cefadroxil, cefazolin, cephalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, teicoplanin, vancomycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, aztreonam, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, nafcillin, penicillin, piperacillin, ticarcillin, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, trovafloxacin, benzamide, bumetanide, chlorthalidone, clopamide, dichlorphenamide, ethoxzolamide, indapamide, mafenide, mefruside, metolazone, probenecid, sulfanilamides, sulfamethoxazole, sulfasalazine, sumatriptan, xipamide, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, chloramphenicol, clindamycin, ethambutol, fosfomycin, fusidic acid, furazolidone, isoniazid, linezolid, metronidazole, mupirocin, nitrofurantoin, platesimycin, pyrazinamide, dalfopristin, rifampin, spectinomycin, and telithromycin. Administration of these antibiotic agents in addition to the above described combination treatment will manage the potential infection and sepsis side effects caused by the combination treatment.

[00484] Anemia treatment agents are compounds directed toward treatment of low red blood cell and platelet production. In addition to myelosuppression, many cancer therapies also cause anemias, deficiencies in concentrations and production of red blood cells and related factors. Anemia treatment agents are recombinant analogs of the glycoprotein, erythropoietin, and function to stimulate erythropoiesis, the formation of red blood cells. Anemia treatment agents include, but are not limited to, recombinant erythropoietin (EPOGEN®, Dynopro®) and Darbepoetin alfa (Aranesp®). Administration of these anemia treatment agents in addition to the above described combination treatment will manage the potential anemia side effects caused by the combination treatment.

[00485] Pain and inflammation side effects arising from the described herein combination treatment may be treated with compounds selected from the group comprising: corticosteroids, non-steroidal anti-inflammatory, muscle relaxants and combinations thereof with other agents, anesthetics and combinations thereof with other agents, expectorants and combinations thereof with other agents, antidepressants, anticonvulsants and combinations thereof; antihypertensives, opioids, topical cannabinoids, and other agents, such as capsaicin.

[00486] For the treatment of pain and inflammation side effects, compounds according to the present invention may be administered with an agent selected from the group comprising: betamethasone dipropionate (augmented and nonaugmented), betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream (Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%)), guaifenesin, guaifenesin/ketoprofen/cyclobenzaprine, amitriptyline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisoxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamezipine, zonisamide, mexiletine, gabapentin/clonidine, gabapentin/carbamazepine, carbamazepine/cyclobenzaprine, antihypertensives including clonidine, codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil; CB1/CB2 ligands, acetaminophen, infliximab) nitric oxide synthase inhibitors, particularly inhibitors of inducible nitric oxide synthase; and other agents, such as capsaicin. Administration of these pain and inflammation analgesic agents in addition to the above described combination treatment will manage the potential pain and inflammation side effects caused by the combination treatment.

Kits

[00487] The agents, pharmaceutical compositions and methods described herein provide kits for the treatment of disorders, such as the ones described herein. These kits comprise a first and second agent or pharmaceutical compositions thereof in a container and, optionally, instructions teaching the use of the kit according to the various methods and approaches described herein. Such kits optionally include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, disease state for which the composition is to be administered, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. In various embodiments, the kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may, in some embodiments, be marketed directly to the consumer. In certain embodiments, the packaging material

further comprises a container for housing the composition and optionally a label affixed to the container. The kit optionally comprises additional components, such as but not limited to syringes for administration of the composition.

5 [00488] In one embodiment of the present invention, the kit described herein contains a therapeutically effect amount of first agent and a therapeutically effective amount of a second agent, wherein the first and second agents are as described herein. In certain embodiments, the present invention provides for a kit comprising a pharmaceutical composition, wherein the pharmaceutical composition contains either one of or both of the first and second agents.

10 [00489] In another embodiment, the kit comprises at least one first pharmaceutical composition and at least one second pharmaceutical composition. The first pharmaceutical composition contains a therapeutically effective amount of the first agent and the second pharmaceutical composition contains a therapeutically effective amount of the second agent. In some embodiments of the present invention, the first pharmaceutical composition does not contain a therapeutically effective amount of the second agent. In certain embodiments, the second pharmaceutical composition does not contain a
15 therapeutically effective amount of the first agent. In other embodiments, the first pharmaceutical composition contains a therapeutically effective amount of the first agent and a therapeutically effective amount of the second agent. In still other embodiments, the second pharmaceutical composition contains a therapeutically effective amount of the second agent and a therapeutically effective amount of the first agent. In some embodiments, the kit further contains a third pharmaceutical composition
20 that contains therapeutically effective amounts of the first and second agents.

[00490] In a specific embodiment, the kit comprises (1) a first pharmaceutical composition that contains a therapeutically effective amount of a first agent and a therapeutically effective amount of the second agent, and (2) a second pharmaceutical composition that contains a therapeutically effective amount of the second agent and does not contain a therapeutically effective amount of the first agent. In another
25 specific embodiment, the kit comprises (1) a first pharmaceutical composition that contains a therapeutically effective amount of a first agent and does not contain a therapeutically effective amount of the second agent, and (2) a second pharmaceutical composition that contains a therapeutically effective amount of the second agent and a therapeutically effective amount of the first agent.

[00491] In some embodiments, the kit comprises a first pharmaceutical composition that is visibly different
30 from a second pharmaceutical composition. The visible differences may be for example shape, size, color, state (e.g. liquid/solid), physical markings (e.g. letters, numbers) or a combination of these and the like. In certain embodiments, the kit comprises a first pharmaceutical composition that is a first color and a second pharmaceutical composition that is a second color. In embodiments wherein the first and second colors are different, the different colors of the first and second pharmaceutical compositions
35 is used, e.g., to distinguish between the first and second pharmaceutical compositions. In further embodiments, the third pharmaceutical composition is a third color.

[00492] In some embodiments, wherein the packaging material further comprises a container for housing the pharmaceutical composition, the kit comprises a first pharmaceutical composition that is in a different physical location within the kit from a second pharmaceutical composition. In some embodiments, the
40 different physical locations containing the first and second pharmaceutical compositions comprise

separately sealed individual compartments. In certain embodiments, the kit comprises a first pharmaceutical composition that is in a first separately sealed individual compartment and a second pharmaceutical composition that is in a second separately sealed individual compartment. In embodiments wherein the first and second compartments are separate, the different locations of the first and second pharmaceutical compositions are used, e.g., to distinguish between the first and second pharmaceutical compositions. In further embodiments, the third pharmaceutical composition is in a third physical location within the kit.

[00493] In some embodiments, where discrimination between the first and second pharmaceutical compositions is desirable, the kit comprises first and second pharmaceutical compositions both of different color and located in different physical locations within the kit.

[00494] The compounds described herein can be utilized for diagnostics and as research reagents. For example, the compounds described herein, either alone or in combination with other compounds, can be used as tools in differential and/or combinatorial analyses to elucidate expression patterns of genes expressed within cells and tissues. As one non-limiting example, expression patterns within cells or tissues treated with one or more compounds are compared to control cells or tissues not treated with compounds and the patterns produced are analyzed for differential levels of gene expression as they pertain, for example, to disease association, signaling pathway, cellular localization, expression level, size, structure or function of the genes examined. These analyses can be performed on stimulated or unstimulated cells and in the presence or absence of other compounds which affect expression patterns.

[00495] Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

[00496] The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

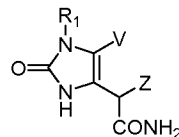
Examples

[00497] The present invention is further illustrated by the following examples, which should not be construed as limiting in any way. The experimental procedures to generate the data shown are discussed in more detail below. The invention has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation.

I Chemical Syntheses

[00498] It should be understood that the following are provided for exemplary purposes and additional compounds and compounds with the additional substitutions are contemplated by the present invention. For example, where a substituent is indicated in the para position of a ring, it should be understood that the substituent may be in the ortho or meta positions instead or that there may be an additional substituent in the ortho or meta positions. Also, where a substituent is exemplified on one compound, it

should be understood that that substituent could also be attached to any of the other compounds described herein.

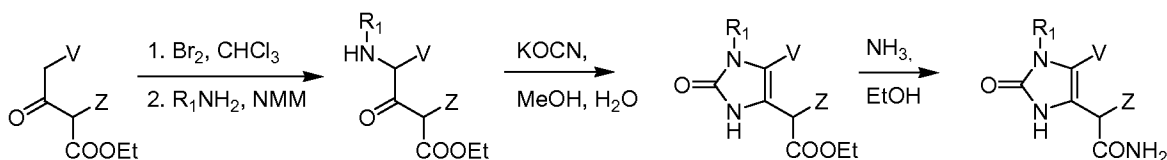


Example 1A: General Synthesis of Compounds of the Formula 1A

5 **[00499]** Compounds of the Formula 1A are synthesized according to Scheme 1A, and by modifications of the procedures described by DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710 and Orr, D. E. and Miah, A. *Chem Ind.* **1983**, 392 (and references therein), where R₁, V and Z are as defined herein.

10 **[00500]** When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 1A



Step 1: Ethyl 4-bromo-2-(Z-substituted)-3-oxo-4-(V-substituted) butanoates

15 **[00501]** Following a modification of the procedure of Orr, D. E. and Miah, A. *Chem Ind.* **1983**, 392, bromine (11 mmol) is added dropwise at 0°C to a solution of the ethyl 2-(Z-substituted)-3-oxo-4-(V-substituted) butanoate derivative (10 mmole) in chloroform (25 mL). The solution is stirred at ambient temperature until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with saturated sodium bicarbonate solution, 1 N hydrochloric acid, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is utilized below in the next step.

Step 2: Ethyl 4-(R₁-substituted)-amino-2-(Z-substituted)-3-oxo-4-(V-substituted) butanoates

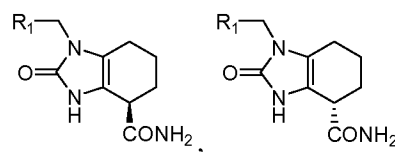
25 **[00502]** Following a modification of the procedure of Orr, D. E. and Miah, A. *Chem Ind.* **1983**, 392, to a solution of the crude ethyl 4-bromo-2-(Z-substituted)-3-oxo-4-(V-substituted) butanoate (10 mmol), prepared above in Step 1, at 0°C under a nitrogen atmosphere is added N-methyl morpholine (20 mmol) followed by the R₁-substituted amine derivative (11 mmol). The solution is stirred at ambient temperature or optionally heated to reflux until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is optionally purified by preparative chromatography, followed conversion to the hydrochloride salt, to afford the product as a solid which is utilized below in the next step.

Step 3: Ethyl 2-(Z-substituted)-2-(1-(R₁-substituted)-2-oxo-5-(V-substituted)-2,3-dihydro-1H-imidazol-4-yl)acetates

[00503] Following a modification of the procedure of DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710, to a solution of ethyl 4-(R₁-substituted)-amino-2-(Z-substituted)-3-oxo-4-(V-substituted) butanoate hydrochloride salt (10 mmol), prepared above in Step 2, in methanol (10 mL) is added potassium isocyanate (11 mmol) dissolved in water (5 mL). After stirring at ambient temperature for three hours, the solution is optionally heated to reflux until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

Step 4: 2-(Z-substituted)-2-(1-(R₁-substituted)-2-oxo-5-(V-substituted)-2,3-dihydro-1H-imidazol-4-yl)acetamides

[00504] Into a Parr pressure bottle, anhydrous ammonia gas (0.10 mole) is charged into a solution of the ethyl 2-(Z-substituted)-2-(1-(R₁-substituted)-2-oxo-5-(V-substituted)-2,3-dihydro-1H-imidazol-4-yl)acetate intermediate (10 mmol), prepared in step 1, at 0°C in ethanol (25 mL). The bottle is sealed and the reaction mixture is stirred at ambient temperature until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent and excess ammonia are removed in vacuo and the resultant crude product is recrystallized from the appropriate solvent or purified by preparative chromatography, affording the desired product as a solid.

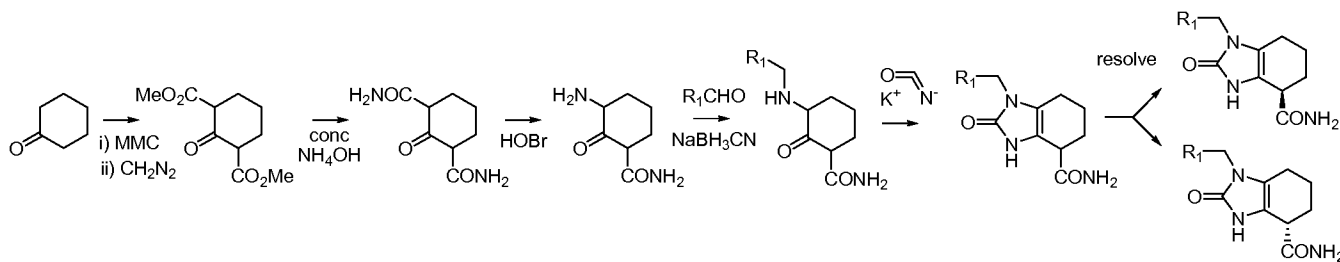


Example 1B: General Synthesis of Compounds of the Formula 1B

[00505] Compounds of the Formula 1B can be synthesized according to Scheme 1B, where R₁ is as defined herein.

[00506] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 1B



Step 1: Dimethyl 2,6-cyclohexanonedicarboxylate

[00507] Cyclohexanone (18.6 mmol) is heated with a magnesium methyl carbonate solution (1.94M; 80 mL) at 120-130°C for 6 hours. After hydrolysis the crude product is extracted into ether, dried, and

treated with ethereal diazomethane. Crystallization from methanol gives the pure product. See Stiles, *J. Am. Chem. Soc.* **1959**, 81, 2598.

Step 2: 2-Oxocyclohexane-1,3-dicarboxamide

[00508] Treatment of dimethyl 2,6-cyclohexanonedicarboxylate with concentrated ammonium hydroxide gives 2-oxocyclohexane-1,3-dicarboxamide

Step 3: 3-Amino-2-oxocyclohexanecarboxamide

[00509] 2-Oxocyclohexane-1,3-dicarboxamide is treated with one equivalent of hypobromous acid to effect a mono Hoffman rearrangement to give 3-amino-2-oxocyclohexanecarboxamide

Step 4: R₁-Amino substituted 3-amino-2-oxocyclohexanecarboxamide

[00510] Amino amide is used to reductively aminate R₁-CHO to give amino substituted 3-amino-2-oxocyclohexanecarboxamide.

Step 5: 1-((R₁)methyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-benzo[d]imidazole-4-carboxamide

[00511] Potassium isocyanate (30 mmol) and R₁-amino substituted 3-amino-2-oxocyclohexanecarboxamide hydrochloride salt (30 mmol) in water (25 mL) are heated on a steam bath for 7 hours. The solution is cooled overnight resulting in the formation of a solid which is isolated by filtration. The solid is washed with water and may be recrystallized from ethanol. See DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710.

Step 6: (*R*)-1-((R₁)methyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-benzo[d]imidazole-4-carboxamide and (*S*)-1-((R₁)methyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-benzo[d]imidazole-4-carboxamide

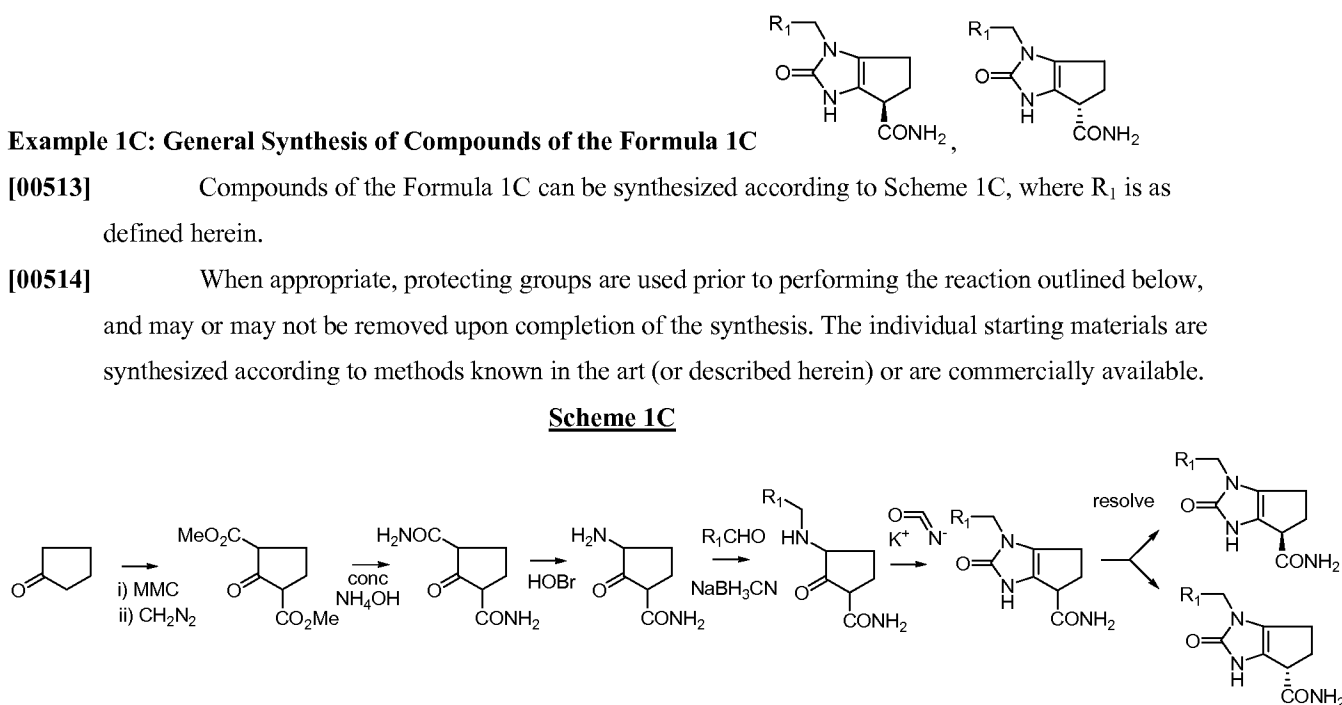
[00512] 1-((R₁)methyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-benzo[d]imidazole-4-carboxamide is resolved into individual enantiomers, (*R*)-1-((R₁)methyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-benzo[d]imidazole-4-carboxamide and (*S*)-1-((R₁)methyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-benzo[d]imidazole-4-carboxamide by standard techniques, including chromatography over a chiral column.

Example 1C: General Synthesis of Compounds of the Formula 1C

[00513] Compounds of the Formula 1C can be synthesized according to Scheme 1C, where R₁ is as defined herein.

[00514] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 1C



Step 1: Dimethyl 2,6-cyclopentanonedicarboxylate

[00515] Cyclopentanone (18.6 mmol) is heated with a magnesium methyl carbonate solution (1.94M; 80 mL) at 120-130°C for 6 hours. After hydrolysis the crude product is extracted into ether, dried, and treated with ethereal diazomethane. Crystallization from methanol gives the pure product. See Stiles, *J. Am. Chem. Soc.* **1959**, 81, 2598.

Step 2: 2-Oxocyclopentane-1,3-dicarboxamide

[00516] Treatment of dimethyl 2,6-cyclopentanonedicarboxylate with concentrated ammonium hydroxide gives 2-oxocyclopentane-1,3-dicarboxamide

Step 3: 3-Amino-2-oxocyclopentanecarboxamide

[00517] 2-Oxocyclopentane-1,3-dicarboxamide is treated with one equivalent of hypobromous acid to effect a mono Hoffman rearrangement to give 3-amino-2-oxocyclopentanecarboxamide

Step 4: R₁-Amino substituted 3-amino-2-oxocyclopentanecarboxamide

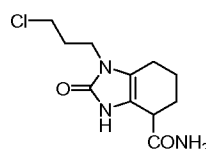
[00518] Amino amide is used to reductively aminate R₁-CHO to give amino substituted 3-amino-2-oxocyclopentanecarboxamide.

Step 5: 1-((R₁)methyl)-1,2,3,4,5,6-hexahydro-2-oxocyclopenta[d]imidazole-4-carboxamide

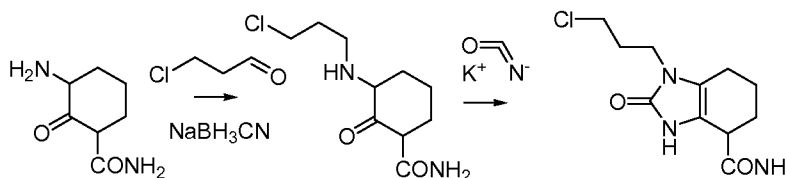
[00519] Potassium isocyanate (30 mmol) and R₁-amino substituted 3-amino-2-oxocyclopentanecarboxamide hydrochloride salt (30 mmol) in water (25 mL) are heated on a steam bath for 7 hours. The solution is cooled overnight resulting in the formation of a solid which is isolated by filtration. The solid is washed with water and may be recrystallized from ethanol. See DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710.

Step 6: (*R*)- 1-((R₁)methyl)-1,2,3,4,5,6-hexahydro-2-oxocyclopenta[d]imidazole-4-carboxamide and (*S*)- 1-((R₁)methyl)-1,2,3,4,5,6-hexahydro-2-oxocyclopenta[d]imidazole-4-carboxamide

[00520] 1-((R₁)methyl)-1,2,3,4,5,6-hexahydro-2-oxocyclopenta[d]imidazole-4-carboxamide is resolved into individual enantiomers, (*R*)- 1-((R₁)methyl)-1,2,3,4,5,6-hexahydro-2-oxocyclopenta[d]imidazole-4-carboxamide and (*S*)- 1-((R₁)methyl)-1,2,3,4,5,6-hexahydro-2-oxocyclopenta[d]imidazole-4-carboxamide by standard techniques, including chromatography over a chiral column.

**Example 1D: Synthesis of the Compound of Formula 1D**

[00521] 1-(3-Chloropropyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-benzo[d]imidazole-4-carboxamide is synthesized according to Scheme 1D.

Scheme 1D*Step 1: 3-Amino-2-oxocyclohexanecarboxamide*

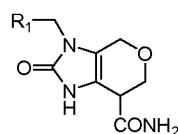
[00522] 3-Amino-2-oxocyclohexanecarboxamide is prepared as described above.

Step 2: 3-(3-chloropropylamino)-2-oxocyclohexanecarboxamide

[00523] 3-Amino-2-oxocyclohexanecarboxamide is reductively aminated with 3-chloropropanal to give 3-(3-chloropropylamino)-2-oxocyclohexanecarboxamide.

Step 2: 1-(3-Chloropropyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-benzo[d]imidazole-4-carboxamide

[00524] Potassium isocyanate (30 mmol) and 3-(3-chloropropylamino)-2-oxocyclohexanecarboxamide hydrochloride (30 mmol) in water (25 mL) are heated on a steam bath for 7 hours. The solution is cooled overnight resulting in the formation of a solid which is isolated by filtration. The solid is washed with water and may be recrystallized from ethanol. See DeStevens, *et al*, *A. J. Am. Chem. Soc.* **1957**, 79, 5710.

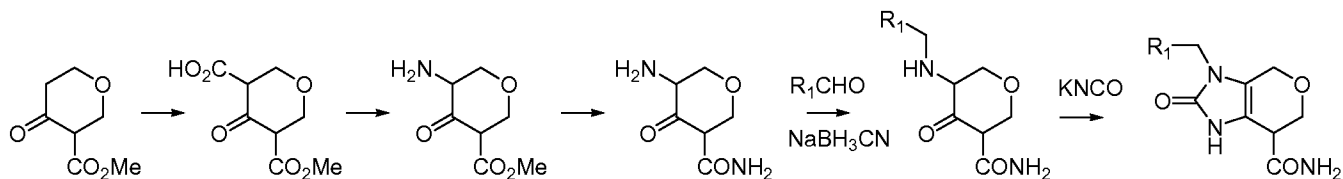


Example 1E: General Synthesis of Compounds of the Formula 1E

[00525] Compounds of the Formula 1E can be synthesized according to Scheme 1E, where R₁ is as defined herein.

[00526] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 1E



Step 1: Methyl tetrahydro-4-oxo-2H-pyran-3-carboxylate

[00527] *n*-Butyllithium (4.38 mL of 10.0 M in hexanes) is added to a solution of diisopropylamine (4.65 g, 45.9 mmol) in THF (50 mL) at -78 °C. This solution is added via cannula to a solution of dimethyl 4-oxa-1,7-heptanedioate (21 mmol) in THF (300 mL) at -78 °C. The solution is stirred at -78 °C for 15 min, and then the reaction quenched by addition of water (25 mL). The solution is partitioned between HCl (1N, 200 mL) and hexanes (200 mL). The resulting aqueous layer is extracted with ethyl acetate (150 mL), and the combined organic layers washed with brine (300 mL). The solution was dried, filtered, and concentrated, and the crude material purified by flash chromatography (1:4 ether/hexanes). See Conroy, *et al. J. Am. Chem. Soc.* **1997**, *119*, 4285.

Step 2: 5-(Methoxycarbonyl)-tetrahydro-4-oxo-2H-pyran-3-carboxylic acid

[00528] Methyl tetrahydro-4-oxo-2H-pyran-3-carboxylate (18.6 mmol) is heated with a magnesium methyl carbonate solution (1.94M; 80 mL) at 120-130°C for 6 hours. After hydrolysis the crude product is extracted into ether, dried, and isolated. Crystallization from methanol gives the pure product. See Stiles, *J. Am. Chem. Soc.* **1959**, *81*, 2598.

Step 3: Methyl 5-amino-tetrahydro-4-oxo-2H-pyran-3-carboxylate

[00529] The acid converted to the amine via Schmidt reaction using hydrazoic acid and sulfuric acid.

Step 4: 5-Amino-tetrahydro-4-oxo-2H-pyran-3-carboxamide

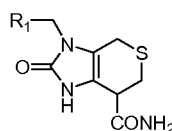
[00530] Treatment with concentrated ammonium hydroxide transforms the ester into the carboxamide.

Step 5: Amino substituted 5-amino-tetrahydro-4-oxo-2H-pyran-3-carboxamide

[00531] The amine group is substituted by reductive amination with R_1 -CHO.

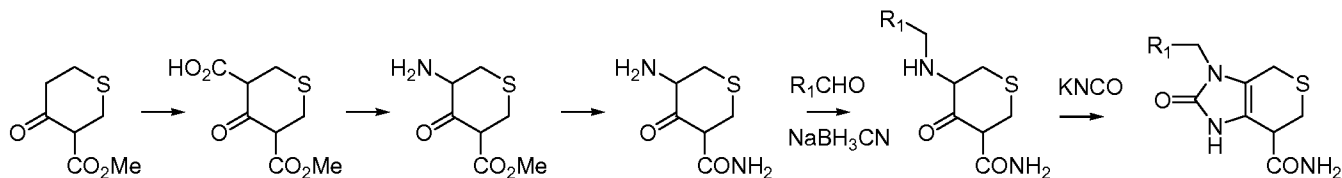
Step 6: 3-((R_1)-Methyl)-1,2,3,4,6,7-hexahydro-2-oxopyrano[4,3-d]imidazole-7-carboxamide

[00532] Potassium isocyanate (30 mmol) and R_1 -amino substituted 5-amino-tetrahydro-4-oxo-2H-pyran-3-carboxamide hydrochloride salt (30 mmol) in water (25 mL) are heated on a steam bath for 7 hours. The solution is cooled overnight resulting in the formation of a solid which is isolated by filtration. The solid is washed with water and may be recrystallized from ethanol. See DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710. Racemic mixtures may be resolved using standard techniques to afford the separate enantiomers, if desired.

**Example 1F: General Synthesis of Compounds of the Formula 1F**

[00533] Compounds of the Formula 1F can be synthesized according to Scheme 1F, where R_1 is as defined herein.

[00534] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 1F*Step 1: Methyl tetrahydro-4-oxo-2H-thiopyran-3-carboxylate*

[00535] *n*-Butyllithium (4.38 mL of 10.0 M in hexanes) is added to a solution of diisopropylamine (4.65 g, 45.9 mmol) in THF (50 mL) at -78 °C. This solution is added via cannula to a solution of dimethyl 4-thia-1,7-heptanedioate (21 mmol) in THF (300 mL) at -78 °C. The solution is stirred at -78 °C for 15 min, and then the reaction quenched by addition of water (25 mL). The solution is partitioned between HCl (1N, 200 mL) and hexanes (200 mL). The resulting aqueous layer is extracted with ethyl acetate (150 mL), and the combined organic layers washed with brine (300 mL). The solution was dried, filtered, and concentrated, and the crude material purified by flash chromatography (1:4 ether/hexanes). See Conroy, *et al. J. Am. Chem. Soc.* **1997**, 119, 4285.

Step 2: 5-(Methoxycarbonyl)-tetrahydro-4-oxo-2H-thiopyran-3-carboxylic acid

[00536] Methyl tetrahydro-4-oxo-2H-thiopyran-3-carboxylate (18.6 mmol) is heated with a magnesium methyl carbonate solution (1.94M; 80 mL) at 120-130°C for 6 hours. After hydrolysis the crude product is extracted into ether, dried, and isolated. Crystallization from methanol gives the pure product. See Stiles, *J. Am. Chem. Soc.* **1959**, 81, 2598.

Step 3: Methyl 5-amino-tetrahydro-4-oxo-2H-thiopyran-3-carboxylate

[00537] The acid converted to the amine via Schmidt reaction using hydrazoic acid and sulfuric acid.

Step 4: 5-Amino-tetrahydro-4-oxo-2H-thiopyran-3-carboxamide

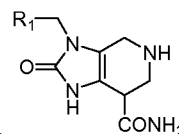
[00538] Treatment with concentrated ammonium hydroxide transforms the ester into the carboxamide.

Step 5: Amino substituted 5-amino-tetrahydro-4-oxo-2H-thiopyran-3-carboxamide

[00539] The amine group is substituted by reductive amination with R_1 -CHO.

Step 6: 3-((R_1)-Methyl)-1,2,3,4,6,7-hexahydro-2-oxothiopyrano[4,3-d]imidazole-7-carboxamide

[00540] Potassium isocyanate (30 mmol) and R_1 -amino substituted 5-amino-tetrahydro-4-oxo-2H-thiopyran-3-carboxamide hydrochloride salt (30 mmol) in water (25 mL) are heated on a steam bath for 7 hours. The solution is cooled overnight resulting in the formation of a solid which is isolated by filtration. The solid is washed with water and may be recrystallized from ethanol. See DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710. Racemic mixtures may be resolved using standard techniques to afford the separate enantiomers, if desired.

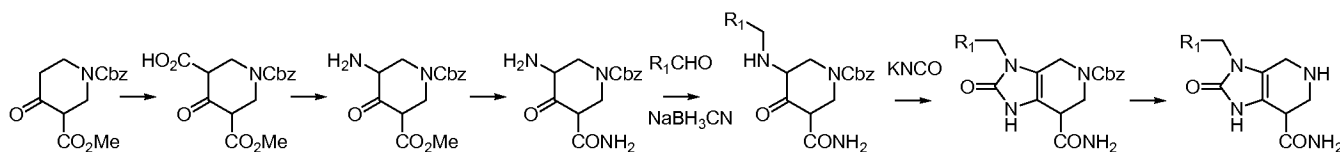


Example 1G: General Synthesis of Compounds of the Formula 1G

[00541] Compounds of the Formula 1G can be synthesized according to Scheme 1G, where R_1 is as defined herein.

[00542] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 1G



Step 1: 1-Benzyl 3-methyl 4-oxopiperidine-1,3-dicarboxylate

[00543] *n*-Butyllithium (4.38 mL of 10.0 M in hexanes) is added to a solution of diisopropylamine (4.65 g, 45.9 mmol) in THF (50 mL) at -78 °C. This solution is added via cannula to a solution of methyl 3-(N-Cbz-2-(methoxycarbonyl)ethylamino)propanoate (21 mmol) in THF (300 mL) at -78 °C. The solution is stirred at -78 °C for 15 min, and then the reaction quenched by addition of water (25 mL). The solution is partitioned between HCl (1N, 200 mL) and hexanes (200 mL). The resulting aqueous layer is extracted with ethyl acetate (150 mL), and the combined organic layers washed with brine (300 mL). The solution was dried, filtered, and concentrated, and the crude material purified by flash chromatography (1:4 ether/hexanes). See Conroy, *et al. J. Am. Chem. Soc.* **1997**, 119, 4285.

Step 2: 1-((benzyloxy)carbonyl)-5-(methoxycarbonyl)-4-oxopiperidine-3-carboxylic acid

[00544] 1-Benzyl 3-methyl 4-oxopiperidine-1,3-dicarboxylate (18.6 mmol) is heated with a magnesium methyl carbonate solution (1.94M; 80 mL) at 120-130°C for 6 hours. After hydrolysis the crude product

is extracted into ether, dried, and isolated. Crystallization from methanol gives the pure product. See Stiles, *J. Am. Chem. Soc.* **1959**, *81*, 2598.

Step 3: 1-Benzyl 3-methyl 5-amino-4-oxopiperidine-1,3-dicarboxylate

[00545] The acid converted to the amine via Schmidt reaction using hydrazoic acid and sulfuric acid.

Step 4: Benzyl 3-amino-5-carbamoyl-4-oxopiperidine-1-carboxylate

[00546] Treatment with concentrated ammonium hydroxide transforms the ester into the carboxamide.

Step 5: Amino substituted benzyl 3-amino-5-carbamoyl-4-oxopiperidine-1-carboxylate

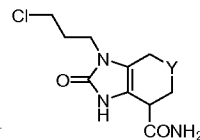
[00547] The amine group is substituted by reductive amination with R_1 -CHO.

Step 6: Benzyl 7-carbamoyl-3-((R_1)methyl)-2,3,6,7-tetrahydro-2-oxo-1H-imidazo[4,5-c]pyridine-5(4H)-carboxylate

[00548] Potassium isocyanate (30 mmol) and amino substituted benzyl 3-amino-5-carbamoyl-4-oxopiperidine-1-carboxylate hydrochloride salt (30 mmol) in water (25 mL) are heated on a steam bath for 7 hours. The solution is cooled overnight resulting in the formation of a solid which is isolated by filtration. The solid is washed with water and may be recrystallized from ethanol. See DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, *79*, 5710. Racemic mixtures may be resolved using standard techniques to afford the separate enantiomers, if desired.

Step 7: 3-((R_1)methyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-imidazo[4,5-c]pyridine-7-carboxamide

[00549] The Cbz *N*-protecting group is removed to give 3-((R_1)methyl)-2,3,4,5,6,7-hexahydro-2-oxo-1H-imidazo[4,5-c]pyridine-7-carboxamide. Racemic mixtures may be resolved using standard techniques to afford the separate enantiomers, if desired.

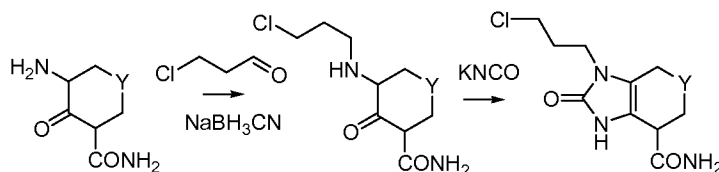


Example 1H: General Synthesis of Compounds of the Formula 1H

[00550] Compounds of the Formula 1H can be synthesized according to Scheme 1H, where Y is O, S, NCbz or NH.

[00551] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 1H



Step 1

[00552] Heterocyclic amino-carboxamides are prepared as described above in examples 1E, 1F or 1G.

Step 2

[00553] Heterocyclic amino-carboxamides are reductively aminated with 3-chloropropanal to give 3-chloropropylamino substituted heterocyclic carboxamides.

Step 3

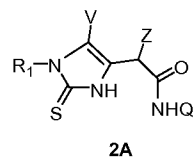
[00554] Treatment with KNCO (DeStevens, G.; Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710) gives the desired compounds. Protecting groups are removed if necessary. Racemic mixtures may be resolved using standard techniques to afford the separate enantiomers, if desired.

5 Examples 1I-1SS

[00555] Compounds 1I-1SS are synthesized as described in Examples 1A-1H using the appropriate starting materials.

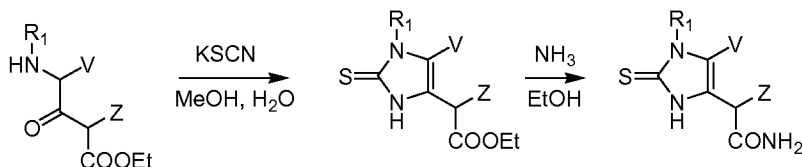
1I		1S		1BB	
1J		1T		1CC	
1K		1U		1DD	
1L		1V		1EE	
1M		1W		1FF	
1N		1X		1GG	
1O		1Y		1HH	
1P		1Z		1II	
1Q		1AA		1JJ	
1R					

1KK	
1LL	
1MM	
1NN	
1OO	
1PP	
1QQ	
1RR	
1SS	
1TT	
1UU	
1VV	
1WW	
1XX	
1YY	
1ZZ	

**Example 2A: General Synthesis of Compounds of the Formula 2A**

[00556] Compounds of the Formula 2A are synthesized according to Scheme 2A, and by modifications of the procedures described by DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710 and Robins, R. K. *J. Org. Chem.* **1963**, 28, 3041 (and references therein), where R₁, V, Z and Q are as defined herein.

[00557] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

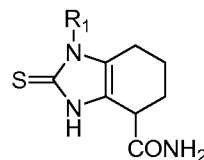
Scheme 2A

Step 1: Ethyl 2-(Z-substituted)-2-(1-(R₁-substituted)-2-thioxo-5-(V-substituted)-2,3-dihydro-1H-imidazol-4-yl)acetates

[00558] Following a modification of the procedure of DeStevens, G. and Halamandaris, A. *J. Am. Chem. Soc.* **1957**, 79, 5710, to a solution of ethyl 4-(R₁-substituted)-amino-2-(Z-substituted)-3-oxo-4-(V-substituted) butanoate hydrochloride salt (10 mmol), prepared above in Example 1, Step 2, in methanol (10 mL) is added potassium isothiocyanate (11 mmol) dissolved in water (5 mL). After stirring at ambient temperature for three hours, the solution is optionally heated to reflux until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

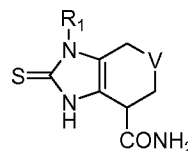
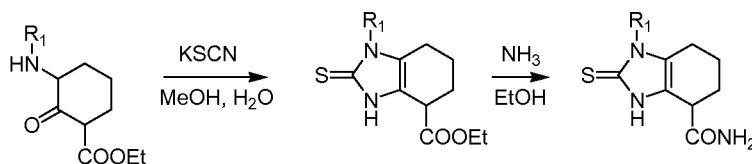
Step 2: 2-(Z-substituted)-2-(1-(R₁-substituted)-2-thioxo-5-(V-substituted)-2,3-dihydro-1H-imidazol-4-yl)acetamides

[00559] Into a Parr pressure bottle, anhydrous ammonia gas (0.10 mole) is charged into a solution of the ethyl 2-(Z-substituted)-2-(1-(R₁-substituted)-2-thioxo-5-(V-substituted)-2,3-dihydro-1H-imidazol-4-yl)acetate intermediate (10 mmol), prepared above in step 1, at 0°C in ethanol (25 mL). The bottle is sealed and the reaction mixture is stirred at ambient temperature until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent and excess ammonia are removed in vacuo and the resultant crude product is recrystallized from the appropriate solvent or purified by preparative chromatography, affording the desired product as a solid.

**Example 2B: General Synthesis of Compounds of the Formula 2B**

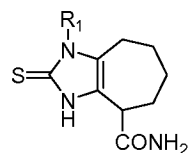
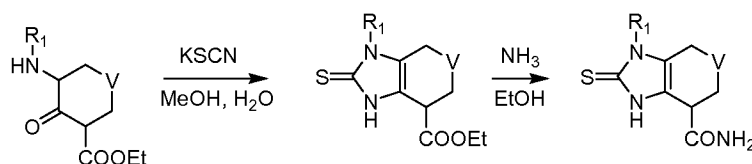
[00560] Compounds of the Formula 2B are synthesized according to Scheme 2B, where R₁ is as described herein.

[00561] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 2B**Example 2C: General Synthesis of Compounds of the Formula 2C**

[00562] Compounds of the Formula 2C are synthesized according to Scheme 2C, where V is O, S, or NH and R₁ is as described herein.

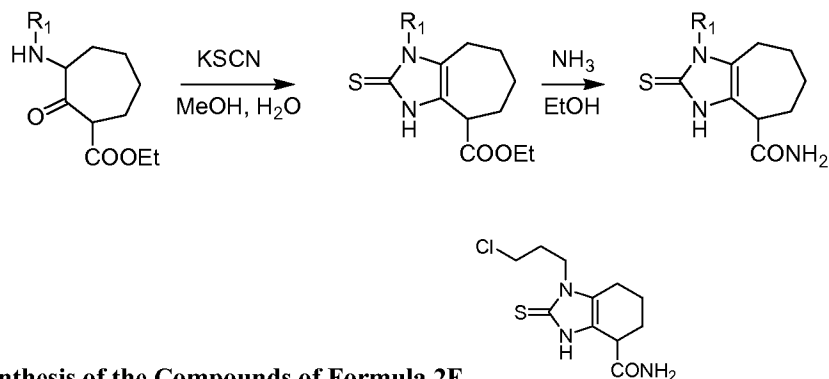
[00563] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 2C**Example 2D: General Synthesis of Compounds of the Formula 2D**

[00564] Compounds of the Formula 2D are synthesized according to Scheme 2D, where R₁ is as described herein.

[00565] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

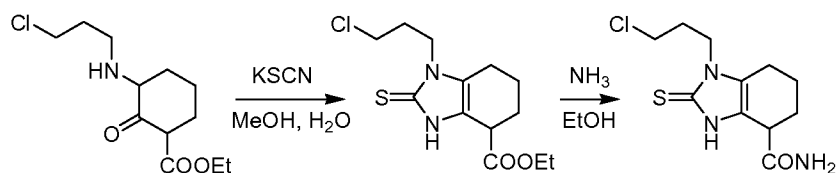
Scheme 2D

**Example 2E: Synthesis of the Compounds of Formula 2E**

[00566] 1-(3-chloropropyl)-2,3,4,5,6,7-hexahydro-2-thioxo-1H-benzo[d]imidazole-4-carboxamide is

5 synthesized according to Scheme 2E.

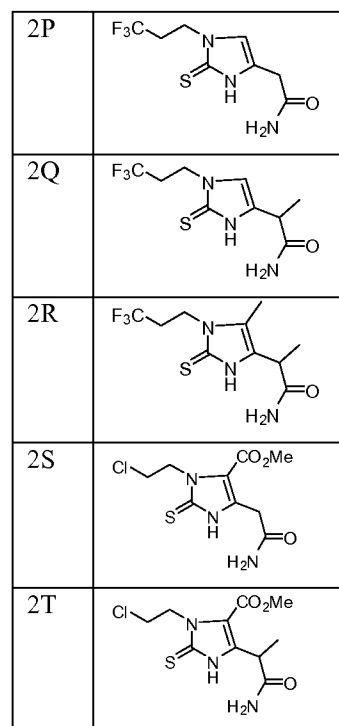
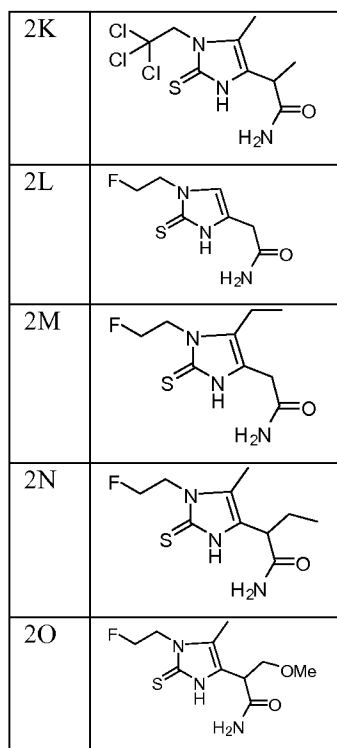
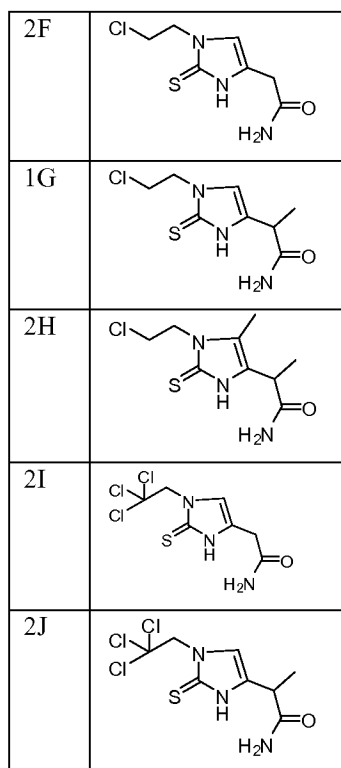
[00567] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

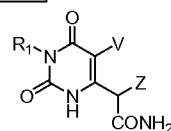
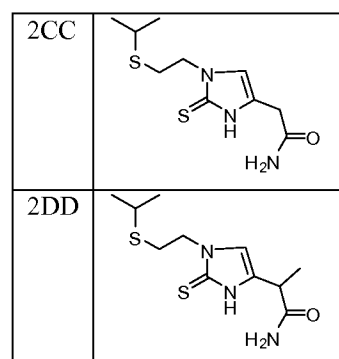
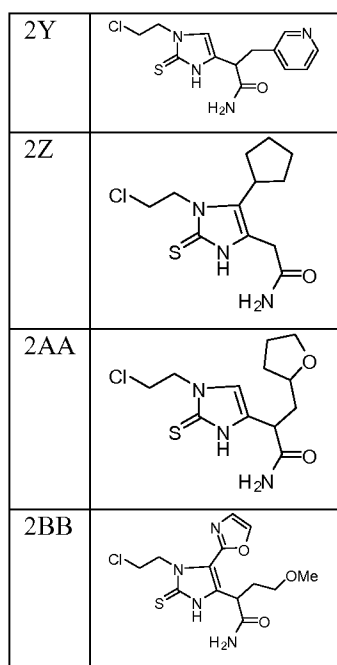
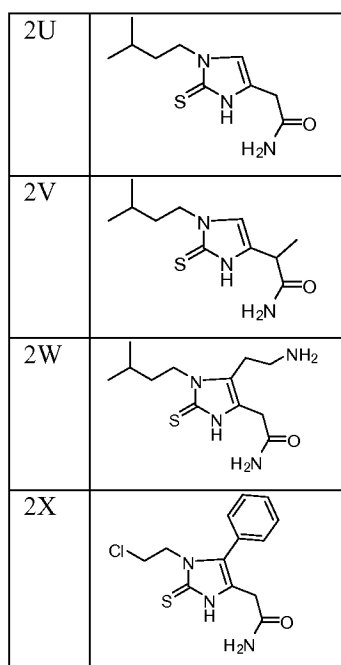
Scheme 2E

10

Examples 2F-2DD

[00568] Compounds 2F-2DD are synthesized as described in Examples 2A-2E using the appropriate starting materials.



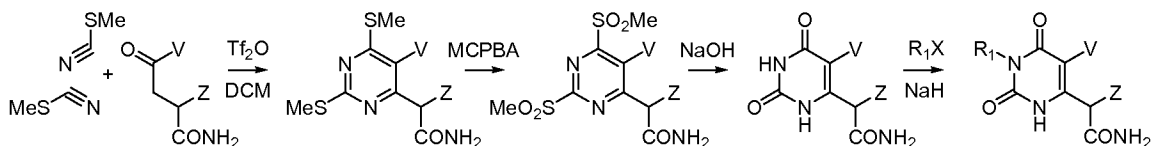


Example 3A: General Synthesis of Compounds of the Formula 3A

[00569] Compounds of the Formula 3A are synthesized according to Scheme 3A, and by modifications of the procedures described by Martinez, A. G. et al., *Tetrahedron* **1996**, 52, 7973, and Strekowski, L. et al., *Synthesis* **1988**, (and references therein), where R₁, V and Z are as described herein.

- 5 **[00570]** When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 3A



10 *Step 1:* 2-(Z-substituted)-2-(5-[V-substituted]-2,6-bis(methylthio)pyrimidin-4-yl)acetamide

[00571] Following modifications of the procedures described by Martinez, A. G. et al., *Tetrahedron* **1996**, 52, 7973, to a solution of methyl thiocyanate (45 mmol) in anhydrous dichloromethane (200 mL) at 0°C under a nitrogen atmosphere is added the 2-(Z-substituted)-4-oxo-4-(V-substituted)butanamide intermediate (15 mmol) followed by triflic anhydride (45 mmol). The solution is allowed to stir at ambient temperature for 24 hours, the reaction is cooled to -10°C, and then quenched with 1N sodium hydroxide solution (60 mL). The mixture is diluted with dichloromethane (200 mL) and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

Step 2: 2-(Z-substituted)-2-(5-[V-substituted]-2,6-bis(methylsulfonyl)pyrimidin-4-yl)acetamide

[00572] Following modifications of the procedures described by Martinez, A. G. et al., *Tetrahedron* **1996**, 52, 7973, to a solution of 2-(Z-substituted)-2-(5-[V-substituted]-2,6-bis(methylthio)pyrimidin-4-yl)acetamide (10 mmol) in anhydrous dichloromethane (100 mL) at 0°C under a nitrogen atmosphere is added 3-chloroperbenzoic acid (45 mmol). The mixture is stirred at ambient temperature for two hours.

5 The solution is extracted with a solution of sodium thiosulfate (5%, 100 mL), saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

Step 3: 2-(Z-substituted)-2-(5-[V-substituted]-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide

10 [00573] Following modifications of the procedures described by Martfnez, A. G. et al., *Tetrahedron* **1996**, 52, 7973, to sodium hydroxide solution (10%, 50 mL) is added the 2-(Z-substituted)-2-(5-[V-substituted]-2,6-bis(methylsulfonyl)pyrimidin-4-yl)acetamide prepared above in Step 2.. The mixture is refluxed until TLC or HPLC/MS analysis indicates completion of the reaction. The solution is cooled to 0°C and 3N hydrochloric acid is added until the pH=2. Filtration and washing with dichloromethane affords the

15 crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

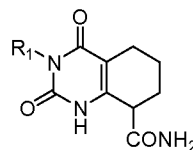
Step 4: 2-(Z-substituted)-2-(5-[V-substituted]-1-[R₁-substituted]-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide

[00574] To a solution of 2-(Z-substituted)-2-(5-[V-substituted]-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide (10 mmol), prepared above in Step 3, in anhydrous DMF(40 mL) at 0°C under nitrogen is added sodium hydride (11 mmol). After stirring for one hour, a solution of the appropriate alkylating agent R₁X (11 mmol , e.g. 3-bromo-1-chloropropane, 2-chloroethyl triflate, allyl chloride, benzyl bromide, propargyl chloride, ethyl 2-(trifluoromethylsulfonyloxy)propanoate) is added. After one hour,

20 the reaction mixture is slowly warmed to ambient temperature and monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The reaction is quenched by addition of saturated ammonium chloride solution (20 mL). Solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent

25 to afford the product as a solid.

30

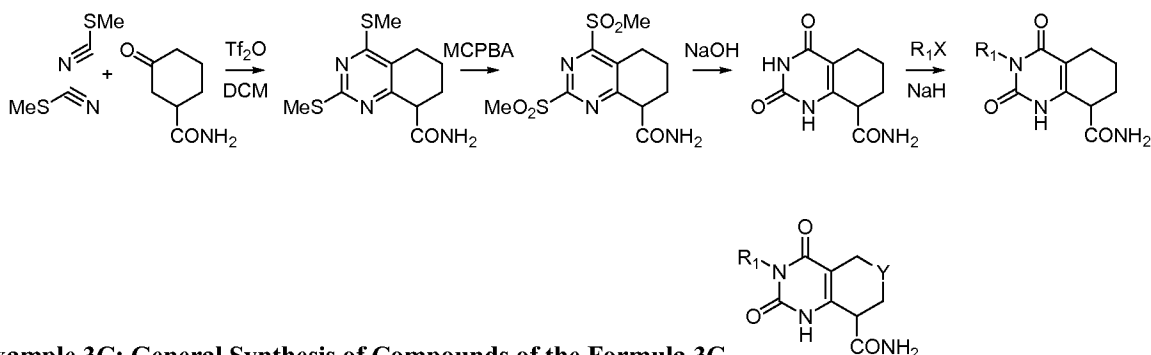


Example 3B: General Synthesis of Compounds of the Formula 3B

[00575] Compounds of the Formula 3B are synthesized according to Scheme 3B, where R₁ is as described herein.

35 [00576] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 3B

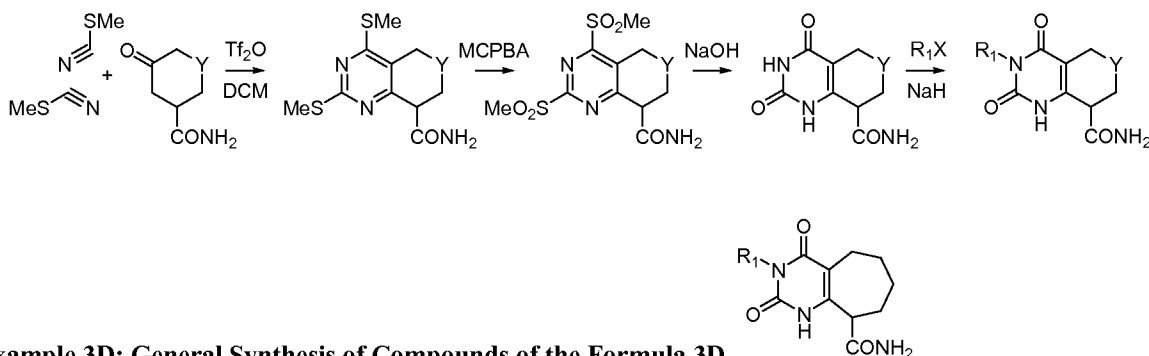


Example 3C: General Synthesis of Compounds of the Formula 3C

[00577] Compounds of the Formula 3C are synthesized according to Scheme 3C, where Y is O, S or NH and R_1 is as described herein.

[00578] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 3C

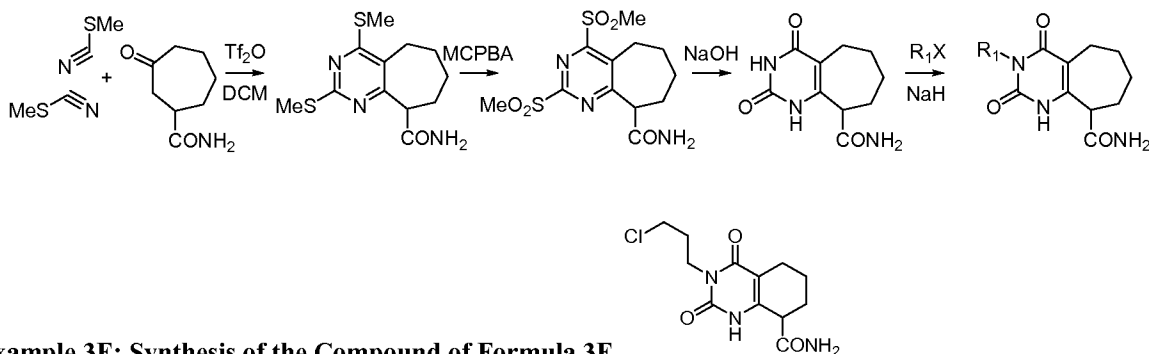


Example 3D: General Synthesis of Compounds of the Formula 3D

[00579] Compounds of the Formula 3D are synthesized according to Scheme 3D, where R_1 is as described herein.

[00580] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 3D

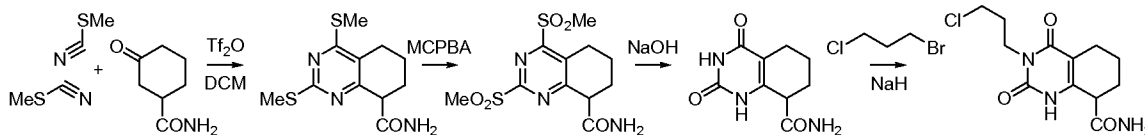


Example 3E: Synthesis of the Compound of Formula 3E

[00581] 3-(3-Chloropropyl)-1,2,3,4,5,6,7,8-octahydro-2,4-dioxoquinazoline-8-carboxamide is synthesized according to Scheme 3E.

[00582] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 3E



Step 1: 5,6,7,8-Tetrahydro-2,4-bis(methylthio)quinazoline-8-carboxamide

[00583] 3-Oxocyclohexanecarboxamide (15 mmol) is added to a solution of methyl thiocyanate (45 mmol) in anhydrous dichloromethane (200 mL) at 0°C under a nitrogen atmosphere, followed by addition of triflic anhydride (45 mmol). The solution is allowed to stir at ambient temperature for 24 hours, cooled to -10°C, and quenched with 1N sodium hydroxide solution (60 mL). The mixture is diluted with dichloromethane (200 mL) and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Martinez, A. G. et al., *Tetrahedron* **1996**, 52, 7973.

Step 2: 5,6,7,8-Tetrahydro-2,4-bis(methylsulfonyl)quinazoline-8-carboxamide

[00584] 3-chloroperbenzoic acid (45 mmol) is added to a solution of 5,6,7,8-tetrahydro-2,4-bis(methylthio)quinazoline-8-carboxamide (10 mmol) in anhydrous dichloromethane (100 mL) at 0°C under a nitrogen atmosphere. The mixture is stirred at ambient temperature for two hours. The solution is extracted with a solution of sodium thiosulfate (5%, 100 mL), saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Martinez, A. G. et al., *Tetrahedron* **1996**, 52, 7973.

Step 3: 1,2,3,4,5,6,7,8-Octahydro-2,4-dioxoquinazoline-8-carboxamide

[00585] 5,6,7,8-Tetrahydro-2,4-bis(methylsulfonyl)quinazoline-8-carboxamide is added to sodium hydroxide solution (10%, 50 mL). The mixture is refluxed until TLC or HPLC/MS analysis indicates completion of the reaction. The solution is cooled to 0°C and 3N hydrochloric acid is added until the pH=2. Filtration and washing with dichloromethane affords the crude product, which is purified by preparative chromatography or recrystallized. See Martfnez, A. G. et al., *Tetrahedron* **1996**, 52, 7973.

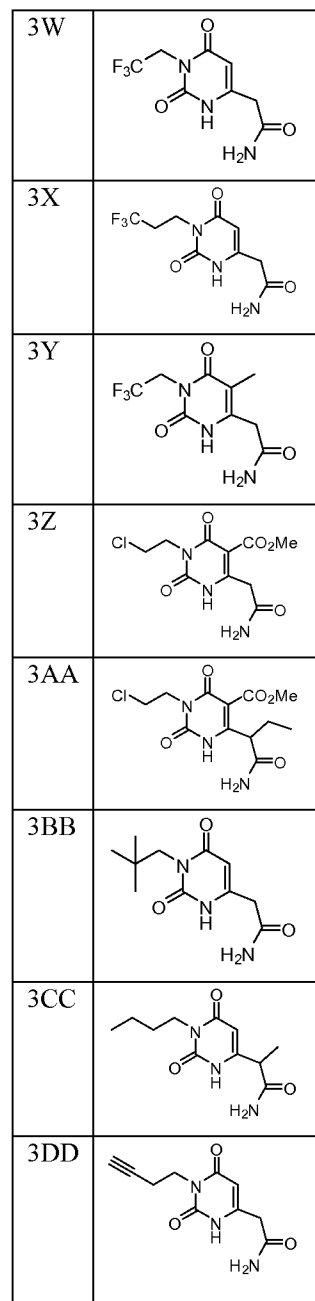
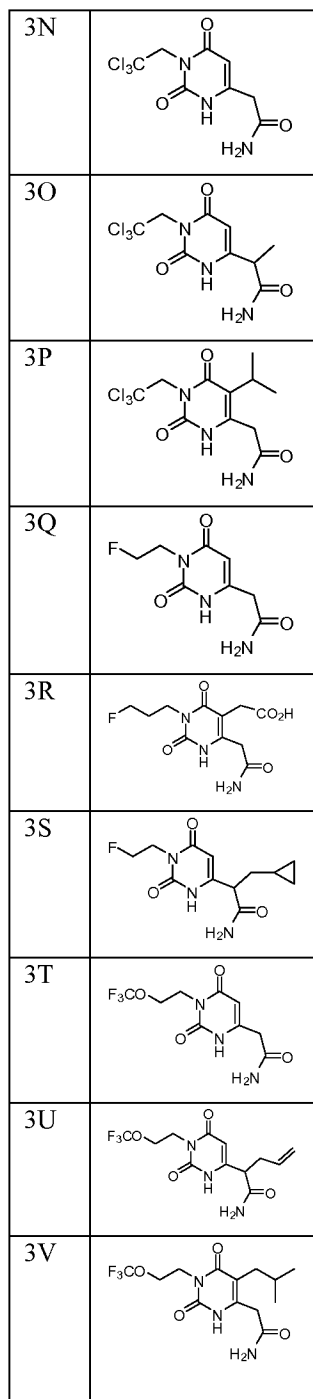
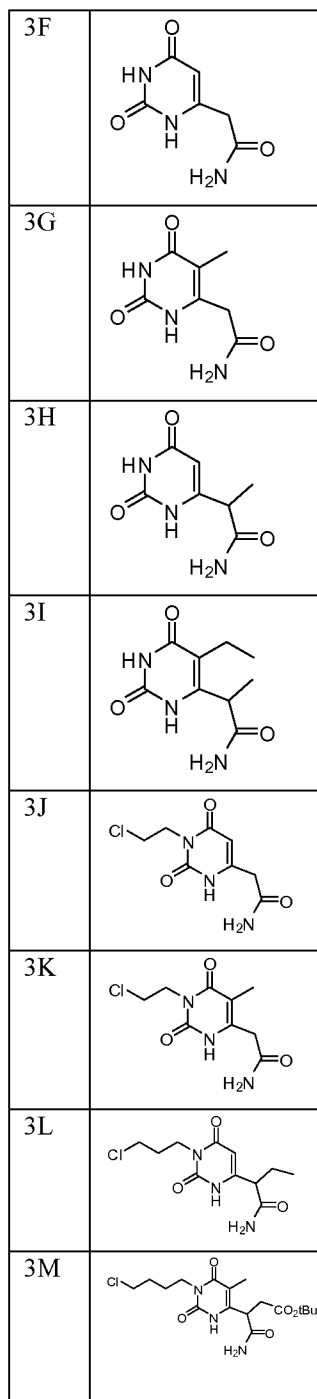
Step 4: 3-(3-chloropropyl)-1,2,3,4,5,6,7,8-octahydro-2,4-dioxoquinazoline-8-carboxamide

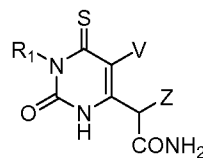
[00586] Sodium hydride (11 mmol) is added to a solution of 1,2,3,4,5,6,7,8-octahydro-2,4-dioxoquinazoline-8-carboxamide (10 mmol) in anhydrous DMF(40 mL) at 0°C under nitrogen. After stirring for one hour, a solution of 1-bromo-3-chloropropane (11 mmol) is added. After one hour, the reaction mixture is slowly warmed to ambient temperature and monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The reaction is quenched by addition of saturated ammonium chloride solution (20 mL). Solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over

anhydrous MgSO_4 . Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized.

Examples 3B-3DD

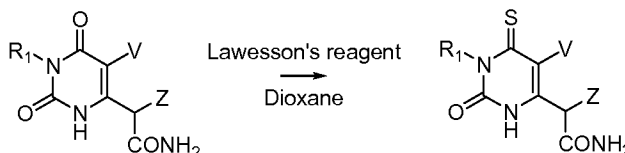
- 5 [00587] Compounds 3B-3DD are synthesized as described in Examples 3A-3E using the appropriate starting materials.



**Example 4A: General Synthesis of Compounds of the Formula 4A**

[00588] Compounds of the Formula 4A are synthesized according to Scheme 4A, and by modifications of the procedures described by Felczak, K.; Bretner, M.; Kulikowski, T.; Shugar, D. *Nucleosides & Nucleotides* **1993**, 12, 245 (and references therein), where R₁, V and Z are as described herein.

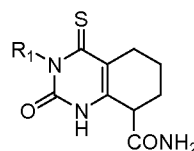
- 5 [00589] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 4A

- 10 *Step 1*: 2-(Z-substituted)-2-(1-[R₁-substituted]-2-oxo-5-[V-substituted]-6-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide

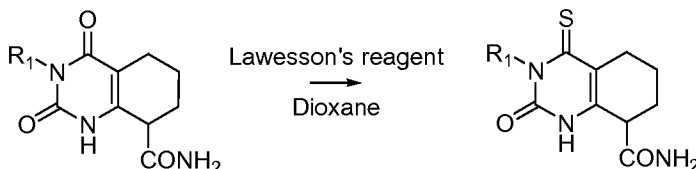
[00590] Following modifications of the procedures described by Felczak, K.; Bretner, M.; Kulikowski, T.; Shugar, D. *Nucleosides & Nucleotides* **1993**, 12, 245, to a solution of 2-(Z-substituted)-2-(5-[V-substituted]-1-[optionally R₁-substituted]-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide (10 mmol), prepared as described above Scheme 3A, Steps 3 and 4, in anhydrous dioxane (25 mL) was added Lawesson's reagent (10 mmol). The solution is refluxed for 3 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

20

**Example 4B: General Synthesis of Compounds of the Formula 4B**

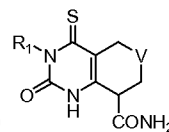
[00591] Compounds of the Formula 4B are synthesized according to Scheme 4B, where R₁ is as described herein.

- 25 [00592] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 4B

Step 1: 1,2,3,4,5,6,7,8-octahydro-3-R₁-2-oxo-4-thioxoquinazoline-8-carboxamide

[00593] Lawesson's reagent (10 mmol) is added to a solution of 1,2,3,4,5,6,7,8-octahydro-3- R_1 -2,4-dioxoquinazoline-8-carboxamide (10 mmol) in anhydrous dioxane (25 mL). The solution is refluxed for 3 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Felczak, *et al.*, *Nucleosides & Nucleotides* **1993**, 12, 245

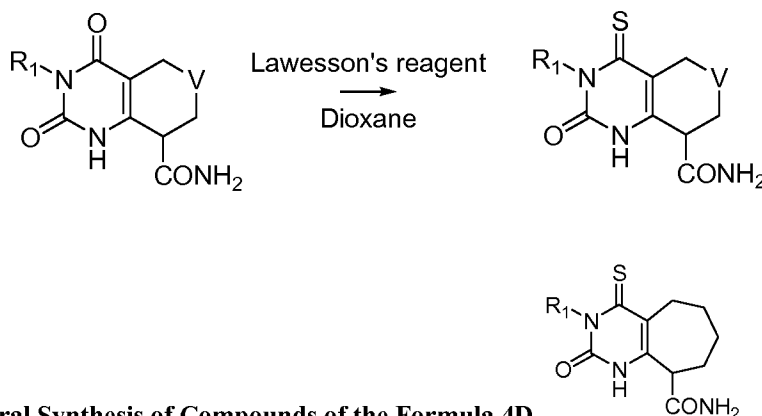


Example 4C: General Synthesis of Compounds of the Formula 4C

[00594] Compounds of the Formula 4C are synthesized according to Scheme 4C, where V is O, S or NH and R_1 is as described herein.

[00595] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 4C

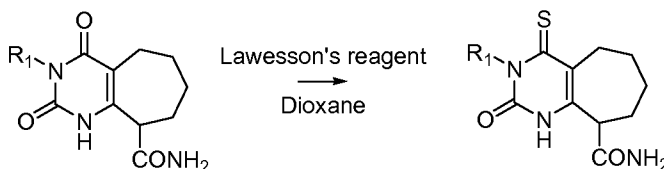


Example 4D: General Synthesis of Compounds of the Formula 4D

[00596] Compounds of the Formula 4D are synthesized according to Scheme 4D, where R_1 is as described herein.

[00597] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

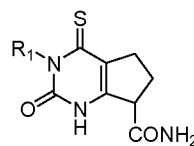
Scheme 4D



Step 1: 2,3,4,5,6,7,8,9-octahydro-3-(R_1)-2-oxo-4-thioxo-1H-cyclohepta[d]pyrimidine-9-carboxamide

[00598] Lawesson's reagent (10 mmol) is added to a solution of 2,3,4,5,6,7,8,9-octahydro-3-(R₁)-2,4-dioxo-1H-cyclohepta[d]pyrimidine-9-carboxamide (10 mmol) in anhydrous dioxane (25 mL). The solution is refluxed for 3 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized.

5 See Felczak, *et al.*, *Nucleosides & Nucleotides* **1993**, 12, 245

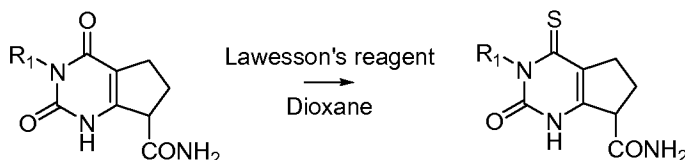


Example 4E: General Synthesis of Compounds of the Formula 4E

[00599] Compounds of the Formula 4E are synthesized according to Scheme 4E, where R₁ is as described herein.

10 [00600] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 4E

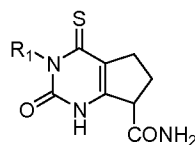


15

Step 1: 2,3,4,5,6,7-hexahydro-3-(R₁)-2-oxo-4-thioxo-1H-cyclopenta[d]pyrimidine-7-carboxamide

[00601] Lawesson's reagent (10 mmol) is added to a solution of 2,3,4,5,6,7-hexahydro-3-(R₁)-2,4-dioxo-1H-cyclopenta[d]pyrimidine-7-carboxamide (10 mmol) in anhydrous dioxane (25 mL). The solution is refluxed for 3 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized.

20 See Felczak, *et al.*, *Nucleosides & Nucleotides* **1993**, 12, 245



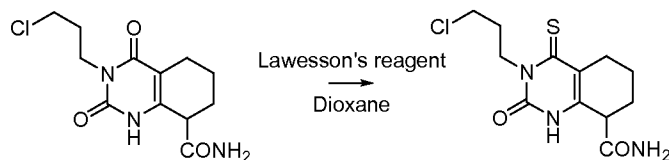
Example 4F: Synthesis of the Compound of Formula 4F

[00602] 3-(3-Chloropropyl)-1,2,3,4,5,6,7,8-octahydro-2-oxo-4-thioxoquinazoline-8-carboxamide is synthesized according to Scheme 4F.

25

[00603] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 4F

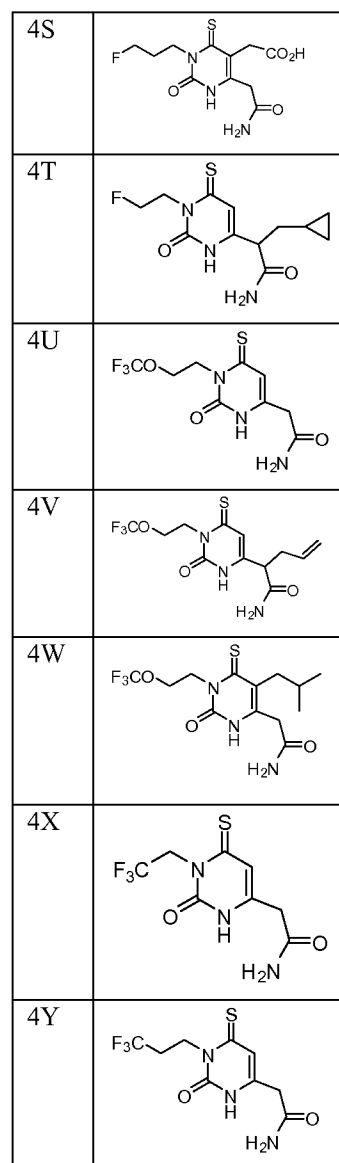
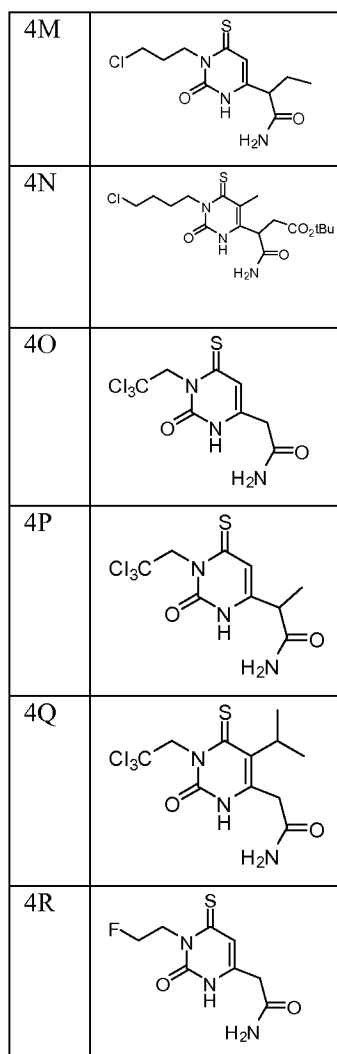
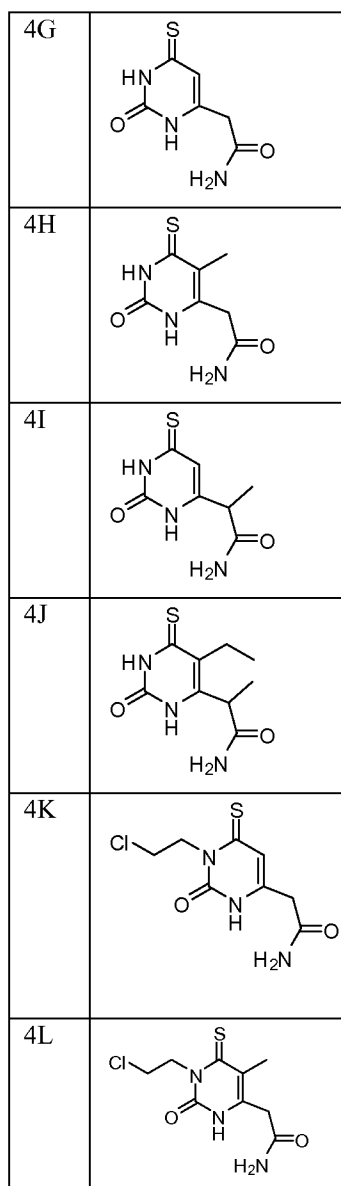


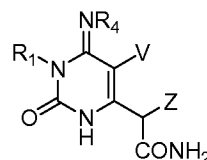
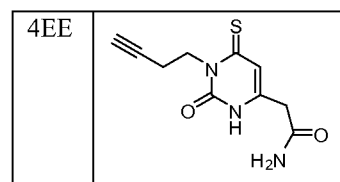
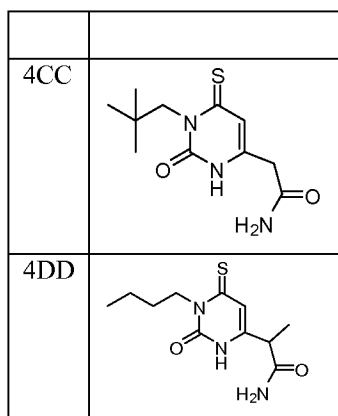
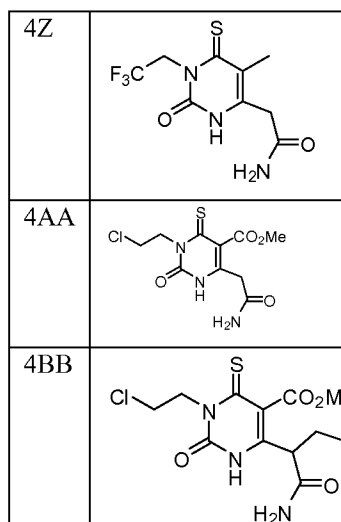
Step 1: 3-(3-Chloropropyl)-1,2,3,4,5,6,7,8-octahydro-2-oxo-4-thioxoquinazoline-8-carboxamide

[00604] Lawesson's reagent (10 mmol) is added to a solution of 3-(3-chloropropyl)-1,2,3,4,5,6,7,8-octahydro-2,4-dioxoquinazoline-8-carboxamide (10 mmol) in anhydrous dioxane (25 mL). The solution is refluxed for 3 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Felczak, *et al.*, *Nucleosides & Nucleotides* **1993**, 12, 245.

Examples 4G-4EE

[00605] Compounds 4G-4EE are synthesized as described in Examples 4A-4F using the appropriate starting materials.



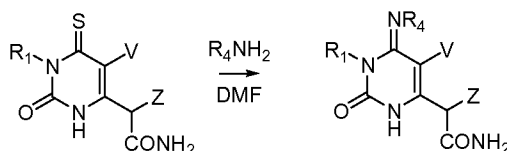


Example 5A: General Synthesis of Compounds of the Formula 5A

[00606] Compounds of the Formula 5A are synthesized according to Scheme 5A, and by modifications of the procedures described by Chauhan, P. M. S., Martins, C. J. A. and Horwell, D. C. *Bioorg. Med. Chem.* **2005**, 13, 3513 (and references therein), where R₁, V, Z and Q are as defined herein.

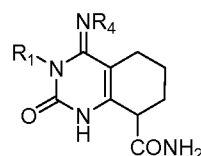
[00607] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 5A



Step 1: 2-(Z-substituted)-2-(1-[R₁-substituted]-6-(R₄-substituted imino)-2-oxo-5-[V-substituted]-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide

[00608] Following modifications of the procedures described by Chauhan, P. M. S., Martins, C. J. A. and Horwell, D. C. *Bioorg. Med. Chem.* **2005**, 13, 3513, to a solution of 2-(Z-substituted)-2-(1-[R₁-substituted]-2-oxo-5-[V-substituted]-6-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)acetamide (10 mmol), prepared as described above Scheme 4A, Step 1, in anhydrous DMF (25 mL) is added the amine R₄NH₂ (11 mmol). The solution is refluxed for 2 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

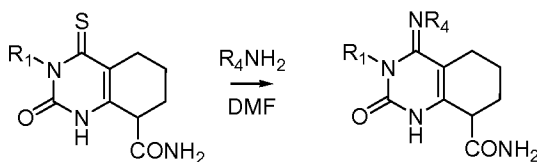


Example 5B: General Synthesis of Compounds of the Formula 5B

[00609] Compounds of the Formula 5B are synthesized according to Scheme 5B, where R₁ and R₄ are as defined herein.

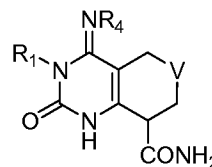
[00610] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 5B



Step 1: 4-((R₄)imino)-1,2,3,4,5,6,7,8-octahydro-3-(R₁)-2-oxoquinazoline-8-carboxamide

[00611] R₄NH₂ amine (11 mmol) is added to a solution of 1,2,3,4,5,6,7,8-octahydro-3-(R₁)-2-oxo-4-thioquinazoline-8-carboxamide (10 mmol) in anhydrous DMF (25 mL). The solution is refluxed for 2 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Chauhan, P. M. S., Martins, C. J. A. and Horwell, D. C. *Bioorg. Med. Chem.* **2005**, *13*, 3513.

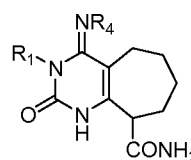
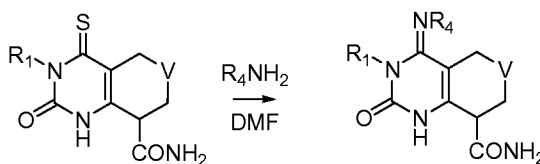


Example 5C: General Synthesis of Compounds of the Formula 5C

[00612] Compounds of the Formula 5C are synthesized according to Scheme 5C, where V and R₄ are as defined herein.

[00613] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 5C

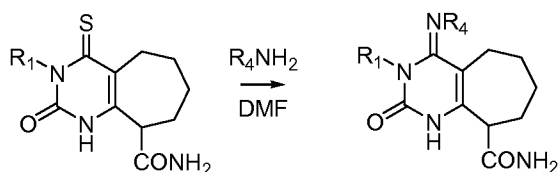


Example 5D: General Synthesis of Compounds of the Formula 5D

[00614] Compounds of the Formula 5D are synthesized according to Scheme 5D, where R₁ and R₄ are as described.

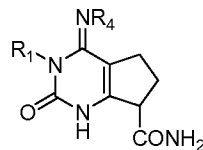
[00615] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 5D



Step 1: 4-((R₄)imino)-2,3,4,5,6,7,8,9-octahydro-3-(R₁)-2-oxo-1H-cyclohepta[d]pyrimidine-9-carboxamide

[00616] R₄NH₂ amine (11 mmol) is added to a solution of 2,3,4,5,6,7,8,9-octahydro-3-(R₁)-2-oxo-4-thioxo-1H-cyclohepta[d]pyrimidine-9-carboxamide (10 mmol) in anhydrous DMF (25 mL). The solution is refluxed for 2 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Chauhan, P. M. S., Martins, C. J. A. and Horwell, D. C. *Bioorg. Med. Chem.* **2005**, 13, 3513.

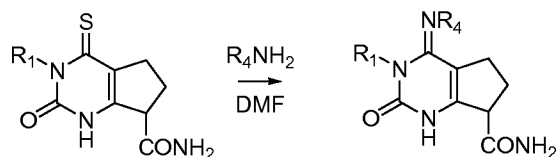


Example 5E: General Synthesis of Compounds of the Formula 5E

[00617] Compounds of the Formula 5E are synthesized according to Scheme 5E, where R₁ and R₄ are as described herein.

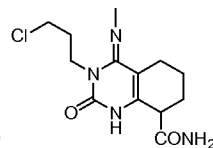
[00618] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 5E



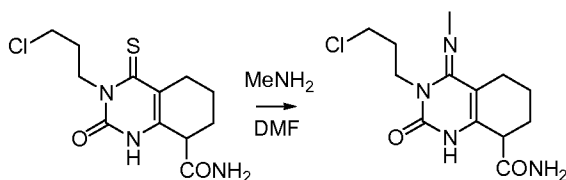
Step 1: 4-((R₄)imino)-2,3,4,5,6,7-hexahydro-3-(R₁)-2-oxo-1H-cyclopenta[d]pyrimidine-7-carboxamide

[00619] R₄NH₂ amine (11 mmol) is added to a solution of 2,3,4,5,6,7,8,9-octahydro-3-(R₁)-2-oxo-4-thioxo-1H-cyclopenta[d]pyrimidine-9-carboxamide (10 mmol) in anhydrous DMF (25 mL). The solution is refluxed for 2 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Chauhan, P. M. S., Martins, C. J. A. and Horwell, D. C. *Bioorg. Med. Chem.* **2005**, 13, 3513.

**Example 5F: Synthesis of the Compound of Formula 5F**

[00620] 3-(3-Chloropropyl)-1,2,3,4,5,6,7,8-octahydro-4-(methylimino)-2-oxoquinazoline-8-carboxamide is synthesized according to Scheme 5F.

[00621] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

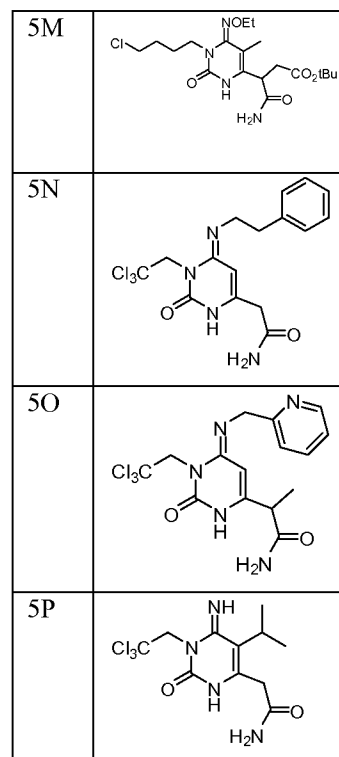
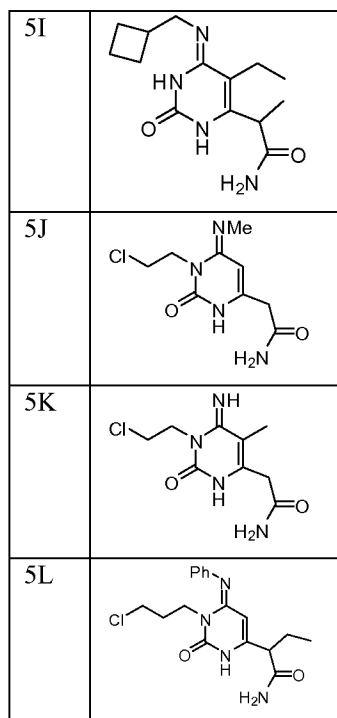
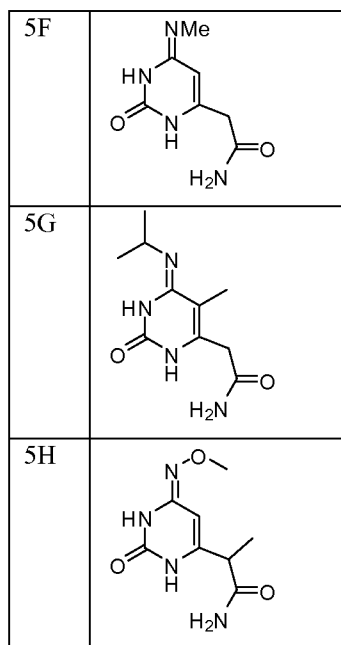
Scheme 5F

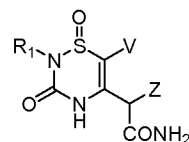
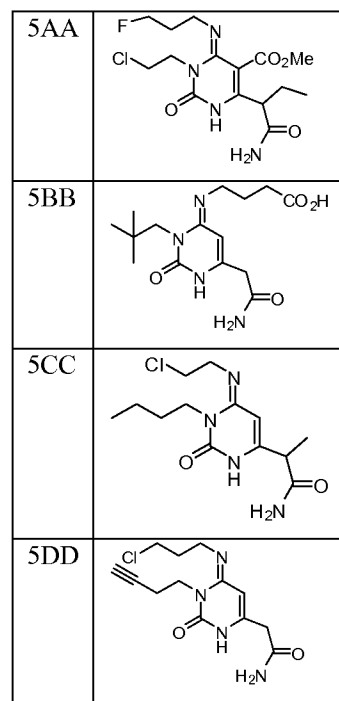
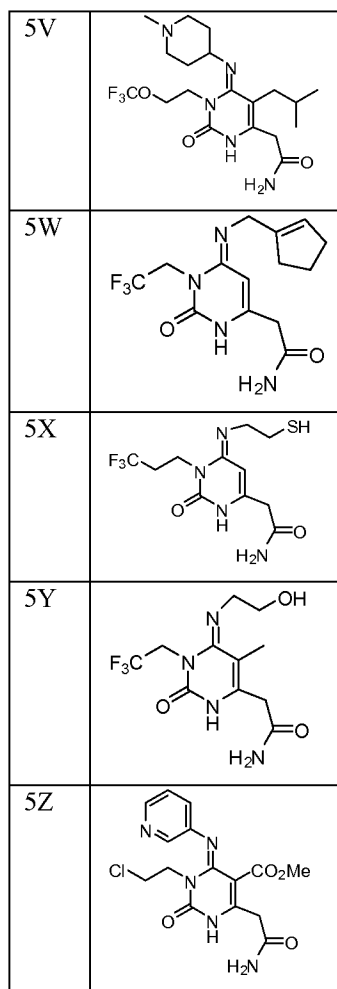
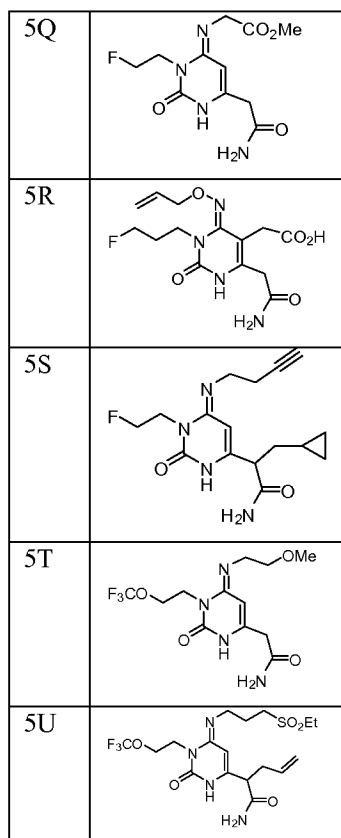
Step 1: 3-(3-Chloropropyl)-1,2,3,4,5,6,7,8-octahydro-4-(methylimino)-2-oxoquinazoline-8-carboxamide

[00622] R_4NH_2 amine (11 mmol) is added to a solution of 3-(3-chloropropyl)-1,2,3,4,5,6,7,8-octahydro-2-oxo-4-thioxoquinazoline-8-carboxamide (10 mmol) in anhydrous DMF (25 mL). The solution is refluxed for 2 hours or until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Chauhan, P. M. S., Martins, C. J. A. and Horwell, D. C. *Bioorg. Med. Chem.* **2005**, 13, 3513.

Examples 5F-5DD

Compounds 5F-5DD are synthesized as described in Examples 5A-5F using the appropriate starting materials.



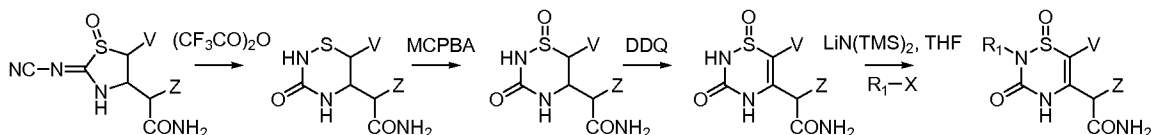


Example 6A: General Synthesis of Compounds of the Formula 6A

[00623] Compounds of the Formula 6A are synthesized according to Scheme 6A, and by modifications of the procedures described by Tanaka, T. et al. *Synlett*. **1997**, 316 (and references therein), where R₁, V and Z are as described herein.

[00624] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 6A



Step 1: 2-(Z-Substituted)-2-(3-oxo-6-[V-substituted]-1,2,4-thiadiazinan-5-yl)acetamides

[00625] Following modifications of the procedures described by Tanaka, T. et al. *Synlett*. **1997**, 316, 2-(Z-substituted)-2-(2-(cyanoimino)-5-[V-substituted]-thiazolidin-4-yl)acetamide S-oxide (10 mmol) is dissolved in trifluoroacetic anhydride (25mL) at 0°C. After one hour, the reaction mixture is warmed to

ambient temperature and optionally up to reflux, progress being monitored until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

Step 2: 2-(Z-Substituted)-2-(3-oxo-6-[V-substituted]-1-oxothia-2,4-diazinan-5-yl)acetamides

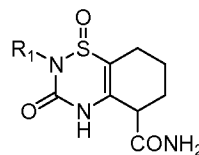
[00626] Following modifications of the procedures described by Tanaka, T. et al. *Synlett*. **1997**, 316, to a solution of 2-(Z-substituted)-2-(3-oxo-6-[V-substituted]-1,2,4-thiadiazinan-5-yl)acetamide (10 mmol), prepared above in Step 1, in anhydrous dichloromethane (40 mL) at 0°C under a nitrogen atmosphere is added 3-chloroperbenzoic acid (11 mmol). The mixture is stirred at ambient temperature for two hours. The solution is extracted with a solution of sodium thiosulfate (5%, 40 mL), saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

Step 3: 2-(Z-Substituted)-2-(3-oxo-6-[V-substituted]-3,4-dihydro-2H-1,2,4-thiadiazin-5-yl)acetamide S-oxides

[00627] A solution of 2-(Z-substituted)-2-(3-oxo-6-[V-substituted]-1-oxothia-2,4-diazinan-5-yl)acetamide (10 mmol), prepared in Step 2 above, in 1,3-dichlorobenzene (25 mL) is treated with DDQ (25 mmol) and the mixture is incrementally heated in 20°C steps from ambient temperature up to reflux, progress being monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The solution is cooled, filtered, solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

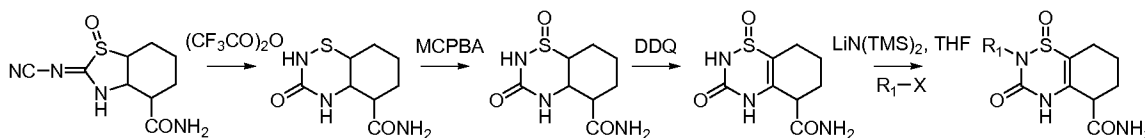
Step 4: 2-(Z-Substituted)-2-(2-[R₁-substituted]-3-oxo-6-[V-substituted]-3,4-dihydro-2H-1,2,4-thiadiazin-5-yl)acetamide S-oxides

[00628] A solution of 2-(Z-substituted)-2-(3-oxo-6-[V-substituted]-3,4-dihydro-2H-1,2,4-thiadiazin-5-yl)acetamide S-oxide (10 mmol) in anhydrous THF under nitrogen at 0° C is treated dropwise with 1M lithium bis(trimethylsilyl)amide solution (11 mL). The solution is warmed to ambient temperature for one hour, recooled to 0° C, and treated dropwise with the appropriate alkylating agent R₁X (11 mmol, e.g. 3-bromo-1-chloropropane, 2-chloroethyl triflate, allyl chloride, benzyl bromide, propargyl chloride, ethyl 2-(trifluoromethylsulfonyloxy)propanoate). After one hour, the solution is stirred at ambient temperature and monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The reaction mixture is quenched with saturated ammonium chloride solution (5 mL), solvents are removed, and the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

**Example 6B: General Synthesis of Compounds of the Formula 6B**

[00629] Compounds of the Formula 6B are synthesized according to Scheme 6B, where R₁ is as described herein.

[00630] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 6B

Step 1: Octahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide

[00631] 2-cyanamido-octahydrobenzo[d]thiazole-4-carboxamide-S-oxide (10 mmol) is dissolved in trifluoroacetic anhydride (25mL) at 0°C. After one hour, the reaction mixture is warmed to ambient temperature and optionally up to reflux, progress being monitored until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent is removed in vacuo, the residue dissolved in ethyl acetate and extracted successively with saturated sodium bicarbonate solution, water, and brine and dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Tanaka, T. et al. *Synlett*. **1997**, 316.

Step 2: Octahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide-S-oxide

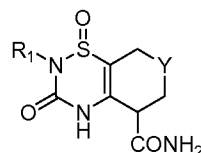
[00632] 3-chloroperbenzoic acid (11 mmol) is added to a solution of octahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide (10 mmol), in anhydrous dichloromethane (40 mL) at 0°C under a nitrogen atmosphere. The mixture is stirred at ambient temperature for two hours. The solution is extracted with sodium thiosulfate solution (5%, 40 mL), saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized. See Tanaka, et al. *Synlett*. **1997**, 316.

Step 3: 3,4,5,6,7,8-hexahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide S-oxide

[00633] A solution of octahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide-S-oxide (10 mmol), in 1,3-dichlorobenzene (25 mL) is treated with DDQ (25 mmol) and the mixture is incrementally heated in 20°C steps from ambient temperature to reflux, progress being monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The solution is cooled, filtered, solvent removed in vacuo, and the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized.

Step 4: Amine substituted 3,4,5,6,7,8-hexahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide S-oxide

[00634] A solution 3,4,5,6,7,8-hexahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide S-oxide (10 mmol) in anhydrous THF under nitrogen at 0° C is treated dropwise with 1M lithium bis(trimethylsilyl)amide solution (11 mL). The solution is warmed to ambient temperature for 1 hour, recooled to 0° C, and treated dropwise with the appropriate alkylating agent R₁X (11 mmol). After one hour, the solution is stirred at ambient temperature and monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The reaction mixture is quenched with saturated ammonium chloride solution (5 mL), solvents are removed, and the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized.

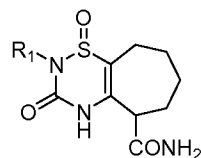
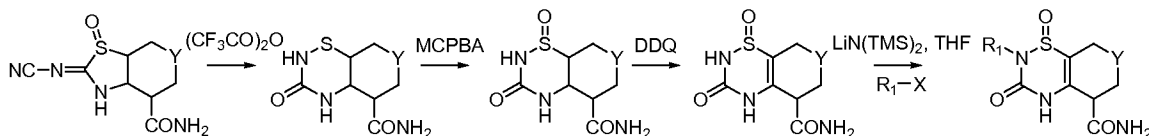


Example 6C: General Synthesis of Compounds of the Formula 6C

[00635] Compounds of the Formula 6C are synthesized according to Scheme 6C, where Y is O, S or NR₃ and R₁ and R₃ are as described herein.

[00636] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 6C

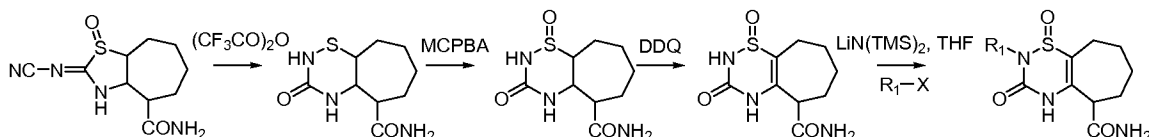


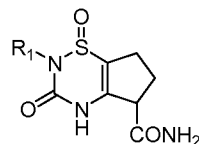
Example 6D: General Synthesis of Compounds of the Formula 6D

[00637] Compounds of the Formula 6D are synthesized according to Scheme 6D, where R₁ is as described herein.

[00638] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

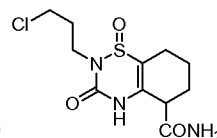
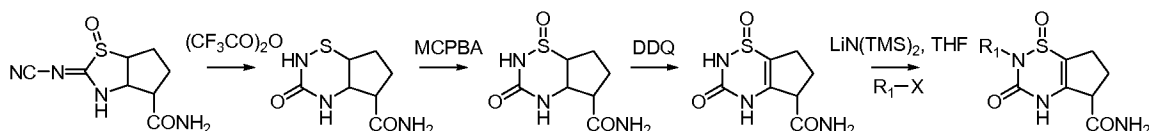
Scheme 6D



**Example 6E: General Synthesis of Compounds of the Formula 6E**

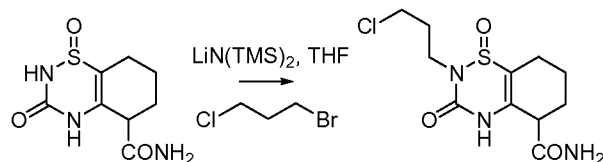
[00639] Compounds of the Formula 6E are synthesized according to Scheme 6E, where R₁ is as described herein.

[00640] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 6E**Example 6F: Synthesis of the Compound of Formula 6F**

[00641] 2-(3-Chloropropyl)-3,4,5,6,7,8-hexahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide S-oxide is synthesized according to Scheme 6F.

[00642] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 6F

Step 1: 3,4,5,6,7,8-hexahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide S-oxide

[00643] 3,4,5,6,7,8-hexahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide S-oxide is prepared as described above in example 6B.

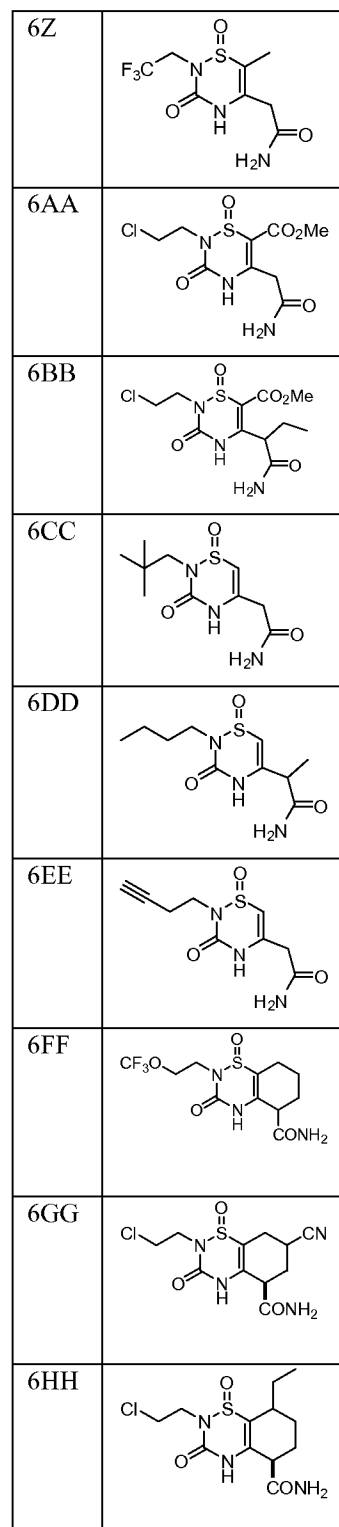
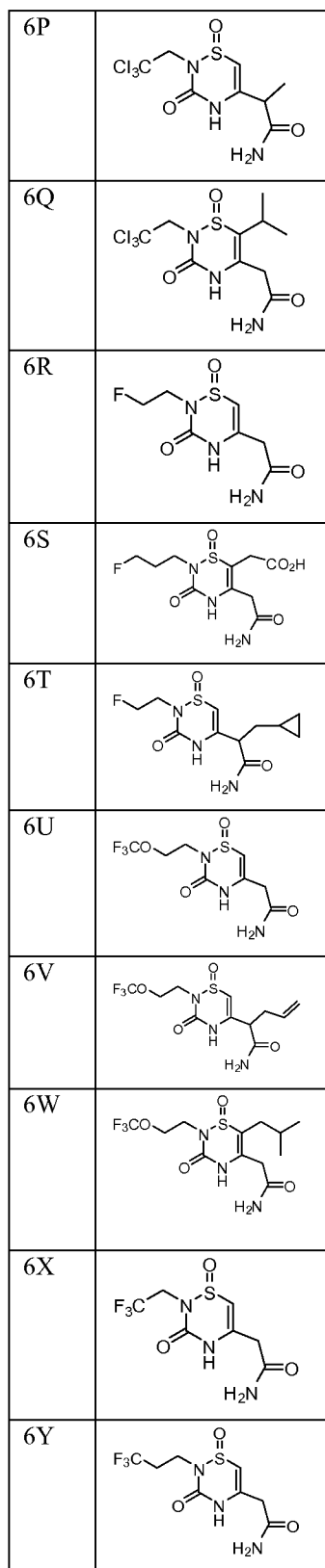
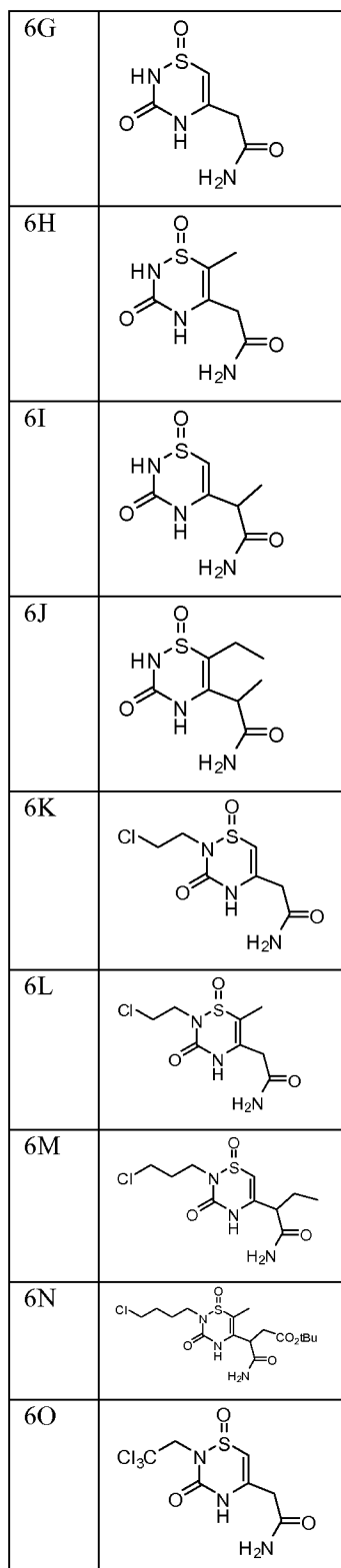
Step 2: 2-(3-chloropropyl)-3,4,5,6,7,8-hexahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide S-oxide

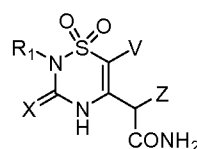
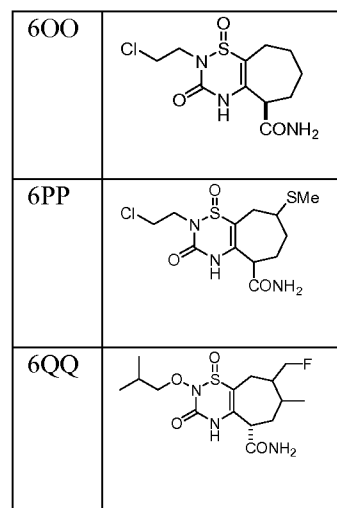
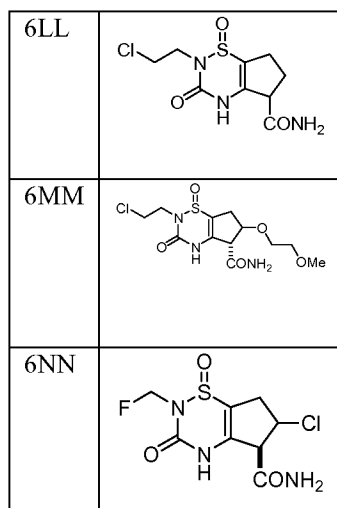
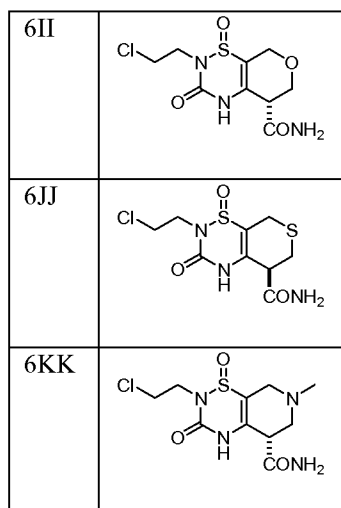
[00644] A solution of 3,4,5,6,7,8-hexahydro-3-oxo-2H-benzo[e][1,2,4]thiadiazine-5-carboxamide S-oxide (10 mmol) in anhydrous THF under nitrogen at 0° C is treated dropwise with 1M lithium bis(trimethylsilyl)amide solution (11 mL). The solution is warmed to ambient temperature for 1 hour, recooled to 0° C, and treated dropwise with 1-bromo-3-chloropropane (11 mmol). After one hour, the solution is stirred at ambient temperature and monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The reaction mixture is quenched with saturated ammonium chloride solution (5 mL), solvents are removed, and the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and

then dried over anhydrous MgSO_4 . Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized.

Examples 6G-6QQ

Compounds 6G-6QQ are synthesized as described in Examples 6A-6F using the appropriate starting materials.



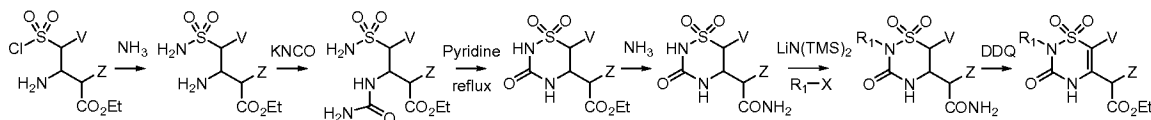


Example 7: General Synthesis of Compounds of the Formula 7A

[00645] Compounds of the Formula 7A are synthesized according to Scheme 7A, and by modifications of the procedures described by Hoogenboom et al. *J. Org. Chem.* **1959**, 24, 1983, Schwenckkraus, P. O. and Hartwig, H. *Liebigs Ann. Chem.* **1994**, 251, and Levenson and Meyer *J. Med. Chem.* **1984**, 27, 228 (and references therein), where R₁, X, V and Z are as described herein.

[00646] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are commercially available or are synthesized according to methods known in the art (or described herein).

Scheme 7A



Step 1: Ethyl 3-amino-2-(Z-substituted)-4-(V-substituted)-4-sulfamoylbutanoate

[00647] Following modifications of the procedures described by Schwenckkraus, P. O. and Hartwig, H. *Liebigs Ann. Chem.* **1994**, 251, a solution of ethyl 3-amino-2-(Z-Substituted)-4-(chlorosulfonyl)-4-(V-substituted)-butanoate (10 mmol) in anhydrous THF (25mL) at 0°C is treated with ammonia gas (50 mmol). After one hour, the reaction mixture is warmed to ambient temperature and progress is monitored until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with saturated 1N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

Step 2: Ethyl 2-(Z-Substituted)-4-(V-substituted)-4-sulfamoyl-3-ureidobutanoates

[00648] Following modifications of the procedures described by Schwenckkraus, P. O. and Hartwig, H. *Liebigs Ann. Chem.* **1994**, 251, to a solution of ethyl 3-amino-2-(Z-substituted)-4-(V-substituted)-4-

sulfamoylbutanoate (10 mmol), prepared above in Step 1, in methanol (10 mL), is added potassium isocyanate (11 mmol) dissolved in water (5 mL). After stirring at ambient temperature for three hours, the solution is optionally heated to reflux until TLC or HPLC/MS analysis indicates completion of the reaction. After cooling to 0°C, water is added and the precipitate is collected by filtration and dried.

Purification by preparative chromatography or recrystallization from the appropriate solvent affords the product as a solid.

[00649] *Step 3:* Ethyl 2-(Z-Substituted)-2-(3-oxo-6--[V-substituted]-1,2,4-thiadiazinan-5-yl)acetate S,S-dioxide

A solution of ethyl 2-(Z-Substituted)-4-(V-substituted)-4-sulfamoyl-3-ureidobutanoates (10 mmol), prepared in Step 2 above, in anhydrous pyridine (25 mL) is heated to reflux, progress being monitored until TLC or HPLC/MS analysis indicates completion of the reaction. Pyridine is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

[00650] *Step 4:* 2-(Z-Substituted)-2-(3-oxo-6-[V-substituted]-1,2,4-thiadiazinan-5-yl)acetamide S,S-dioxide

[00651] Into a Parr pressure bottle, anhydrous ammonia gas (0.10 mole) is charged into a solution of the ethyl 2-(Z-substituted)-2-(3-oxo-6--[V-substituted]-1,2,4-thiadiazinan-5-yl)acetate S,S-dioxide (10 mmol), prepared above in Step 3, at 0°C in ethanol (25 mL). The bottle is sealed and the reaction mixture is stirred at ambient temperature until TLC or HPLC/MS analysis indicates completion of the reaction. Solvent and excess ammonia are removed in vacuo and the resultant crude product is recrystallized from the appropriate solvent or purified by preparative chromatography, affording the desired product as a solid.

[00652] *Step 5:* 2-(Z-Substituted)-2-(2-[R₁-substituted]-3-oxo-6-[V-substituted]-1,2,4-thiadiazinan-5-yl)acetamide S,S-dioxide

A solution of 2-(Z-Substituted)-2-(3-oxo-6-[V-substituted]-1,2,4-thiadiazinan-5-yl)acetamide S,S-dioxide (10 mmol) in anhydrous THF under nitrogen at 0° C is treated dropwise with 1M lithium bis(trimethylsilyl)amide solution (11 mL). The solution is warmed to ambient temperature for one hour, recooled to 0° C, and treated dropwise with the appropriate alkylating agent R₁X (11 mmol, e.g. 3-bromo-1-chloropropane, 2-chloroethyl triflate, allyl chloride, benzyl bromide, propargyl chloride, ethyl 2-(trifluoromethylsulfonyloxy)propanoate). After one hour, the solution is stirred at ambient temperature and monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The reaction mixture is quenched with saturated ammonium chloride solution (5 mL), solvents are removed, and the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO₄. Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

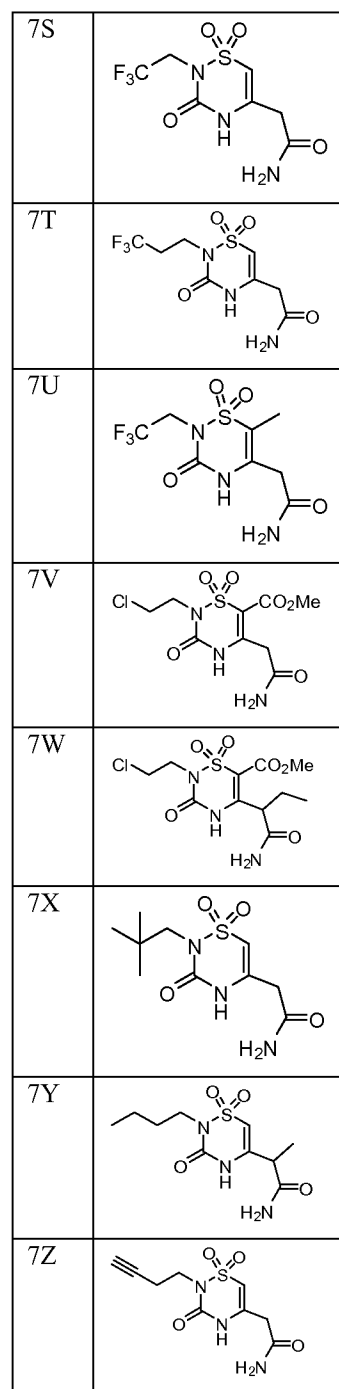
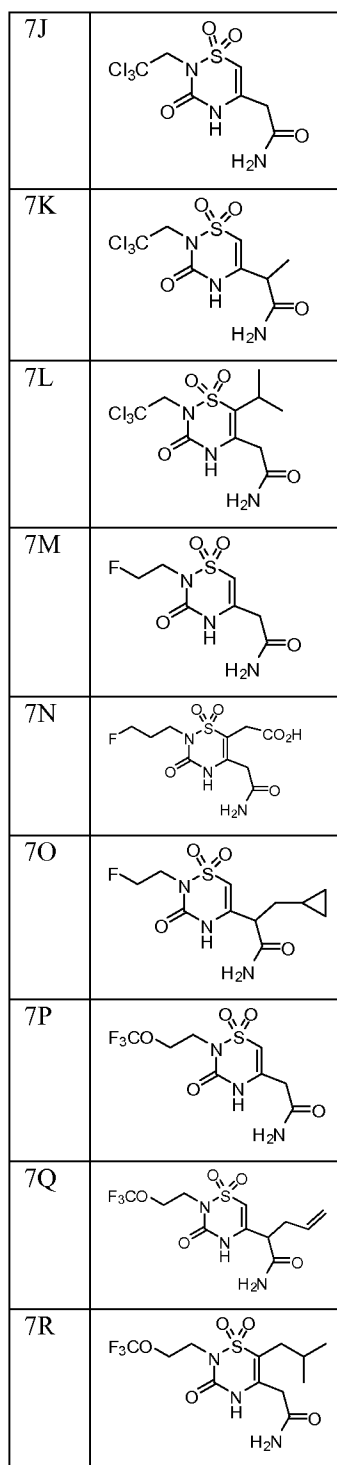
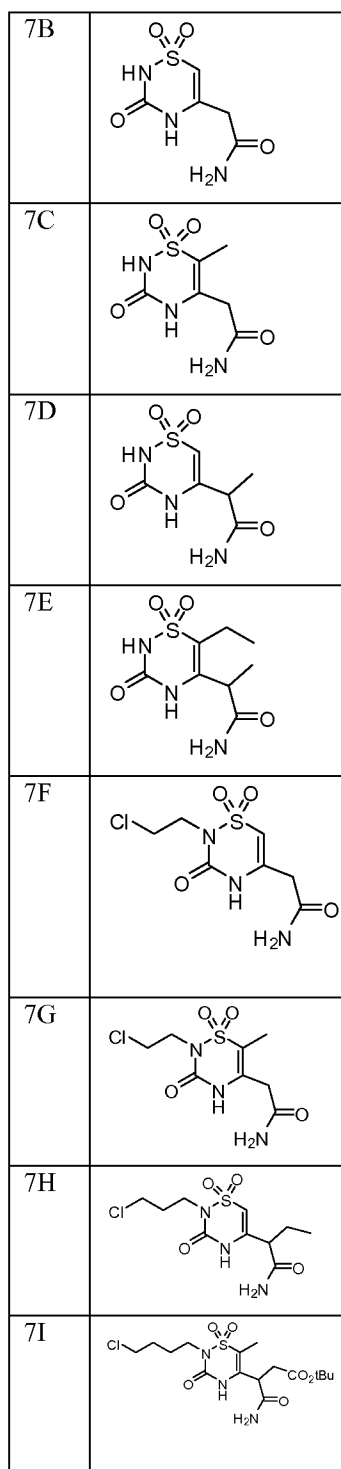
Step 6: 2-(Z-substituted)-2-(2-[R₁-substituted]-3-oxo-6-[V-substituted]-3,4-dihydro-2H-1,2,4-thiadiazin-5-yl)acetamide S,S-dioxide

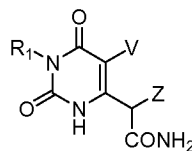
[00653] A solution of 2-(Z-Substituted)-2-(2-[R₁-substituted]-3-oxo-6-[V-substituted]-1,2,4-thiadiazinan-5-yl)acetamide S,S-dioxide (10 mmol), prepared in Step 5 above, in 1,3-dichlorobenzene (25 mL) is treated with DDQ (25 mmol) and the mixture is incrementally heated in 20°C steps from ambient

temperature up to reflux, progress being monitored until TLC or HPLC/MS analysis indicates completion of the reaction. The solution is cooled, filtered, solvent is removed in vacuo, the residue is dissolved in ethyl acetate and extracted successively with 1 N hydrochloric acid, saturated sodium bicarbonate solution, water, and brine and then dried over anhydrous MgSO_4 . Filtration and solvent removal affords the crude product, which is purified by preparative chromatography or recrystallized from the appropriate solvent to afford the product as a solid.

Examples 7B-7Z

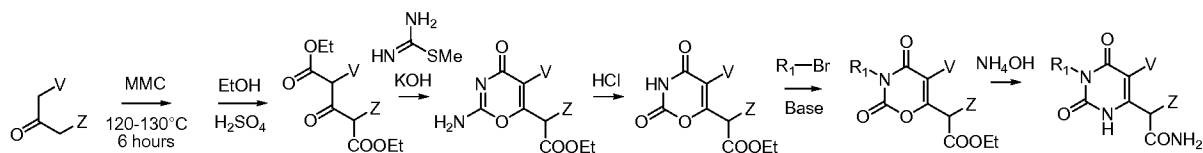
Compounds 7B-7Z are synthesized as described in Example 7A using the appropriate starting materials.



**Example 8A: General Synthesis of Compounds of the Formula 8A**

[00654] Compounds of the Formula 8A can be synthesized according to Scheme 8A, where R₁, V and Z are as defined herein.

[00655] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 8A**Step 1: diethyl 2-(Z)-4-(V)-3-oxopentanedioate**

[00656] 1-(V), 3-(Z)-propan-2-one (1.82 g., 018.6 mmol) and methyl magnesium carbonate (80 mL, 1.94M solution) are heated at 120-130°C for 6 hours. After hydrolysis the crude product is extracted into ether, dried, and the free diacid isolated by crystallization from ether/petroleum ether. (See Stiles, *J. Am. Chem. Soc.* **1959**, *81*, 2598). The di-acid is converted to the diester by treatment with acidic ethanol.

Step 2: ethyl 2-(2-amino-5-(V)-4-oxo-4H-1,3-oxazin-6-yl)-2-(Z) acetate

[00657] Potassium hydroxide (20.5 mmol) is added to a solution of 2-(S-methylthio)isourea (9.77 mmol) in water (10 mL). Under stirring, diethyl 2-(Z)-4-(V)-3-oxopentanedioate (9.74 mmol) is added and the inhomogeneous mixture stirred for 18 h at room temp. The mixture is filtered and the solid washed with water and ether. (See Larsen, J. S. et al., *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3035).

Step 3: ethyl 2-(Z)-2-(5-(V)-3,4-dihydro-2,4-dioxo-2H-1,3-oxazin-6-yl)acetate

[00658] A solution of ethyl 2-(Z)-2-(5-(V)-3,4-dihydro-2,4-dioxo-2H-1,3-oxazin-6-yl)acetate (12 mmol) in 3M HCl (8mL) is heated to reflux for 1 hour, cooled and filtered. The isolated solid is washed with water. (See Larsen, J. S. et al., *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3035).

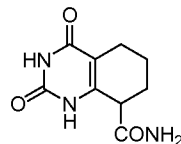
Step 4: ethyl 2-(Z)-2-(5-(V)-3,4-dihydro-3-(R₁)-2,4-dioxo-2H-1,3-oxazin-6-yl)acetate

[00659] N,O-bis(trimethylsilyl)-acetamide (BSA) (4.54 mmol) is added to a suspension of ethyl 2-(Z)-2-(5-(V)-3,4-dihydro-2,4-dioxo-2H-1,3-oxazin-6-yl)acetate (2.27 mmol) in dry chloroform and stirring continued until all starting material dissolves. R₁ chloride (2.27 mmol) is added and the reaction mixture stirred until TLC shows no change in amount of starting material. Solvent is removed *in vacuo*, and the residue obtained is purified by column chromatography. (See Larsen, J. S. et al., *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3035).

Step 5: 2-(Z)-2-(5-(V)-1,2,3,6-tetrahydro-1-(R₁)-2,6-dioxypyrimidin-4-yl)acetamide

[00660] A solution of ethyl 2-(Z)-2-(5-(V)-3,4-dihydro-3-(R₁)-2,4-dioxo-2H-1,3-oxazin-6-yl)acetate in 12M ammonium hydroxide (4.5 mL) is heated to reflux for 18 hours, cooled and filtered. The isolated

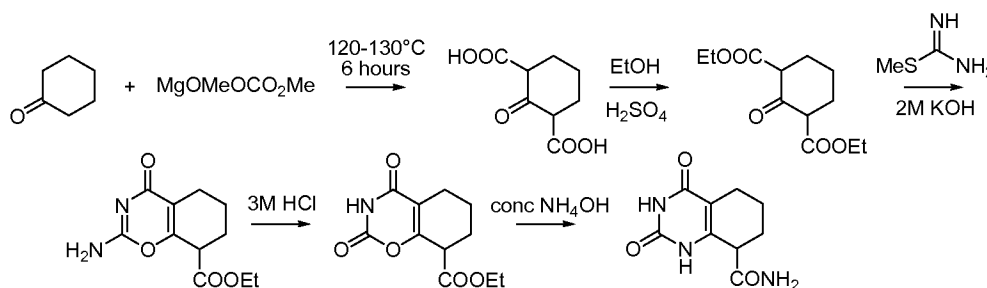
solid is washed with water and purified by chromatography. (See Larsen, J. S. et al., *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3035).



Example 8B: Synthesis of the Compound of Formula 8B

- 5 [00661] 1,2,3,4,5,6,7,8-octahydro-2,4-dioxoquinazoline-8-carboxamide, 8B, can be synthesized according to Scheme 8B.

Scheme 8B



Step 1: 2-Oxocyclohexane-1,3-dicarboxylic acid

- 10 [00662] Cyclohexanone (1.82 g., 018.6 mmol) and methyl magnesium carbonate (80 mL, 1.94M solution) are heated at 120-130°C for 6 hours. After hydrolysis the crude product is extracted into ether, dried, and the free diacid isolated by crystallization from etherpetroleum ether. (See Stiles, *J. Am. Chem. Soc.* **1959**, 81, 2598).

Step 2: Diethyl 2-oxocyclohexane-1,3-dicarboxylate

- 15 [00663] 2-Oxocyclohexane-1,3-dicarboxylic acid is converted to the diester by treatment with acidic ethanol.

Step 3: Ethyl 2-amino-5,6,7,8-tetrahydro-4-oxo-4H-benzo[e][1,3]oxazine-8-carboxylate

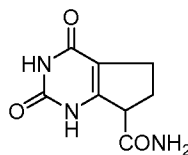
- [00664] Potassium hydroxide (20.5 mmol) is added to a solution of 2-(S-methylthio)isourea (9.77 mmol) in water (10 mL). Under stirring, diethyl 2-oxocyclohexane-1,3-dicarboxylate (9.74 mmol) is added and the inhomogenous mixture stirred for 18 h at room temp. The mixture is filtered and the solid washed with water and ether. (See Larsen, J. S. et al., *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3035).

Step 4: Ethyl 3,4,5,6,7,8-hexahydro-2,4-dioxo-2H-benzo[e][1,3]oxazine-8-carboxylate

- [00665] A solution of ethyl 2-amino-5,6,7,8-tetrahydro-4-oxo-4H-benzo[e][1,3]oxazine-8-carboxylate (12 mmol) in 3M HCl (8mL) is heated to reflux for 1 hour, cooled and filtered. The isolated solid is washed with water.

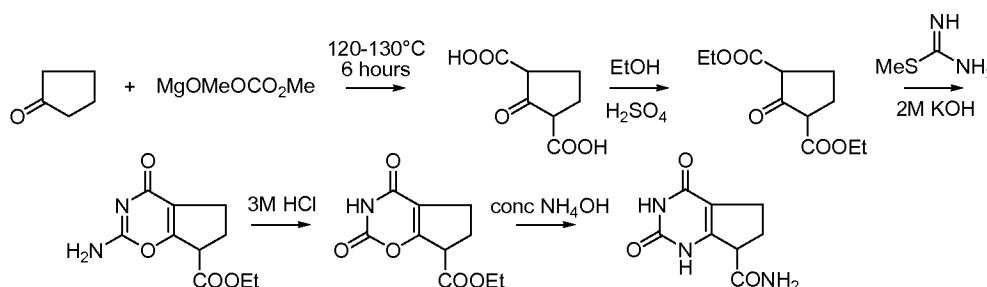
Step 5: 1,2,3,4,5,6,7,8-octahydro-2,4-dioxoquinazoline-8-carboxamide

- [00666] A solution of ethyl 3,4,5,6,7,8-hexahydro-2,4-dioxo-2H-benzo[e][1,3]oxazine-8-carboxylate in 12M ammonium hydroxide (4.5 mL) is heated to reflux for 18 hours, cooled and filtered. The isolated solid is washed with water.

**Example 8C: Synthesis of the Compound of Formula 8C**

[00667] 2,3,4,5,6,7-Hexahydro-2,4-dioxo-1H-cyclopenta[d]pyrimidine-7-carboxamide, 8C, can be synthesized according to Scheme 8C.

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Scheme 8C*Step 1: 2-Oxocyclopentane-1,3-dicarboxylic acid*

[00668] Cyclopentanone (1.82 g, 018.6 mmol) and methyl magnesium carbonate (80 mL, 1.94M solution) are heated at 120-130°C for 6 hours. After hydrolysis the crude product is extracted into ether, dried, and the free diacid isolated by crystallization from ether/petroleum ether. See Stiles, *J. Am. Chem. Soc.* **1959**, 81, 2598.

Step 2: Diethyl 2-oxocyclopentane-1,3-dicarboxylate

[00669] 2-Oxocyclopentane-1,3-dicarboxylic acid is converted to the diester by treatment with acidic ethanol.

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Step 3: Ethyl 2-amino-4,5,6,7-tetrahydro-4-oxocyclopenta[e][1,3]oxazine-7-carboxylate

[00670] Potassium hydroxide (20.5 mmol) is added to a solution of 2-(S-methylthio)isourea (9.77 mmol) in water (10 mL). Under stirring, diethyl 2-oxocyclopentane-1,3-dicarboxylate (9.74 mmol) is added and the inhomogenous mixture stirred for 18 h at room temp. The mixture is filtered and the solid washed with water and ether. (See Larsen, J. S. et al., *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3035).

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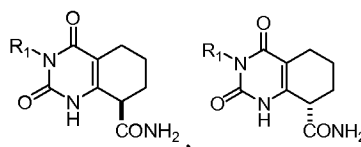
Step 4: Ethyl 2,3,4,5,6,7-hexahydro-2,4-dioxocyclopenta[e][1,3]oxazine-7-carboxylate

[00671] A solution of ethyl 2-amino-4,5,6,7-tetrahydro-4-oxocyclopenta[e][1,3]oxazine-7-carboxylate (12 mmol) in 3M HCl (8mL) is heated to reflux for 1 hour, cooled and filtered. The isolated solid is washed with water.

Step 5: 2,3,4,5,6,7-Hexahydro-2,4-dioxo-1H-cyclopenta[d]pyrimidine-7-carboxamide

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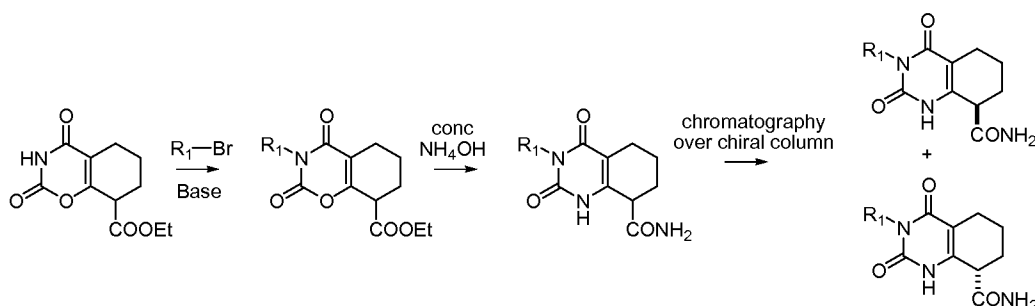
[00672] A solution of ethyl 2,3,4,5,6,7-hexahydro-2,4-dioxocyclopenta[e][1,3]oxazine-7-carboxylate in 12M ammonium hydroxide (4.5 mL) is heated to reflux for 18 hours, cooled and filtered. The isolated solid is washed with water.

**Example 8D: Synthesis of Compounds of Formula 8D, 8E**

[00673] (*R*)-1,2,3,4,5,6,7,8-octahydro-3-(R_1)-2,4-dioxoquinazoline-8-carboxamide, 8D, and (*S*)-1,2,3,4,5,6,7,8-octahydro-3-(R_1)-2,4-dioxoquinazoline-8-carboxamide, 8E, can be synthesized according to Scheme 8D.

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Scheme 8D

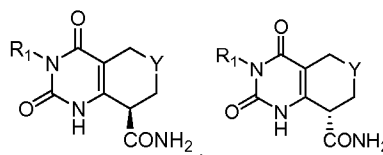
Step 1: 1,2,3,4,5,6,7,8-octahydro-2,4-dioxoquinazoline-8-carboxamide

[00674] 1,2,3,4,5,6,7,8-octahydro-2,4-dioxoquinazoline-8-carboxamide, is prepared according to example 8B.

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Step 2: (*R*)-1,2,3,4,5,6,7,8-octahydro-3-(R_1)-2,4-dioxoquinazoline-8-carboxamide and (*S*)-1,2,3,4,5,6,7,8-octahydro-3-(R_1)-2,4-dioxoquinazoline-8-carboxamide

[00675] The racemic mixture prepared in step 1 is passed over a chiral chromatography column and the separate *R* and *S* isomers are isolated.



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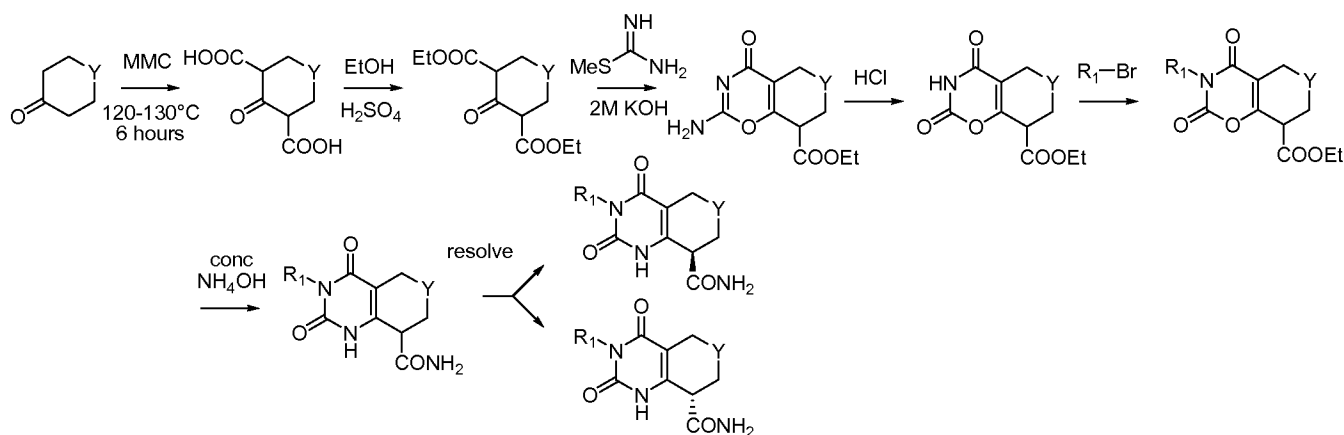
Example 8E: Synthesis of Compounds of Formula 8F, 8G

[00676] Compounds of the Formula 8F, 8G can be synthesized according to Scheme 8E, where Y and R_1 are as defined herein.

[00677] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

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Scheme 8E



Step 1: 2-Oxoheterocyclohexane-1,3-dicarboxylic acid

[00678] Heterocyclohexanone (018.6 mmol) and methyl magnesium carbonate (80 mL, 1.94M solution) are heated at 120-130°C for 6 hours. After hydrolysis the crude product is extracted into ether, dried, and the free diacid isolated by crystallization from ether/petroleum ether. (See Stiles, *J. Am. Chem. Soc.* **1959**, *81*, 2598).

Step 2: Diethyl 2-oxoheterocyclohexane-1,3-dicarboxylate

[00679] 2-Oxoheterocyclohexane-1,3-dicarboxylic acid is converted to the diester by treatment with acidic ethanol.

Step 3: Ethyl 2-amino-5,6,7,8-tetrahydro-4-oxo-4H-heterocyclo[1,3]oxazine-8-carboxylate

[00680] Potassium hydroxide (20.5 mmol) is added to a solution of 2-(S-methylthio)isourea (9.77 mmol) in water (10 mL). Under stirring, diethyl 2-oxoheterocyclohexane-1,3-dicarboxylate (9.74 mmol) is added and the inhomogenous mixture stirred for 18 h at room temp. The mixture is filtered and the solid washed with water and ether. (See Larsen, *et al.*, *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3035).

Step 4: Ethyl 3,4,5,6,7,8-hexahydro-2,4-dioxo-2H-heterocyclo[1,3]oxazine-8-carboxylate

[00681] A solution of ethyl 2-amino-5,6,7,8-tetrahydro-4-oxo-4H- heterocyclo[1,3]oxazine-8-carboxylate (12 mmol) in 3M HCl (8mL) is heated to reflux for 1 hour, cooled and filtered. The isolated solid is washed with water.

Step 5: Amino substituted Ethyl 3,4,5,6,7,8-hexahydro-2,4-dioxo-2H-heterocyclo[1,3]oxazine-8-carboxylate

[00682] The above compound is treated with R₁Br.

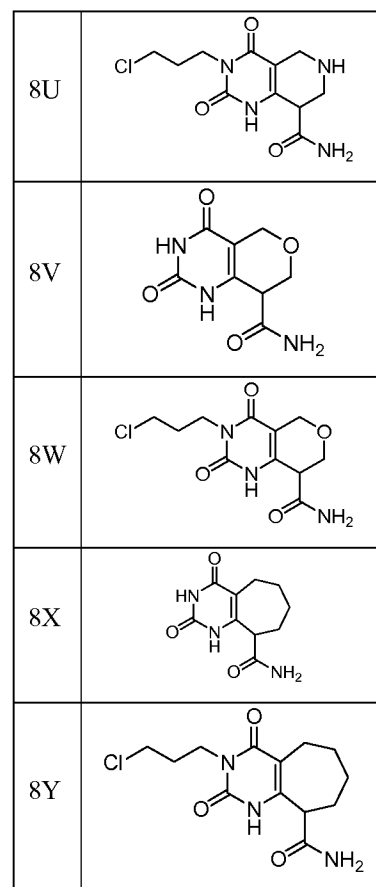
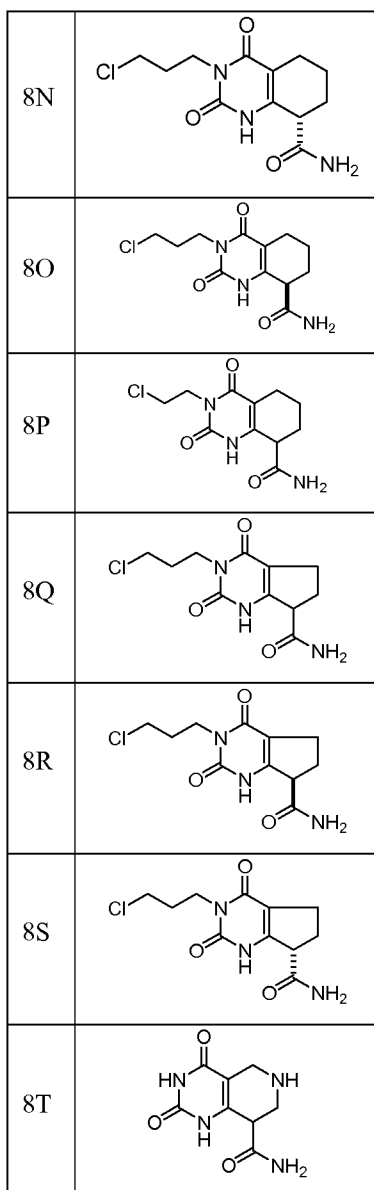
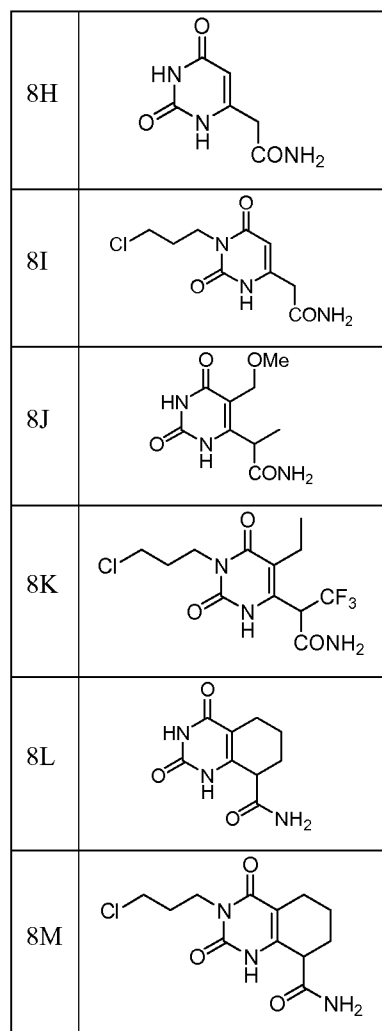
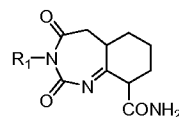
Step 6:

[00683] A solution of the above compound in 12M ammonium hydroxide (4.5 mL) is heated to reflux for 18 hours, cooled and filtered. The isolated solid is washed with water.

The racemic mixture is passed over a chiral chromatography column and the separate *R* and *S* isomers are isolated

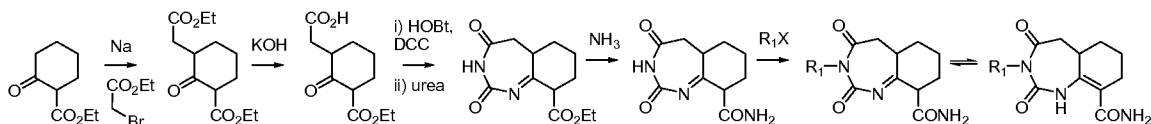
Examples 8H-8Y

[00684] Compounds 8H-1Y are synthesized as described in Example 8A-8E using the appropriate starting materials and intermediates with selective protection and deprotection when necessary.

**Example 9A: General Synthesis of Compounds of the Formula 9A**

[00685] Compounds of the Formula 9A can be synthesized according to Scheme 9A, where R_1 is as defined herein.

- 5 [00686] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 9A

Step 1: Ethyl 3-((ethoxycarbonyl)methyl)-2-oxocyclohexanecarboxylate

[00687] Ethyl 2-oxocyclohexanecarboxylate (0.59mol) is added, in one portion to a well-stirred mixture of finely divided sodium (0.59 mol) and dry benzene (500 mL.). The mixture is refluxed for 2.5 hr. and then treated with ethyl bromoacetate (0.59 mol), added dropwise during reflux. The resulting solution is heated for a further 5 hours and then cooled to room temperature. Addition of 5% sulfuric acid (250 mL) yields an organic layer which is washed successively with dilute sulfuric acid, sodium bicarbonate and water, and dried over sodium sulfate. Solvent is removed in vacuo and the remaining oil fractionated through a Vigreux column, yielding three fractions, (b.p. 139-143°C, 3.4 mm.) of clear colorless oil. The oil (0.18mol) is added, in one portion, to a solution of sodium (0.2mol) in anhydrous ethanol (60 mL) and heated at reflux for 8 hours. The solvent is removed in vacuo and the remaining oil treated with ice-cold 5% sulfuric acid (150 mL) and extracted with ether. The ether extract is washed, dried and the ether removed in vacuo and the remaining oil fractionated through a Vigreux column.

Step 2: 2-(3-(Ethoxycarbonyl)-2-oxocyclohexyl)acetic acid

[00688] A solution of potassium hydroxide (0.18mol) in anhydrous ethanol (50 mL) is added to ethyl 3-carbethoxy-2-oxocyclohexaneacetate (0.04mol) and the mixture stirred at room temperature for 1.5 hours. The precipitate formed is isolated by filtration, washed with anhydrous ethanol and ether, and dissolved in water (15 mL). The ice-cold solution is slowly treated with concentrated hydrochloric acid:water (1: 1; 14 mL), to form an oily precipitate which crystallizes on standing.

Step 3: Ethyl 3,4,5,5a,6,7,8,9-octahydro-2,4-dioxo-2H-benzo[d][1,3]diazepine-9-carboxylate

[00689] 2-(3-(Ethoxycarbonyl)-2-oxocyclohexyl)acetic acid is activated by treatment with HOBt/DCC. The resulting activated carboxylic acid is then condensed with urea to provide the cyclic urea derivative.

Step 4: 3,4,5,5a,6,7,8,9-Octahydro-2,4-dioxo-2H-benzo[d][1,3]diazepine-9-carboxamide

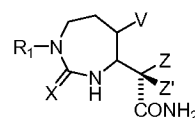
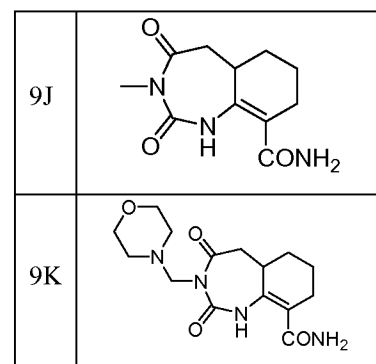
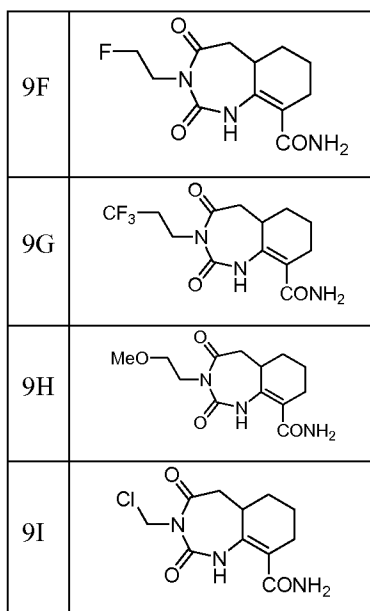
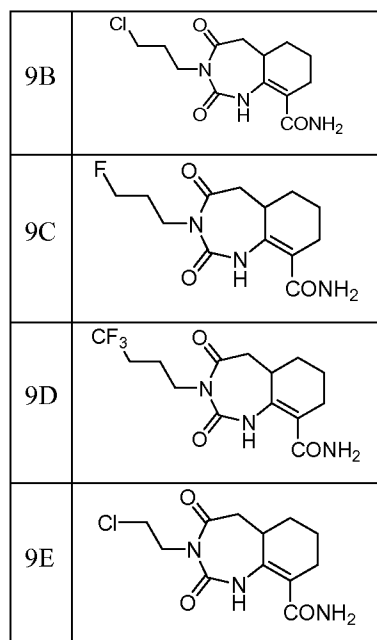
[00690] Treatment of 2-(3-(Ethoxycarbonyl)-2-oxocyclohexyl)acetic acid with ammonia converts the ethyl ester to the caboxamide.

Step 5: (E)-3,4,5,5a,6,7,8,9-octahydro-3-(R₁)-2,4-dioxo-2H-benzo[d][1,3]diazepine-9-carboxamide

[00691] Treatment of 3,4,5,5a,6,7,8,9-Octahydro-2,4-dioxo-2H-benzo[d][1,3]diazepine-9-carboxamide with R₁-Br effects selective *N*-alkylation. It should be noted that the product exists as a tautomeric equilibrium, as shown above.

Examples 9B-9K

[00692] Compounds 9B-9K are synthesized as described in Example 9A using the appropriate starting materials and intermediates with selective protection and deprotection when necessary.

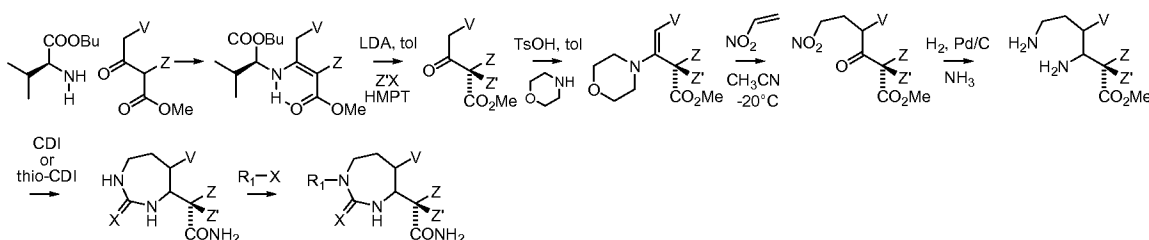


Example 10A: General Synthesis of Compounds of the Formula 10A

[00693] Compounds of the Formula 10A can be synthesized according to Scheme 10A, where X, V, Z, Z' and R₁ are as defined herein.

- 5 [00694] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 10A



10

Step 1: Enamine formation

[00695] Valine and β -keto ester are condensed according to procedures described by Hashimoto *et al*, (*Chem. Pharm. Bull.* **1979**, 27, 2760) to form the enamine.

Step 2: Alkylated β -keto ester

- 15 [00696] LDA (1.2 equiv) is added to a solution of enamine (1-5 mmol) in toluene (0.1-0.5 M) at -78°C, and stirring continued for 1 hour. HMPT (1-3 equiv) is then added at -78°C, and stirring continued for 1 hour. Alkylating agent, Z'-X (1-5 equiv) is then added at -55 to -78°C and the mixture stirred for a further 3-25 h. Acidic hydrolysis and purification by silica gel column chromatography (or bulb-to-bulb distillation) provides the alkylated β -keto ester. See Tomika, *et al*, *J. Am. Chem. Soc.*, **1984**, 106, 2718.

Step 3: Morpholine enamines

[00697] Morpholine and alkylated β -keto ester are condensed according to procedures described by Kuehne *et al*, (*Chem. Pharm. Bull.* **1979**, 27, 2760) to form the enamine.

Step 4: Addition of nitro ethylene

[00698] Morpholinoenamine (8.4 mmol) and 2-acetoxynitroethane (10.0 mmol) in dry acetonitrile (5 mL) is cooled to -23°C , under nitrogen, and stirred at 25°C for 18 hr. Excess 10% hydrochloric acid is added and stirring continued for 20 hr. Extraction with dichloromethane and distillation at $83\text{--}84^{\circ}\text{C}$ (0.2 mm.) provides the desired nitro ethylene β -keto ester.

Step 5: Diamine formation

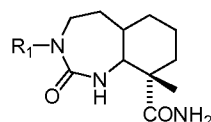
[00699] The nitro group of the nitro ethylene β -keto ester is reduced and ketone group undergoes reductive amination by reaction with hydrogen and ammonia in the presence of a palladium/charcoal catalyst, providing the diamino ester.

Step 6: Cyclization

[00700] The diamine is reacted with carbonyl di-imidazole or thiocarbonyl di-imidazole to cyclize to the 2-(2-oxo-1,3-diazepan-4-yl)acetamide or 2-(2-thioxo-1,3-diazepan-4-yl)acetamide.

Step 7: Alkylation

[00701] The (thio)oxo-1,3-diazepan is reacted with an alkyl halide to alkylate the N_1 position.

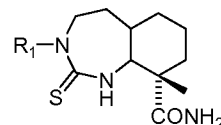
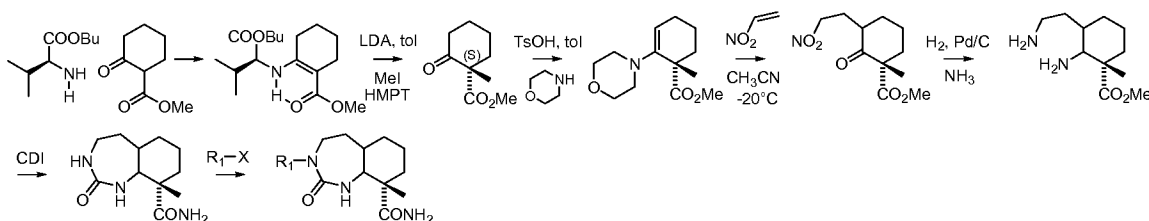


Example 10B: General Synthesis of Compounds of the Formula 10B

[00702] Compounds of the Formula 10B can be synthesized according to Scheme 10B and procedures described above, where R_1 is as defined herein.

[00703] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 10B

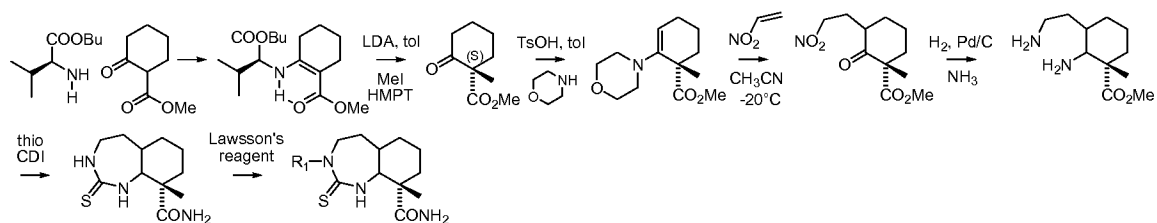


Example 10C: General Synthesis of Compounds of the Formula 10C

[00704] Compounds of the Formula 10C can be synthesized according to Scheme 10C and procedures described above, where R_1 is as defined herein.

[00705] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

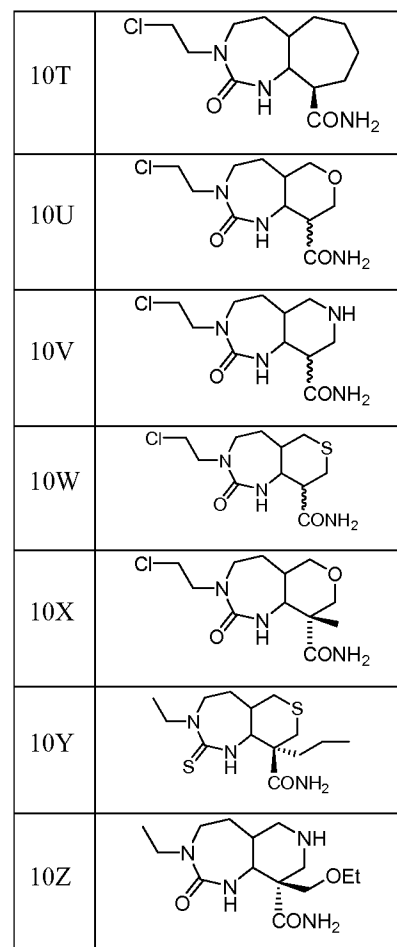
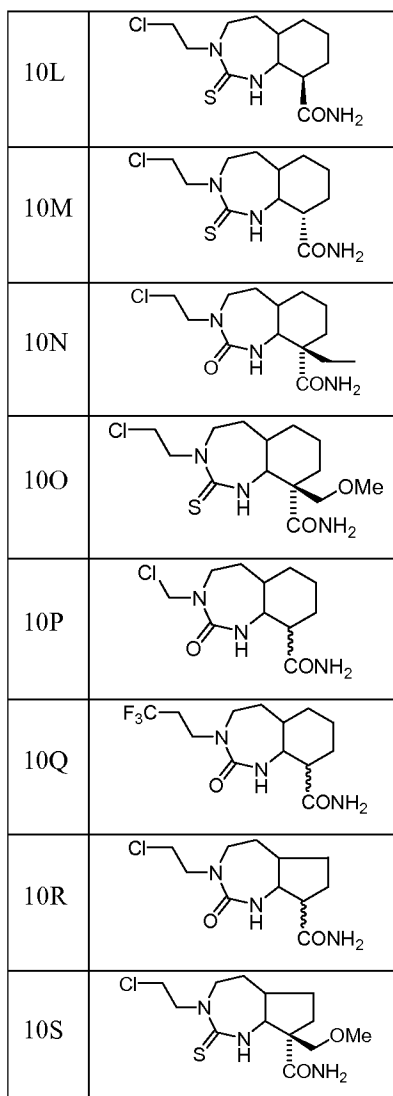
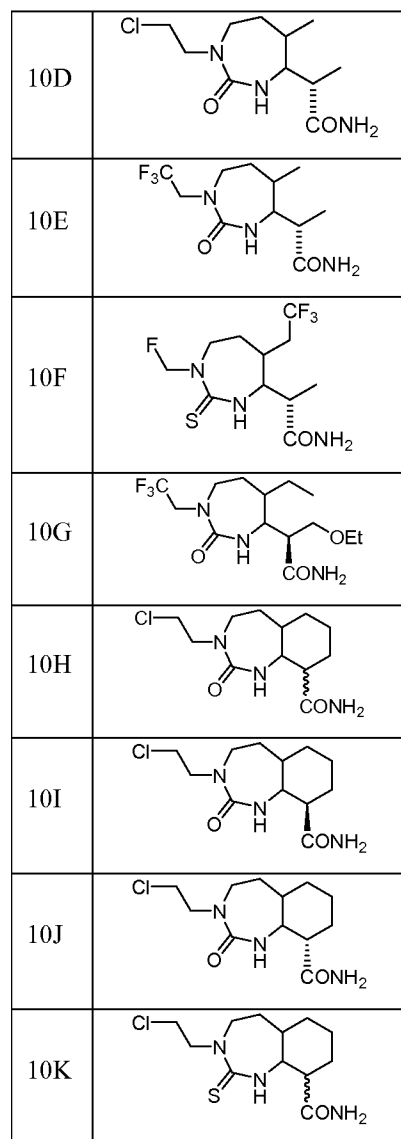
Scheme 10C



Examples 10D-10Z

[00706] Compounds 10D-10Z are synthesized as described in Examples 10A-10C using the

5 appropriate starting materials and intermediates with selective protection and deprotection when necessary.

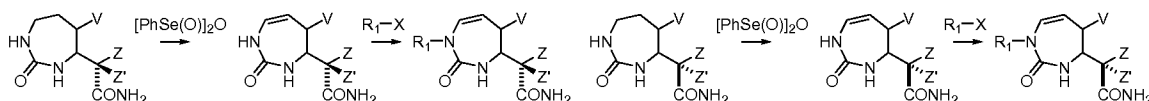


Example 11A: General Synthesis of Compounds of the Formula 11A, 11B

[00707] Compounds of the Formula 11A or 11B can be synthesized according to Scheme 11A, where X, V, Z, Z' and R₁ are as defined herein.

- 5 [00708] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 11A



Step 1: Oxo-1,3-diazepan and thiooxo-1,3-diazepan formation

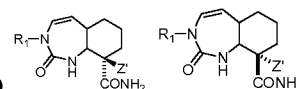
[00709] The oxo-1,3-diazepan and thiooxo-1,3-diazepan compounds are prepared as described above.

Step 2: 2-(2,3,4,5-Tetrahydro-2-oxo-1H-1,3-diazepin-4-yl)acetamide

[00710] A solution of 2-(2-oxo-1,3-diazepan-4-yl)acetamide (or thio-oxo derivative) in toluene is reacted with benzeneselenenic anhydride and the resulting solution refluxed for 1 hour. The product is isolated and purified. See Kim *et al. JOC*, **1987**, 52, 1979.

Step 3: Alkylation

5 [00711] The reduced oxo-1,3-diazepan is reacted with an alkyl halide, R_1-X , to alkylate the less hindered N_1 position.

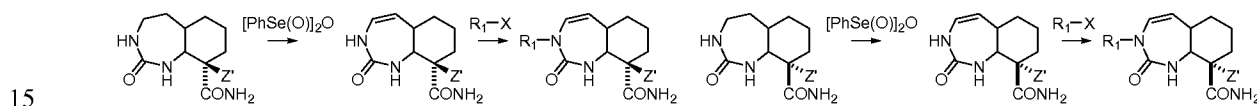


Example 11B: General Synthesis of Compounds of the Formula 11C, 11D

10 [00712] Compounds of the Formula 11C, 11D can be synthesized according to Scheme 11B, where Z' and R_1 are as defined herein.

[00713] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 11B

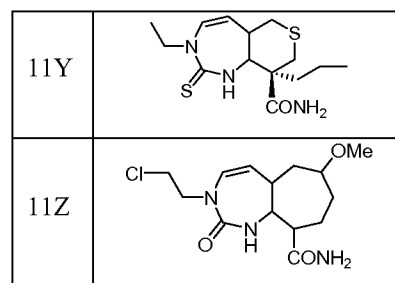
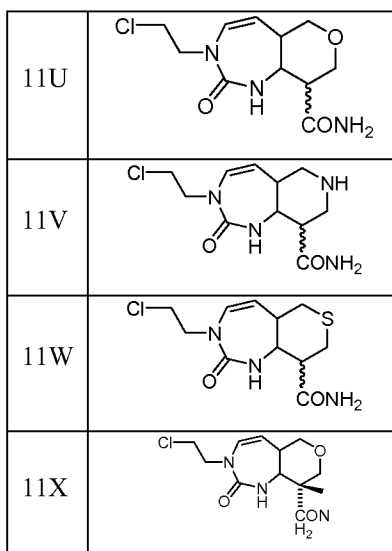
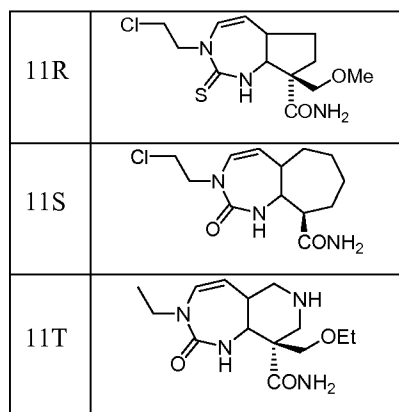


Examples 11C-11Z

[00714] Compounds 11C-11Z are synthesized as described in Examples 11A-11B using the appropriate starting materials and intermediates with selective protection and deprotection when necessary.

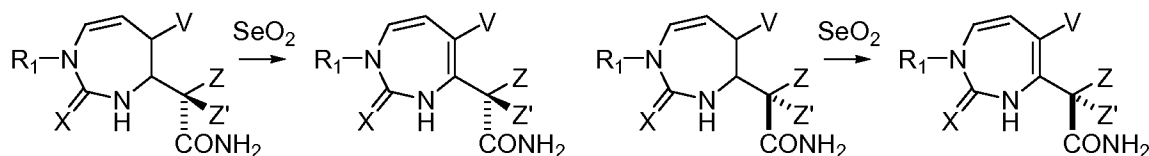
20

11C		11H		11M	
11D		11I		11N	
11E		11J		11O	
11F		11K		11P	
11G		11L		11Q	

**Example 12A: General Synthesis of Compounds of the Formula 12A, 12B**

[00715] Compounds of the Formula 12A, 12B can be synthesized according to Scheme 12A, where X, V, Z, Z' and R₁ are as defined herein.

[00716] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

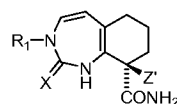
Scheme 12A

Step 1: 2-Oxo-1,3-diazepin formation

[00717] 1-(R₁)-2,3,4,5-tetrahydro-2-oxo-1H-1,3-diazepin-4-yl)acetamide is prepared as described above.

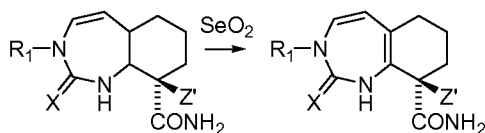
Step 2: Dehydrogenation

[00718] 1-(R₁)-2,3,4,5-tetrahydro-2-oxo-1H-1,3-diazepin-4-yl)acetamide is treated with SeO₂ to give the 1-(R₁)-2,3-dihydro-2-oxo-1H-1,3-diazepin-4-yl)acetamide.

**Example 12B: General Synthesis of Compounds of the Formula 12C**

[00719] Compounds of the Formula 12C, can be synthesized according to Scheme 12B, where X, Z' and R₁ are as defined herein.

[00720] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 12B

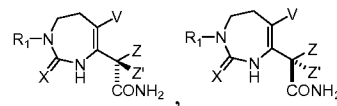
5

Examples 12C-12Z

[00721] Compounds 12C-12Z are synthesized as described in Examples 12A-12C using the appropriate starting materials and intermediates with selective protection and deprotection when necessary.

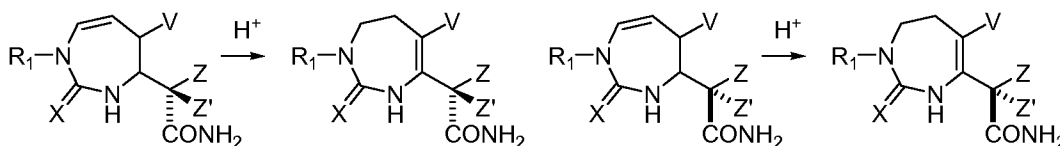
12B		12K		12T	
12C		12L		12U	
12D		12M		12V	
12E		12N		12W	
12F		12O		12X	
12G		12P		12Y	
12H		12Q		12Z	
12I		12R			
12J		12S			

10

Example 13A: General Synthesis of Compounds of the Formula 13A, 13B

[00722] Compounds of the Formula 13A, 13B can be synthesized according to Scheme 13A, where X, V, Z, Z' and R₁ are as defined herein.

5 [00723] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

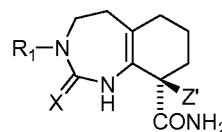
Scheme 13A

10 Step 1: 2-Oxo-1,3-diazepin formation

[00724] 1-(R₁)-2,3,4,5-tetrahydro-2-oxo-1H-1,3-diazepin-4-yl)acetamide is prepared as described above.

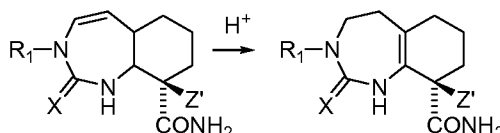
Step 2: Isomerization

[00725] 1-(R₁)-2,3,4,5-tetrahydro-2-oxo-1H-1,3-diazepin-4-yl)acetamide is treated with acid to give the 1-(R₁)-2,3,6,7-tetrahydro-2-oxo-1H-1,3-diazepin-4-yl)acetamide.

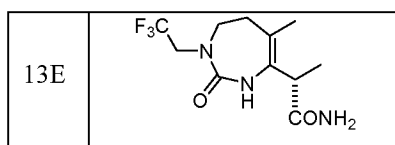
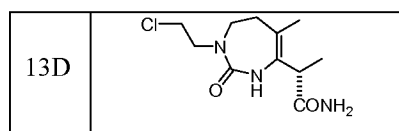
**Example 13B: General Synthesis of Compounds of the Formula 13C**

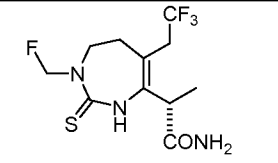
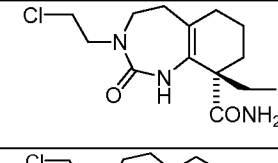
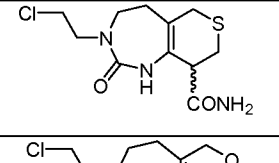
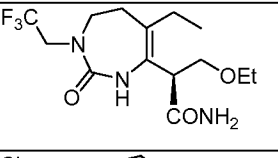
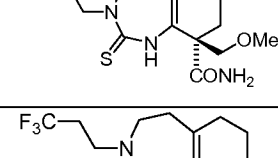
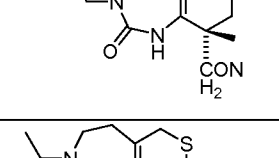
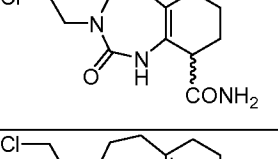
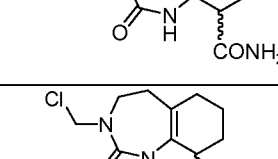
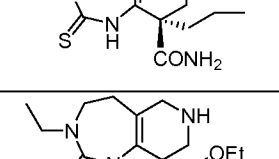
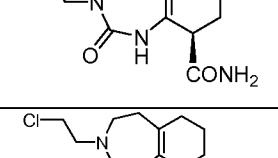
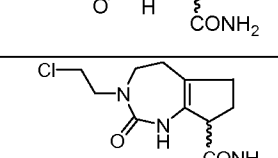
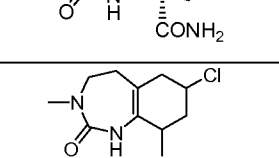
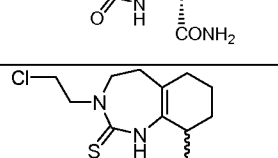
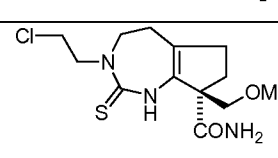
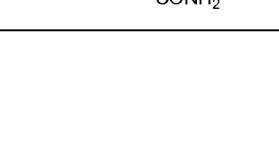
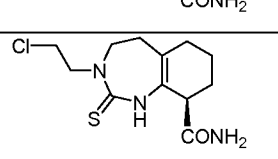
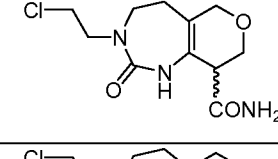
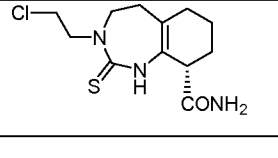
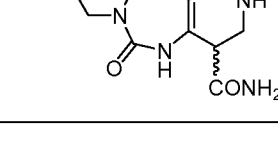
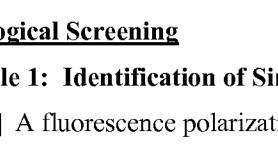
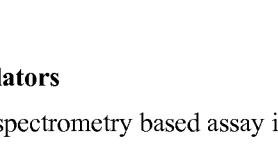
[00726] Compounds of the Formula 13C, can be synthesized according to Scheme 13B, where X, Z' and R₁ are as defined herein.

20 [00727] When appropriate, protecting groups are used prior to performing the reaction outlined below, and may or may not be removed upon completion of the synthesis. The individual starting materials are synthesized according to methods known in the art (or described herein) or are commercially available.

Scheme 13B**Examples 13D-13Z**

[00728] Compounds 13D-13Z are synthesized as described in Examples 13A-13B using the appropriate starting materials and intermediates with selective protection and deprotection when necessary.



13F		13N		13V	
13G		13O		13W	
13H		13P		13X	
13I		13Q		13Y	
13J		13R		13Z	
13K		13S			
13L		13T			
13M		13U			

II Biological Screening

Example 1: Identification of Sirtuin Modulators

[00729] A fluorescence polarization or mass spectrometry based assay is used to identify modulators of SIRT1 activity. The same assay is used to identify modulators of any sirtuin protein. The fluorescence polarization assays utilizes one of two different peptides based on a fragment of p53, a known sirtuin deacetylation target.

[00730] The compounds described herein are tested using a substrate containing peptide 1 having 14 amino acid residues as follows: GQSTSSHSK(Ac)NleSTEG (SEQ ID NO: 1) wherein K(Ac) is an acetylated lysine residue and Nle is a norleucine. The peptide is labeled with the fluorophore MR121 (excitation 635 nm/emission 680 nm) at the C-terminus and biotin at the N-terminus. The sequence of the peptide substrate is based on p53 with several modifications. In particular, all arginine and leucine residues other than the acetylated lysine are replaced with serine so that the peptide is not susceptible to trypsin cleavage in the absence of deacetylation. In addition, the methionine residues naturally present in the

sequence are replaced with the norleucine because the methionine may be susceptible to oxidation during synthesis and purification.

[00731] The compounds described herein are also tested using a substrate containing peptide 2 having 20 amino acid residues as follows: EE-K(biotin)-GQSTSSHSK(Ac)NleSTEG-K(MR121)-EE-NH₂ (SEQ ID NO: 2) wherein K(biotin) is a biotinylated lysine residue, K(Ac) is an acetylated lysine residue, Nle is norleucine and K(MR121) is a lysine residue modified by an MR121 fluorophore. This peptide is labeled with the fluorophore MR121 (excitation 635 nm/emission 680 nm) at the C-termini and biotin at the N-termini. The sequence of the peptide substrates are based on p53 with several modifications. In particular, all arginine and leucine residues other than the acetylated lysine residues are replaced with serine so that the peptides are not susceptible to trypsin cleavage in the absence of deacetylation. In addition, the methionine residues naturally present in the sequences are replaced with the norleucine because the methionine may be susceptible to oxidation during synthesis and purification.

[00732] As an alternative substrate in the assay, the following peptide 3 are used for testing: Ac-EE-K(biotin)-GQSTSSHSK(Ac)NleSTEG-K(5TMR)-EE-NH₂ (SEQ ID NO: 3) wherein K(Ac) is an acetylated lysine residue and Nle is a norleucine. The peptide is labeled with the fluorophore 5TMR (excitation 540 nm/emission 580 nm) at the C-terminus. The sequence of the peptide substrate is also based on p53 with several modifications. In addition, the methionine residue naturally present in the sequence is replaced with the norleucine because the methionine may be susceptible to oxidation during synthesis and purification.

[00733] The peptide substrates are exposed to a sirtuin protein in the presence of NAD⁺ to allow deacetylation of the substrate and render it sensitive to cleavage by trypsin. Trypsin is then added and the reaction is carried to completion (i.e., the deacetylated substrate is cleaved) releasing the MR121 or 5TMR fragment. Streptavidin is then added to the reaction where it can bind both the uncleaved substrate (i.e., any remaining acetylated substrate) and the non-fluorescent portion of the cleaved peptide substrate (i.e., the biotin containing fragment). The fluorescence polarization signal observed for the full length peptide substrates bound to streptavidin is higher than the fluorescence polarization signal observed for the released MR121 or 5TMR C-terminal fragment. In this way, the fluorescence polarization obtained is inversely proportional to the level of deacetylation (e.g., the signal is inversely proportional to the activity of the sirtuin protein). Results are read on a microplate fluorescence polarization reader (Molecular Devices Spectramax MD) with appropriate excitation and emission filters.

[00734] The fluorescence polarization assays using peptide 1 is conducted as follows: 0.5 μ M peptide substrate and 150 μ M β NAD⁺ are incubated with 0.1 μ g/mL of SIRT1 for 60 minutes at 37°C in a reaction buffer (25 mM Tris-acetate pH8, 137 mM Na-Ac, 2.7 mM K-Ac, 1 mM Mg-Ac, 0.05% Tween-20, 0.1% Pluronic F1 27, 10 mM CaCl₂, 5 mM DTT, 0.025% BSA, 0.15 mM Nicotinamide). Test compounds are solubilized in DMSO and added to the reaction at 11 concentrations ranging from 0.7 μ M to 100 μ M.

[00735] Fluorescence polarization assays using peptide 2 is conducted as follows: 0.5 μ M peptide substrate and 120 μ M β NAD⁺ are incubated with 3 nM SIRT1 for 20 minutes at 25°C in a reaction buffer (25 mM Tris-acetate pH8, 137 mM Na-Ac, 2.7 mM K-Ac, 1 mM Mg-Ac, 0.05% Tween-20, 0.1% Pluronic

F127, 10 mM CaCl₂, 5 mM DTT, 0.025% BSA). Test compounds are solubilized in DMSO and added to the reaction at 10 concentrations ranging from 300 μ M to 0.15 μ M in three-fold dilutions.

[00736] After the incubation with SIRT1, nicotinamide is added to the reaction to a final concentration of 3 mM to stop the deacetylation reaction and 0.5 μ g/mL of trypsin is added to cleave the deacetylated substrate. The reaction is incubated for 30 minutes at 37°C in the presence of 1 μ M streptavidin. Fluorescent polarization is determined at excitation (650 nm) and emissions (680 nm) wavelengths. The level of activity of the sirtuin protein in the presence of the various concentrations of test compound is then determined and may be compared to the level of activity of the sirtuin protein in the absence of the test compound, and/or the level of activity of the sirtuin proteins in the negative control (e.g., level of inhibition) and positive control (e.g., level of activation) described below.

[00737] For the Fluorescence Polarization assays, a control for inhibition of sirtuin activity is conducted by adding 1 μ L of 500 mM nicotinamide as a negative control at the start of the reaction (e.g., permits determination of maximum sirtuin inhibition). A control for activation of sirtuin activity is conducted using 3 nM of sirtuin protein, with 1 μ L of DMSO in place of compound, to reach baseline deacetylation of the substrate (e.g., to determine normalized sirtuin activity).

[00738] The mass spectrometry based assay utilizes a peptide having 20 amino acid residues as follows: Ac-EE-K(biotin)-GQSTSSHSK(Ac)NleSTEG-K(5TMR)-EE-NH₂ (SEQ ID NO: 3) wherein K(Ac) is an acetylated lysine residue and Nle is a norleucine. The peptide is labeled with the fluorophore 5TMR (excitation 540 nm/emission 580 nm) at the C-terminus. The sequence of the peptide substrate is based on p53 with several modifications. In addition, the methionine residue naturally present in the sequence is replaced with the norleucine because the methionine may be susceptible to oxidation during synthesis and purification.

[00739] The mass spectrometry assay is conducted as follows: 0.5 μ M peptide substrate and 120 μ M β NAD⁺ is incubated with 10 nM SIRT1 for 25 minutes at 25°C in a reaction buffer (50 mM Tris-acetate pH 8, 137 mM NaCl, 2.7 mM KCl, 1 mM MgCl₂, 5 mM DTT, 0.05% BSA). Test compounds may be added to the reaction as described above. The SirT1 gene is cloned into a T7-promoter containing vector and transformed into BL21(DE3). After the 25 minute incubation with SIRT1, 10 μ L of 10% formic acid is added to stop the reaction. Reactions are sealed and frozen for later mass spec analysis. Determination of the mass of the substrate peptide allows for precise determination of the degree of acetylation (i.e. starting material) as compared to deacetylated peptide (product).

[00740] For the mass spectrometry based assay, a control for inhibition of sirtuin activity is conducted by adding 1 μ L of 500 mM nicotinamide as a negative control at the start of the reaction (e.g., permits determination of maximum sirtuin inhibition). A control for activation of sirtuin activity is conducted using 10 nM of sirtuin protein, with 1 μ L of DMSO in place of compound, to determine the amount of deacetylation of the substrate at a given time point within the linear range of the assay. This time point is the same as that used for test compounds and, within the linear range, the endpoint represents a change in velocity.

[00741] For each of the above assays, SIRT1 protein is expressed and purified as follows. The SirT1 gene is cloned into a T7-promoter containing vector and transformed into BL21(DE3). The protein is expressed by induction with 1 mM IPTG as an N-terminal His-tag fusion protein at 18°C overnight and

harvested at 30,000×g. Cells are lysed with lysozyme in lysis buffer (50 mM Tris-HCl, 2 mM Tris[2-carboxyethyl] phosphine (TCEP), 10 μM ZnCl₂, 200 mM NaCl) and further treated with sonication for 10 min for complete lysis. The protein is purified over a Ni-NTA column (Amersham) and fractions containing pure protein are pooled, concentrated and run over a sizing column (Sephadex S200 26/60 global). The peak containing soluble protein is collected and run on an Ion-exchange column (MonoQ). Gradient elution (200 mM-500 mM NaCl) yielded pure protein. This protein is concentrated and dialyzed against dialysis buffer (20 mM Tris-HCl, 2 mM TCEP) overnight. The protein is aliquoted and frozen at -80°C until further use.

[00742] Results can be used to determine if the test compounds activate or inhibit SIRT1. ED₅₀ and IC₅₀ values can be determined.

Example 2: HeLa Apoptosis Assay

[00743] The compounds described herein are evaluated for their effect on a HeLa cell apoptosis assay using the Cell Death Detection ELISA plus kit from Roche Applied Science.

Example 3

[00744] In order to determine if the mammalian enzyme is inhibited by the compounds described herein, 293T cells are transfected with a construct designed to express human SIRT1 fused to glutathione-S-transferase to allow for rapid purification from cell extracts. Following lysis, cell extracts are incubated with glutathione-Sepharose beads followed by several washes in lysis buffer and a final wash in SIRT1 enzyme assay buffer. Beads with bound GST-SIRT1 are added to the Fleur-de-lys assay (Biomol) in the presence of a range of concentrations of the compounds described herein. The EC₅₀ value of the compound described herein for mammalian SIRT1 can be compared to that obtained for the recombinant bacterially produced human enzyme.

[00745] NCI-H460 cells are treated with 20 uM etoposide (a DNA damaging agent) in the presence or absence of SIRT1 inhibitors, either the compound described herein or nicotinamide, and the amount of acetylated p53 (at lysine 382) is visualized by Western blot. Observe for increase in p53 acetylation.

Example 4

[00746] Enantiomers of the compounds described herein are tested, where each enantiomer has a purity of greater than 90% enantiomeric excess, to determine if a single enantiomer is more potent than a mixture of enantiomers. NCI-H460 cells are treated for 6 hours with the enantiomers in the presence of 20 micromolar etoposide followed by lysis and immunoprecipitation of p53 using Ab-6 (Oncogene Science). Extracts are probed with an antibody that recognizes acetylated lysine 382 of p53 (Cell Signaling). Observe for active and inactive enantiomers.

Example 5

[00747] The compounds described herein' ability to increase p53 acetylation can be correlated with its in vitro potency against SIRT1. A series of structurally similar compounds are added to cells at 1 uM concentration. Observe the IC₅₀ of the compounds that increased p53 acetylation.

Example 6

[00748] Strain SL8c (URA at the telomere) are used for yeast based assay to screen compounds. Cells are grown in -URA media to select de-silenced cells. The next day, cells are diluted 1:20 into fresh YPD with 2% glucose, then grown for 5 hrs. Cells are then diluted OD=0.01 in both SD and SD+0.1%

5FOA media. The compounds are then serially diluted into 10 µl of SD or SD+0.1% 5FOA medium. Then 140 µl of cells are pipetted into a 96 well plate and grown at 30°C for 18-24 hrs. Observe for effects of enantiomeric activity on cell growth, inhibition of SIRT1 and expression of URA3 which blocks growth in the presence of 5-fluorouracil.

5 **Example 7**

[00749] Cell lines U2OS and MCF7 cell lines are treated with the compounds described herein in the presence of 20 micromolar etoposide (TOPO) for 6 hours followed by lysis and immunoprecipitation with p53 Ab-6 conjugated to agarose beads. Samples are analyzed by SDS-PAGE and immunoblotted with an antibody that recognizes acetylated lysine 382 of p53. Observe for SIRT1 inhibition in a variety of cell lines with similar effects on P53 acetylation.

Example 8

[00750] In order to assess whether the affects of the compounds described herein on p53 acetylation lead to changes in p53 function, an experiment is performed to measure cell survival after DNA damage. NCI-H460 cells are damaged with varying concentrations of etoposide in the presence or absence of SIRT1 inhibitors. Observe for modulation of the p53 function.

Example 9

[00751] Cells are plated at a density of 800 per well in 96 well cytoStar plates in the presence of a range of etoposide concentrations and 1 micromolar of the claimed compounds. Thymidine incorporation is measured at 24 hours intervals. Observe for synergy between etoposide and the compounds described herein on the growth characteristics of NCI-H460 cells under conditions in which the compound is added concurrent to, prior to, and after treatment with etoposide.

Example 10

[00752] HEK293 cells are serum starved in the presence or absence of the compounds described herein for 24 hrs followed by lysis and immunoblotting analysis of p27 protein. Observe for abrogation of serum starvation-mediated upregulation of the cell cycle inhibitor p27.

Example 11

[00753] Hela cells are transfected with GFP-hSIRT2 isoform 1 (green). At 36 hours post transfection 1 µM of TSA and either DMSO or 50 µM of the compound described herein are added. The next morning cells are fixed, permeabilized, and stained for acetylated tubulin (red). Observe for acetylated tubulin in cells expressing SIRT2.

[00754] It is also possible to observe the effect of the compounds using Western analysis. 293T cells are transfected with either eGFP (control) or with mouse SIRT2 Isoform 1 (mSIRT2). TSA is added to increase amount of acetylated tubulin and at the same time either DMSO or the compound described herein is added to 10 µM.

35 **Example 12: Metabolic Activities of Sirtuin Activators in a Diet Induced Obesity (DIO) Mouse Model**

[00755] In order to define whether SIRT-1 activators protect against the development of obesity and associated insulin-resistance, the compound described herein is chronically administered (via food admix) to male C57BL6J mice that are subjected during 16 weeks to a high fat diet. The mice undergo an extensive phenotypic and molecular analysis to define the regulatory pathways affected by Sirt-1 activation.

[00756] In this long-term study, 50 male C57BL6J mice (5 weeks of age) are analyzed during a period of 18 weeks. Five groups of 10 animals are assigned as follows: (1) chow diet, (2) chow diet+compound disclosed herein (200 mg/kg/day), (3) high fat diet, (4) high fat diet+ compound disclosed herein (200 mg/kg/day), (5): high fat diet+ compound disclosed herein (400 mg/kg/day).

[00757] During the entire study, body weight and food intake are monitored twice weekly. During week 1, body composition is analyzed, for all groups, by dual energy X-ray absorptiometry (dexascan). During week 2, serum levels of glucose, triglycerides, cholesterol, HDL-C, LDL-C and insulin are measured in all groups after a fasting period of 12 h and mice are then placed on the diets as indicated (Day 0). During week 10, glucose tolerance is determined by subjecting all the animals to an intraperitoneal glucose tolerance test (IPGTT). Animals are fasted for 12 h prior to this test.

[00758] Nocturnal energy expenditure of groups 1, 3 and 5 (chow diet, high fat diet and high fat diet 400 mg) is measured by indirect calorimetry. During week 12, body weight composition is again analysed by dexascan for all groups. During week 13, circadian activity of groups 3, 4 and 5 (high fat diet fed mice) is studied during a period of 30 h. During week 14, measurement of blood pressure and heart rate is performed on groups 3, 4 and 5. During week 15, rectal temperature of all animals is measured at room temperature at 10:00 am. A circadian activity measurement is performed on groups 1, 2 and 3.

[00759] During week 16, glucose tolerance is analysed by performing an oral glucose tolerance test (OGTT) on a subset of animals (n=5) of groups 3, 4 and 5, and an intraperitoneal insulin sensitivity test (IPISIT) on another subset of animals (n=5). During these experiments, blood is also collected to analyze insulin levels. Animals are fasted 12 h prior these tests. Feces are collected in all groups over a 24 h time period and fecal lipids content are measured.

[00760] During week 17, serum levels of compound disclosed herein are measured on a subset of mice (n=5) at 7:00 am which corresponds to the beginning of the light cycle and on another subset of mice (n=5) three hours later (10:00 am). Moreover, thyroid hormone T3 levels are measured in the blood collected at 7:00 am and plasma lipoproteins levels are measured in the blood collected at 10:00 am.

[00761] During week 18, a cold test is performed on all animals by measuring body temperature of animals exposed to 4°C. Three days later, animals are sacrificed. At sacrifice, blood is collected and analyzed for: plasma lipids (TC, TG, HDL-C, FFAs); liver functions (ALAT, ASAT, alkaline Pase, γ -GT); and glucose and insulin lipoprotein profiles of selected groups of plasma (size-exclusion chromatography).

[00762] Liver, small intestine, adipose tissues (WAT and BAT), pancreas, heart and muscle are collected and weighed. These can be analyzed by standard histology (HE staining, succinate dehydrogenase staining, oil-red-O staining and cell morphology); for tissue lipid content; and by electron microscopy on BAT and muscle to analyze mitochondria. RNA isolation can be conducted for expression studies of selected genes involved in metabolism and energy homeostasis by quantitative RT-PCR. Microarray experiments can also be performed on selected tissues. In addition, protein extraction can be performed for the study of changes in protein level and post-translational modifications such as acetylation of proteins of interest (e.g. PGC-1 α).

Methods

[00763] Animal housing and handling. Mice are group housed (5 animals/cage) in specific pathogen-free conditions with a 12 h: 12 h (on at 7:00) light-dark cycle, in a temperature (20-22°C.) and humidity

controlled vivarium, according to the European Community specifications. Animals are allowed free access to water and food.

[00764] Drinking water. Chemical composition of the tap water is regularly analyzed to verify the absence of potential toxic substances at the Institut d'Hydrologie, ULP, Strasbourg. Drinking water is treated with HCl and HClO₄ to maintain pH between 5 and 5.5 and chlorin concentration between 5 and 6 ppm.

[00765] Diet. The standard rodent chow diet is obtained from UAR and the high fat diet is obtained from Research Diet. Mice are fed, either with chow diet (16% protein, 3% fat, 5% fiber, 5% ash) or with high fat diet (26.2% protein, 26.3% carbohydrate, 34.9% fat). The compound disclosed herein is mixed with either powdered chow diet or powdered high fat diet and pellets are reconstituted. Control groups receive pellets as provided by the company. Due to the consistency of the high fat diet, it is not necessary to add water to mix it with the compound disclosed herein. In case of the chow, which is harder to reconstitute, a minimal amount of water is added to the powder to reconstitute pellets, which are then air-dried. New batches of food are prepared weekly.

[00766] Blood collection. Blood is collected either from the retro-orbital sinus or from the tail vein.

[00767] Anesthesia. For the dexamethasone scanning experiment, animals are anesthetized with a mixture of ketamine (200 mg/kg)/Xylazine (10 mg/kg) administered by intra-peritoneal injection.

Biochemistry

[00768] Tests are performed with an Olympus AU-400 automated laboratory work station using commercial reagents (Olympus). Analysis of lipids and lipoproteins. Serum triglycerides, total and HDL cholesterol are determined by enzymatic assays. Serum HDL cholesterol content is determined after precipitation of apo B-containing lipoproteins with phosphotungstic acid/Mg (Roche Diagnostics, Mannheim, Germany). Free fatty acids level is determined with a kit from Wako (Neuss, Germany) as specified by the provider.

[00769] Metabolic and endocrine exploration. Blood glucose concentration is measured by a Precision Q.I.D analyzer (Medisense system), using Medisense Precis electrodes (Abbot Laboratories, Medisense products, Bedford, USA). This method has been validated, by comparing Precision Q.I.D analyzer values with classical glucose measurements. The Precision Q.I.D method is chosen since it requires a minimal amount of blood and can hence be employed for multiple measurements such as during an IPGTT. Plasma insulin (Crystal Chem, Chicago, Ill.) is determined by ELISA according to the manufacturer's specifications. Plasma level of T3 is determined by standard radio-immunoassays (RIA) according to the protocol specified by the providers.

Metabolic Testing

[00770] Lipoprotein profiles. Lipoprotein profiles are obtained by fast protein liquid chromatography, allowing separation of the three major lipoprotein classes VLDL, LDL, and HDL.

[00771] Intraperitoneal glucose tolerance test--Oral glucose tolerance test. IPGTT and OGTT are performed in mice which are fasted overnight (12 h). Mice are either injected intraperitoneally (IPGTT) or orally gavaged (OGTT) with a solution of 20% glucose in sterile saline (0.9% NaCl) at a dose of 2 g glucose/kg body weight. Blood is collected from the tail vein, for glucose and insulin monitoring, prior to and at 15, 30, 45, 75, 90, 120, 150, 180 min after administration of the glucose solution. The

incremental area of the glucose curve is calculated as a measure of insulin sensitivity, whereas the corresponding insulin levels indicate insulin secretory reserves.

[00772] Intraperitoneal insulin sensitivity test. Fasted animals are submitted to an IP injection of regular porcine insulin (0.5-1.0 IU/kg; Lilly, Indianapolis, Ind.). Blood is collected at 0, 15, 30, 45, 60, and 90 min after injection and glucose analyzed as described above. Insulin sensitivity is measured as the slope of the fall in glucose over time after injection of insulin.

[00773] Energy expenditure. Energy expenditure is evaluated through indirect calorimetry by measuring oxygen consumption with the Oxymax apparatus (Columbus Instruments, Columbus, Ohio) during 12 h. This system consists of an open circuit with air coming in and out of plastic cages (one mouse per cage). Animals are allowed free access to food and water. A very precise CO₂ and O₂ sensor measures the difference in O₂ and CO₂ concentrations in both air volumes, which gives the amount of oxygen consumed in a period of time given that the air flow of air coming in the cage is constant. The data coming out of the apparatus are processed in a connected computer, analyzed, and shown in an exportable Excel file. The values are expressed as ml.kg⁻¹.h⁻¹, which is commonly known as the VO₂.

[00774] Determination of body fat content by DEXA scanning. The DEXA analyses are performed by the ultra high resolution PIXIMUS Series Densitometer (0.18×0.18 mm pixels, GE Medical Systems, Madison, Wis., USA). Bone mineral density (BMD in g/cm²) and body composition are determined by using the PIXIMUS software (version 1.4x, GE Medical Systems).

Non-invasive Blood Pressure and Heart Rate Measurements

[00775] The Visitech BP-2000 Blood Pressure Analysis System is a computer-automated tail cuff system that is used for taking multiple measurements on 4 awake mice simultaneously without operator intervention. The mice are contained in individual dark chambers on a heated platform with their tails threaded through a tail cuff. The system measures blood pressure by determining the cuff pressure at which the blood flow to the tail is eliminated. A photoelectric sensor detects the specimen's pulse. The system generates results that applicants have shown correspond closely with the mean intra-arterial pressure measured simultaneously in the carotid artery. This allows obtaining reproducible values of systolic blood pressure and heart beat rate. This requires training of the animals for one week in the system.

Circadian Activity

[00776] Spontaneous locomotor activity is measured using individual boxes, each composed with a sliding floor, a detachable cage, and equipped with infra-red captors allowing measurement of ambulatory locomotor activity and rears. Boxes are linked to a computer using an electronic interface (Imetronic, Pessac, France). Mice are tested for 32 h in order to measure habituation to the apparatus as well as nocturnal and diurnal activities. The quantity of water consumed is measured during the test period using an automated lickometer.

Example 13: Effect of Resveratrol on Insulin Resistance

[00777] The current gold standard method for measuring insulin resistance is the euglycemic clamp. In this method glucose is "clamped" at a predetermined value (5 mmol/L for euglycaemia) by titrating a variable-rate of glucose (glucose infusion rate: GIR) against a fixed-infusion rate of insulin. Two to three days in advance of the study, a catheter is established in the femoral vein, under anesthesia (ketamine and xylazine), with the catheter fed underneath the mouse's skin and affixed behind their

head. After surgery, mice are housed individually and allowed to recover for at least 48 hours, preferably enough time for them to regain their body weight. The clamps are performed in awake, unrestrained, unstressed and light-cycle inverted mice following a 5 hour fast. Mice are acclimatized (1 hour) to the tops of cages while their catheter is attached to a syringe-infusion pump. The catheter from the mouse is bifurcated to allow for simultaneous constant and variable injection of insulin and glucose, respectively. Base-line glucose values are measured by tail vein sampling prior to the injection of insulin. Catheter placement is assessed with a short priming dose (6 μ l/min, 1 min) of insulin prior to the constant infusion of insulin at a flow rate of 2 μ l/min equivalent to 18 mU of insulin/kg/min. Blood glucose values are monitored every 5 minutes throughout the test and within 15 minutes blood glucose is lowered and glucose infusion (20% solution in saline) can be started. The glucose infusion rate (GIR) is varied until euglycemia ($\pm$ 15%) has been reached and maintained. At this point the animal is "clamped" and the degree of insulin resistance is inversely related to the amount of glucose necessary to maintain the required blood glucose concentrations. The GIR (mg glucose/kg animal*min) is then calculated as an average during the last 60 minutes of the clamp. When the average GIR of one animal is greater than another, it indicates better insulin sensitivity or that the clearance of glucose from the plasma is much faster.

Example 14: Cell-Based Assays of Sirtuin Activity

[007778] Fat mobilization assay. 3T3 L1 cells are plated with 2 ml of 30,000 cells/ml in Dulbecco's Modified Eagle Medium (DMEM)/10% newborn calf serum in 24-well plates. Individual wells are then allowed to differentiate by addition of 100 nM Rosiglitazone. Undifferentiated control cells are maintained in fresh DMEM/10% newborn calf serum throughout the duration of the assay. At 48 hours (2 days), adipogenesis is initiated by addition of DMEM/10% fetal calf serum/0.5 mM 3-isobutyl-1-methylxanthine (IBMX)/1 μ M dexamethasone. At 96 hours (4 days), adipogenesis is allowed to progress by removal of the media and adding 2 ml of DMEM/10% fetal calf serum to each well along with either 10 μ g/mL insulin or 100 nM Rosiglitazone. At 144 hours (6 days) and 192 hours (8 days), all wells are changed to DMEM/10% fetal calf serum.

[007779] At 240 hours (10 days from the original cell plating), test compounds at a range of concentrations are added to individual wells in triplicate along with 100 nM Rosiglitazone. Three wells of undifferentiated cells are maintained in DMEM/10% newborn calf serum and three wells of differentiated control cells are maintained in fresh DMEM/10% newborn calf serum with 100 nM Rosiglitazone. As a positive control for fat mobilization, resveratrol (a SIRT1 activator) is used at concentrations ranging in three fold dilutions from 100 μ M to 0.4 μ M.

[00780] At 312 hours (13 days), the media is removed and cells are washed twice with PBS. 0.5 mL of Oil Red O solution (supplied in Adipogenesis Assay Kit, Cat.# ECM950, Chemicon International, Temecula, Calif.) is added per well, including wells that have no cells as background control. Plates are incubated for 15 minutes at room temperature, and then the Oil Red O staining solution is removed and the wells are washed 3 times with 1 mL wash solution (Adipogenesis Assay Kit). After the last wash is removed, stained plates are visualized, scanned or photographed. Dye is extracted (Adipogenesis Assay Kit) and quantified in a plate reader at 520 nM.

[00781] Primary dorsal root ganglion (DRG) cell protection assay. Test compounds are tested in an axon protection assay as described (Araki et al. (2004) Science 305(5686):1010-3). Briefly, mouse DRG explants from E12.5 embryos are cultured in the presence of 1 nM nerve growth factor. Non-neuronal cells are removed from the cultures by adding 5-fluorouracil to the culture medium. Test compounds are added 12 to 24 hours prior to axon transections. Transection of neurites are performed at 10-20 days in vitro (DIV) using an 18-gauge needle to remove the neuronal cell bodies.

Example 15: Treatment of Hodgkin's Lymphoma

[00782] A patient with relapsed or refractory Hodgkin's Lymphoma is administered 2-4 mg/m² of a compound of Formula I on days 3 and day 10. Treatment with the compound of Formula I is repeated every 28 days for at least 6 and up to 24 courses in the absence of unacceptable toxicity.

Example 16: Treatment of Non-Hodgkin's Lymphoma

[00783] A patient diagnosed with non-hodgkin's lymphoma is administered 2-4 mg/m² of a compound of Formula I on days 3 and day 10. Treatment with the compound of Formula I is repeated every 28 days for at least 6 and up to 24 courses in the absence of unacceptable toxicity.

Example 17: Treatment of Glioblastoma After Radiotherapy

[00784] A patient diagnosed with glioblastoma undergoes conventional radiotherapy once daily, 5 days a week, for 6 weeks. During this time, the patient is concomitantly administered 2-4 mg/m² of a compound of Formula I on days 3 and day 10. Treatment with the compound of Formula I is repeated every 28 days during radiation treatment in the absence of unacceptable toxicity.

Example 18: Treatment of Melanoma (IL-2 Combination Therapy)

[00785] A patient diagnosed with melanoma is administered high-dose bolus IL-2 (720 000 IU/Kg) intravenously every 8 hours as tolerated but not to exceed 15 doses. During this time, the patient is also administered 2-4 mg/m² of a compound of Formula I on days 3 and day 10. Treatment with the compound of Formula I is repeated every 28 days during radiation treatment in the absence of unacceptable toxicity.

Example 19: Treatment of Renal Cell Cancer (IL-2 Combination Therapy)

[00786] A patient diagnosed with renal cell cancer is administered high-dose bolus IL-2 (720 000 IU/Kg) intravenously every 8 hours as tolerated but not to exceed 15 doses. During this time, the patient is also administered 2-4 mg/m² of a compound of Formula I on days 3 and day 10. Treatment with the compound of Formula I is repeated every 28 days during radiation treatment in the absence of unacceptable toxicity.

Example 20: Treatment of Prostate Cancer (13-cis Retinoic Acid Combination Therapy)

[00787] A patient diagnosed with prostate cancer receives oral 13-cis Retinoic Acid at a dose of 1.0 mg/kg/day, given as a single daily dose and rounded to the nearest 10 mg, for a period of 12 months. The 13-cis Retinoic Acid is provided in the form of soft gelatin capsule of 10, 20 or 40 mg. On days 3 and 10, the patient also receives 2-4 mg/m² of a compound of Formula I. Treatment with the compound of Formula I is repeated every 28 days for at least 6 and up to 24 courses in the absence of unacceptable toxicity.

Example 21: Treatment of Non-Small Cell Lung Cancer (Erlotinib Combination Therapy)

[00788] A patient diagnosed with non-small cell lung cancer is administered 100-150 mg/day of erlotinib for three weeks and 2-4 mg/m² of a compound of Formula I on days 3 and 10. This treatment is repeated every 28 days for at least 6 and up to 24 courses in the absence of unacceptable toxicity.

Example 22: Treatment of AML (ATRA Combination Therapy)

5 [00789] A patient diagnosed with AML is administered 45 mg/m² ATRA daily and 2-4 mg/m² of a compound of Formula I on days 3 and day 10. Treatment with the compound of Formula I is repeated every 28 days for at least 6 and up to 24 courses in the absence of unacceptable toxicity.

Example 23: Treatment of AML (Anti-Estrogen Combination Therapy)

10 [00790] A patient diagnosed with AML is administered 200-700 mg/day p.o. for 7 days in combination 2-4 mg/m² of a compound of Formula I on day 3 and day 10. Courses are repeated every 21 days in the absence of disease progression or unacceptable toxicity.

Example 24: Treatment of AML (Decitabine Combination Therapy)

15 [00791] A patient diagnosed with AML is administered 15-20mg/m²/IV over 1 hr daily for 10 days and 2-4 mg/m² of a Compound of Formula I on day 3 and 10. Courses are repeated every 21 days in the absence of disease progression or unacceptable toxicity.

Example 25: Testing of Neuroprotective Effects in a Retinal Ganglion Cell Injury Model

[00792] Administration of Test Compounds: Stock solutions for administration the test compound (125 mM in water).

Endpoints

20 [00793] RGC density is determined by immunohistochemistry with brn-3 labeled retinal ganglion cells (RGC). RGCs are counted in 12 standard retinal locations per flat mount.

Test Substance Administration

25 [00794] On days 0, 2 and 4, 2 µl of test substance or vehicle (2% HPMC, 0.2% DOSS) is injected into the intravitreal space of anesthetised (intraperitoneal ketamine, xylazine) to the right eye of all 3-month old adult Swiss white mice (25 to 30 g, n=12 per treatment) using a microsyringe driver attached to a micropipette.

Sham Injections

30 [00795] Vehicle (2 µl, n=12) is injected on days 0, 2 and 4 to the right eye of all mice using a microsyringe driver attached to a micropipette. Water (n=4) is injected days 0, 2 and 4 to the right eye of all mice using a microsyringe driver attached to a micropipette to serve as controls for nicotinamide riboside and NMN.

RGC Injury Models

35 [00796] Intravitreal NMDA injection (100 nM in 2 µl) is administered to the right eye of all mice (test substance or sham injected animals) using a microsyringe driver attached to a micropipette. This injection induces reproducible RGC apoptosis, which peaks between 12 and 24 hours after injection.

RGC Density

[00797] This is quantified from retinal flatmounts created 6 days after NMDA injection. RGCs are identified by anti-brn-3 staining³. RGC density is determined for 12 retinal locations per flat mount (3 per quadrant at set distances from the optic nerve head). To generate flatmounts, mice are perfusion fixed with 4%

paraformaldehyde, eyes enucleated and fixed overnight in 4% paraformaldehyde. Retinas are then collected and placed onto subbed slides, labeled and counted.

Mouse Summary for Each Test Substance:

[00798] Injections are performed to right eyes only (in accordance with ARVO statements for the use of animals in ophthalmic and vision research).

Example 26: Treatment of Multiple Sclerosis (Murine Modulator) using Sirtuin Modulators

[00799] Experimental autoimmune encephalomyelitis (EAE) is an animal model of MS induced by immunization with proteolipid protein (PLP). Animals mount an immune response resulting in inflammation, demyelination, and neuronal damage in the brain, spinal cord, and optic nerve, similar to MS patients. Assessment of clinical/neurological symptoms, and histological analysis of demyelination and axonal damage in the thoracic spinal cord are examined.

[00800] Chronic relapsing EAE is induced in 8-12 week old female SJL mice by subcutaneous (s.c.) injection with an emulsion containing PLP 139-151 peptide and complete Freund's adjuvant containing 150 µg of peptide and 200 µg of Mycobacterium tuberculosis in a total volume of 0.2 ml. In addition, mice are injected intraperitoneally (i.p.) with 200 ng pertussis toxin (List Biological, Campbell, Calif.) in 0.1 ml PBS on day 0 (day of immunization) and again on day 2. The animals are housed in standard conditions: constant temperature (22 ± 1°C.), humidity (relative, 25%) and a 12-h light/12-h dark cycle, and are allowed free access to food and water. Animals are assessed daily for weight and clinical signs of EAE, beginning 11 days after immunization. Assessment continues until day 40 after the initial inoculation. During this time animals undergo an initial phase of EAE, followed by recovery. A relapse of EAE typically occurs 20-30 days post-immunization. Mice are considered to have had a relapse if they have an increase by 1 on the clinical scale for two or more days after a period of five or more days of stable or improved appearance.

[00801] Female SJL/J mice are immunized by a subcutaneous (s.c.) injection with proteolipid protein 139-151 peptide in complete Freund's adjuvant. Mice are treated with the sirtuin modulator (125 mM resveratrol in 40% Captisol, pH app. 6.0) or vehicle (40% Captisol) for 30 days by daily IP injection at a dose of either 200 mg/kg/day (low dose) or 400 mg/kg/day (high dose) beginning on day 11 (onset of paralysis) and perfused on day 40. As a positive control, the immunosuppressant FK506 (tacrolimus) is used at 5 mg/kg/day.

[00802] During the initial few weeks of treatment, most of the mice develop sores and scabbing. The mice receiving the high dose of the test compound are very irritated after injection, scratched their head area raw and, many developed a black hued skin color. Under direction from a veterinarian, antibiotic treatment is applied. Over the course of the next week, the skin lesions largely disappeared and the irritation following injection resolved.

[00803] Blood is collected at the time of perfusion, 1-1.25 hours after the last injection of sirtuin modulator. The blood is centrifuged, serum collected, frozen prior to analysis.

[00804] Mice are examined for clinical signs of EAE daily beginning 11 days after immunization using the following scale: 0, no paralysis; 1, limp tail with minimal hind limb weakness (animal cannot be flipped easily onto its back); 2, mild hind limb weakness (animal can be easily flipped onto its back but rights itself easily); 3, moderate hind limb weakness; 4, moderately severe hind limb weakness; 5, severe hind

limb weakness; 6, complete hind limb paralysis; 7, hind limb paralysis with mild fore limb weakness; 8, hind limb paralysis with moderate fore limb weakness; 9, hind limb paralysis with severe fore limb weakness. After initiation of treatment, mice are graded for EAE blinded to treatment status. To assess the severity of the initial clinical episode of EAE, a 10-Day Cumulative Disease Score (10 Day-CDS) is calculated for each animal by adding the daily disease score on 10 consecutive days commencing on the first day of disease. To assess severity throughout the course of chronic relapsing EAE, a Total Disease Score is determined by adding the daily disease score beginning on the first day of disease until the animals are sacrificed. Following recovery from the initial episode of EAE, mice are considered to have had a relapse if they had an increase in EAE score by 1 or more for >2 consecutive days after a period of >5 days of having stable or improving scores.

[00805] At day 40 post-immunization, mice from each group are sacrificed with an overdose of ketamine/xylazine. Spinal cords are dissected, fixed in 10% buffered formalin, and embedded in paraffin. Five micron thick sections are stained with Hematoxylin and Eosin (H&E) and Luxol Fast Blue (LFB) to assess myelin loss. Bielshowesky's silver impregnation is used to evaluate axonal integrity. To assess the amount of axonal loss, paraffin sections are exposed to monoclonal antibodies against mouse non-phosphorylated neurofilament H (Clone SMI-32, Stemberger Monoclonals, Baltimore, USA) and monoclonal antibodies against APP (Clone 22C11, Chemicon). SMI-32 is detected with a Cy3-labeled antibody and visualized by fluorescence microscopy. Anti-APP antibodies are detected by incubation with ColonoPAP, and APP-positive axons are visualized with 3,3'-diaminobenzidine (DAB).

[00806] To evaluate the extent of axonal loss, images of slides are captured and the areas stained by immunohistochemistry are quantified blinded to treatment status. Axonal integrity and demyelination are assessed qualitatively.

[00807] The percentage of the spinal cord showing damage is determined in the cervical, thoracic and lumbar cord. At each level, regions in the 1) dorsal columns and 2) the lateral and ventral white matter tracts containing damaged fibers is circumscribed on photomontages (final magnification $\times 100$) of the entire spinal cord. Damaged areas in each of the two regions are measured using a SummaSketch III (Summagraphics, Seymour, Conn.) digitizing tablet and BIOQUANT Classic 95 software (R&M Biometrics, Nashville, Tenn.). Measurements are also be made of the total area (damaged and nondamaged) of the 1) dorsal columns and 2) the lateral and ventral columns. For each section (one section per animal), the cumulative percent lesion areas are calculated for each region (dorsal column, lateral and ventral columns).

III. Pharmaceutical Compositions

Example 1: Parenteral Composition

[00808] An i.v. solution is prepared in a sterile isotonic solution of water for injection and sodium chloride (~300 mOsm) at pH 11.2 with a buffer capacity of 0.006 mol/l/pH unit. The protocol for preparation of 100 ml of a 5 mg/ml a compound of Formula I-XI for i.v. infusion is as follows: add 25 ml of NaOH (0.25 N) to 0.5 g of a compound of Formula I-XI and stir until dissolved without heating. Add 25 ml of water for injection and 0.55 g of NaCl and stir until dissolved. Add 0.1N HCl slowly until the pH of the solution is 11.2. The volume is adjusted to 100 ml. The pH is checked and maintained between 11.0

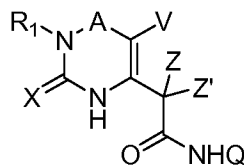
and 11.2. The solution is subsequently sterilized by filtration through a cellulose acetate (0.22 μ m) filter before administration.

Example 2: Oral Composition

5 **[00809]** To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formulas I-XXI is mixed with 750 mg of a starch. The mixture is incorporated into an oral dosage unit, such as a hard geletin capsule or coated tablet, which is suitable for oral administration.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



Formula I

5 or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

R_1 is hydrogen, halogen, -CN, -L-OH, -L-NH₂, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂;

10 A is a bond, C=O, C=S, S=O, S(O)₂, C=N-R₄, CR_aR_a, CR_aR_a-CR_aR_a, CR_a=CR_a, or A taken together with the nitrogen to which it is attached is -N=CH- and R_1 is not present,

wherein R₄ is hydrogen or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, mercaptoalkyl, haloalkyl and carboxyalkyl;

15 wherein each R_a is independently hydrogen or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, mercaptoalkyl, haloalkyl and carboxyalkyl;

and wherein n is 1 or 2;

X is O, S or N-O-R²,

20 wherein R² is hydrogen or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, mercaptoalkyl, haloalkyl, and carboxyalkyl;

V, Z and Z' are each independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl,

25 wherein L is a bond, -C(O)-, -S(O)-, or -S(O)₂-,

or when taken together V and Z form a saturated or unsaturated, substituted or unsubstituted 5-7 member ring which incorporates 0, 1 or 2 heteroatoms selected from O, S and N; and

Q is hydrogen or hydroxyl; and

provided that when A is a bond and V is OH, then R_1 is not amidoalkyl or carboxyalkyl.

30 2. The compound or pharmaceutically acceptable salt according to Claim 1.

3. The compound of Claim 1, wherein Z' is hydrogen.

4. The compound of Claim 1 wherein A is a bond.

5. The compound of Claim 1, wherein A is C=O.

6. The compound of Claim 1, wherein A is C=S.

35 7. The compound of Claim 1, wherein A is S=O.

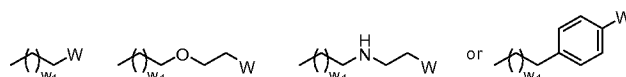
8. The compound of Claim 1, wherein A is S(O)₂.

9. The compound of Claim 1 wherein A taken together with the nitrogen to which it is attached is -N=CH- and R_1 is not present.

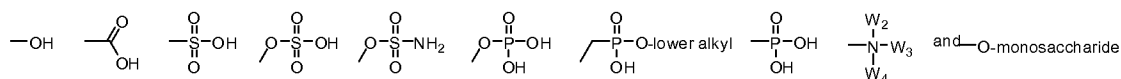
10. The compound of Claim 1, wherein A is C=N-R₄.

40 11. The compound of Claim 1, wherein A is CR_aR_a, CR_aR_a-CR_aR_a or CR_a=CR_a.

12. The compound of Claim 10, wherein R₄ is hydrogen or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl.
13. The compound of Claim 10, wherein R₄ is C₁-C₄ alkyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ aminoalkyl, C₁-C₄ alkylamino, C₁-C₄ alkylthio, C₁-C₄ perfluoroalkyl, C₁-C₄ perfluoroalkoxy, C₁-C₄ alkoxycarbonyl, aryl or heteroaryl.
14. The compound of Claim 10, wherein R₄ is an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.
15. The compound of Claim 11, wherein each R_a is independently hydrogen or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl.
16. The compound of Claim 11, wherein each R_a is independently hydrogen, C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl.
17. The compound of Claim 11, wherein each R_a is independently hydrogen or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.
18. The compound of Claim 11, wherein each R_a is hydrogen.
19. The compound of Claim 1, wherein A is CR_aR_a.
20. The compound of Claim 1, wherein A is CR_aR_a-CR_aR_a.
21. The compound of Claim 1, wherein A is CR_a=CR_a.
22. The compound of Claim 1, wherein Q is hydrogen.
23. The compound of Claim 1, wherein Q is hydroxyl.
24. The compound of Claim 1, wherein X is O.
25. The compound of Claim 1, wherein X is S.
26. The compound of Claim 1, wherein X is N-O-R².
27. The compound of Claim 26, wherein R² is hydrogen or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl.
28. The compound of Claim 26, wherein R² is C₁-C₄ alkyl, C₃-C₈ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ aminoalkyl, C₁-C₄ alkylamino, C₁-C₄ alkylthio, C₁-C₄ perfluoroalkyl, C₁-C₄ perfluoroalkoxy, C₁-C₄ alkoxycarbonyl, aryl or heteroaryl.
29. The compound of Claim 26, wherein R² is an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.
30. The compound of Claim 1, wherein X is O and A is C=O or a bond.
31. The compound of Claim 1, wherein X is S and A is C=S or a bond.
32. The compound of Claim 1, wherein X is N-O-R² and A is a bond.
33. The compound of Claim 1, wherein V and Z are each independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-C₁-C₄ alkyl, L-C₂-C₅ alkenyl, L-C₂-C₅ alkynyl, -L-C₃-C₇ cycloalkyl, L-C₃-C₇ cycloalkenyl, -L-C₃-C₇ heterocycloalkyl, -L-C₁-C₄ haloalkyl, -L-C₁-C₄ alkoxy, -L-C₁-C₄ alkylamine, -L-(C₁-C₄)₂dialkylamine, -L-C₅-C₇ aryl and -L-C₅-C₇ heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:

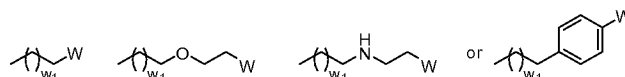


wherein W is selected from:

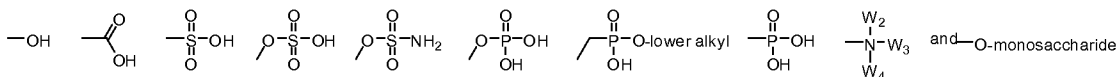


wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom.

34. The compound of Claim 1, wherein V and Z are each independently hydrogen or a substituted or unsubstituted group selected from C_1 - C_4 alkyl, C_2 - C_5 alkenyl, C_2 - C_5 alkynyl, C_3 - C_7 cycloalkyl, C_3 - C_7 cycloalkenyl, C_3 - C_7 heterocycloalkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylamine, $(C_1$ - C_4)₂dialkylamine, C_5 - C_7 aryl and C_5 - C_7 heteroaryl.
35. The compound of Claim 1, wherein Z' is hydrogen and V and Z are each independently hydrogen or an unsubstituted group selected from C_1 - C_4 alkyl, C_1 - C_4 heteroalkyl, C_3 - C_5 cycloalkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylamine, and $(C_1$ - C_4)₂dialkylamine.
36. The compound of any of Claims 33-35, wherein Z' is hydrogen.
37. The compound of any of Claims 33-35, wherein Z' is other than hydrogen.
38. The compound of Claim 1, wherein V and Z form a saturated unsubstituted 5-7 member ring.
39. The compound of Claim 38, wherein the saturated unsubstituted 5-7 member ring is a cycloalkyl group.
40. The compound of Claim 38, wherein the saturated unsubstituted 5-7 member ring is a heterocycloalkyl group.
41. The compound of Claim 1, wherein V and Z form a partially unsaturated unsubstituted 5-7 member ring.
42. The compound of Claim 41, wherein the partially unsaturated unsubstituted 5-7 member ring is a cycloalkenyl group.
43. The compound of Claim 41, wherein the partially unsaturated unsubstituted 5-7 member ring is a heterocycloalkenyl group.
44. The compound of Claim 1, wherein V and Z form an unsaturated, unsubstituted 5-7 member ring.
45. The compound of Claim 44, wherein the unsaturated, unsubstituted 5-7 member ring is a heteroaryl group.
46. The compound of Claim 44, wherein the unsaturated, unsubstituted 5-7 member ring is an aryl group.
47. The compound of Claim 1, wherein V and Z form a saturated, substituted 5-7 member ring.
48. The compound of Claim 47, wherein the saturated, substituted 5-7 member ring is a cycloalkyl group.
49. The compound of Claim 47, wherein the saturated, substituted 5-7 member ring is a heterocycloalkyl group.
50. The compound of Claim 1, wherein V and Z form a partially unsaturated, substituted 5-7 member ring.
51. The compound of Claim 50, wherein the partially unsaturated, substituted 5-7 member ring is a cycloalkenyl group.
52. The compound of Claim 50, wherein the partially unsaturated, substituted 5-7 member ring is a heterocycloalkenyl group.
53. The compound of Claim 1, wherein V and Z form an unsaturated, substituted 5-7 member ring.
54. The compound of Claim 53, wherein the unsaturated, substituted 5-7 member ring is a heteroaryl group.
55. The compound of Claim 53, wherein the unsaturated, substituted 5-7 member ring is an aryl group.
56. The compound of any of Claims 47-55, wherein the ring is substituted with 1-3 substituents selected from halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L- C_1 - C_4 alkyl, L- C_2 - C_5 alkenyl, L- C_2 - C_5 alkynyl, -L- C_3 - C_7 cycloalkyl, L- C_3 - C_7 cycloalkenyl, -L- C_3 - C_7 heterocycloalkyl, -L- C_1 - C_4 haloalkyl, -L- C_1 - C_4 alkoxy, -L- C_1 - C_4 alkylamine, -L- $(C_1$ - C_4)₂dialkylamine, -L- C_5 - C_7 aryl and -L- C_5 - C_7 heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:

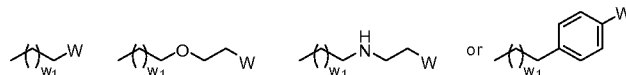


wherein W is selected from:

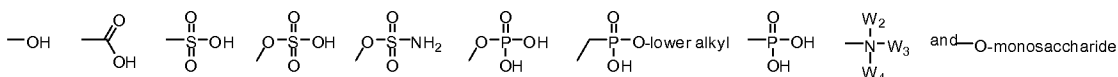


wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom.

57. The compound of any of Claims 47-55, wherein the ring is substituted with 1-3 substituents selected from halogen, -CN, -OH, -NH₂, or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl.
58. The compound of any of Claims 47-55, wherein the ring is substituted with 1-3 substituents selected from halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.
59. The compound of any of Claims 47-55, wherein the ring is substituted with 1-3 substituents selected from halogen, -CN, -OH, -NH₂, or a substituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine, wherein the substituted group is substituted with a substituent selected from halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.
60. The compound of any of Claims 47-55, wherein Z' is hydrogen.
61. The compound of any of Claims 47-55, wherein Z' is other than hydrogen.
62. The compound of Claim 1, wherein R₁ is hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-C₁-C₄ alkyl, L-C₂-C₅ alkenyl, L-C₂-C₅ alkynyl, -L-C₃-C₇ cycloalkyl, L-C₃-C₇ cycloalkenyl, -L-C₃-C₇ heterocycloalkyl, -L-C₁-C₄ haloalkyl, -L-C₁-C₄ alkoxy, -L-C₁-C₄ alkylamine, -L-(C₁-C₄)₂dialkylamine, -L-C₅-C₇ aryl and -L-C₅-C₇ heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom.

63. The compound of Claim 1, wherein R₁ is hydrogen, halogen, -CN, -OH, -NH₂, or a substituted or unsubstituted group selected from C₁-C₄ alkyl, C₂-C₅ alkenyl, C₂-C₅ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, C₃-C₇ heterocycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, (C₁-C₄)₂dialkylamine, C₅-C₇ aryl and C₅-C₇ heteroaryl.
64. The compound of Claim 1, wherein R₁ is hydrogen, halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃-C₅ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.
65. The compound of Claim 1, wherein R₁ is hydrogen, -CN, -OH, -NH₂, or a substituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₃ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine, wherein the substituted group is substituted with a substituent selected from halogen, -CN, -OH, -NH₂, or an unsubstituted group selected from C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ alkylamine, and (C₁-C₄)₂dialkylamine.
66. The compound of Claim 1, wherein Z and Z' are different and the carbon atom to which they are attached is in the S configuration.

67. The compound of Claim 1, wherein Z and Z' are different and the carbon atom to which they are attached is in the R configuration.

68. The compound of Claim 1, wherein

V and Z taken together form a saturated or unsaturated, substituted or unsubstituted 5-7 member ring which incorporates 0, 1 or 2 heteroatoms selected from O, S and N; and

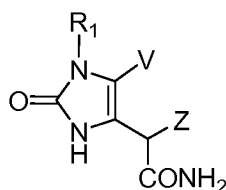
the carbon atom to Z' is attached is in the S configuration.

69. The compound of Claim 1, wherein

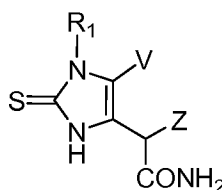
V and Z taken together form a saturated or unsaturated, substituted or unsubstituted 5-7 member ring which incorporates 0, 1 or 2 heteroatoms selected from O, S and N; and

the carbon atom to Z' is attached is in the R configuration.

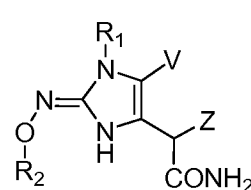
70. The compound of Claim 1 according to Formula IIA, Formula IIB, or Formula IIC:



Formula IIA



Formula IIB

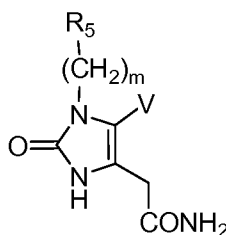


Formula IIC

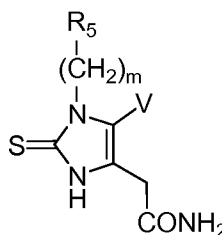
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof.

71. The compound or pharmaceutically acceptable salt of Claim 70.

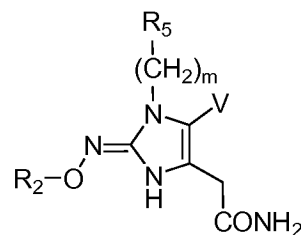
72. The compound of Claim 1 according to Formula IIIA, Formula IIIB, or Formula IIIC:



Formula IIIA



Formula IIIB



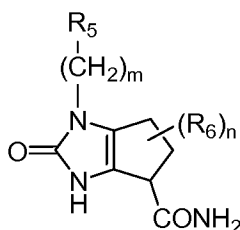
Formula IIIC

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

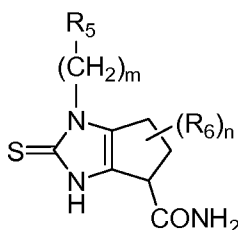
R₅ is hydrogen, halogen, -CN, -OH, or -NH₂; and

m is 1, 2, 3, 4 or 5.

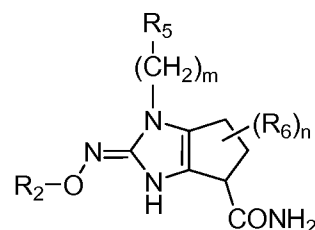
73. The compound of Claim 1 according to Formula VA, Formula VB, or Formula VC:



Formula VA



Formula VB



Formula VC

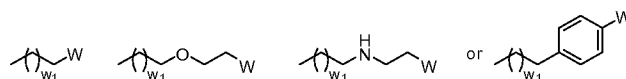
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

R₅ is hydrogen, halogen, -CN, -OH, or -NH₂;

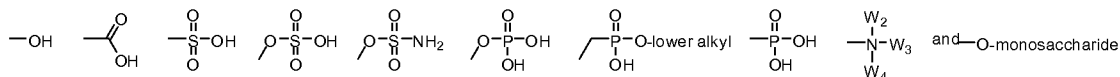
m is 1, 2, 3, 4 or 5;

each R₆ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-

heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



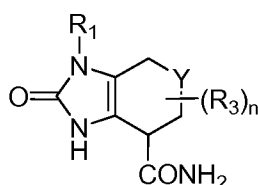
wherein W is selected from:



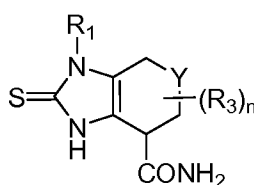
wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

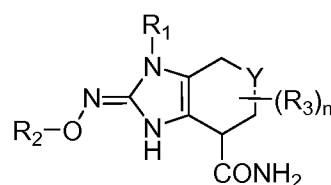
74. The compound of Claim 1 according to Formula VIA, Formula VIB or Formula VIC:



Formula VIA



Formula VIB

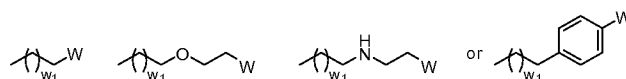


Formula VIC

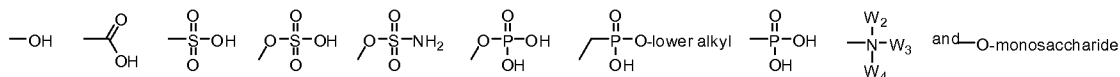
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y is O, S, NR₃ or CR₃R₃;

each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



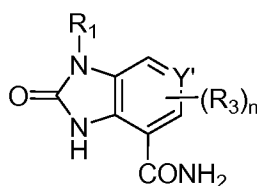
wherein W is selected from:



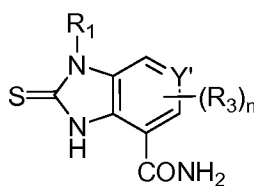
wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

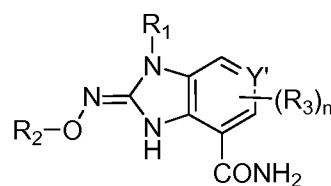
75. The compound of Claim 1 according to Formula VIA', Formula VIB' or Formula VIC':



Formula VIA'



Formula VIB'



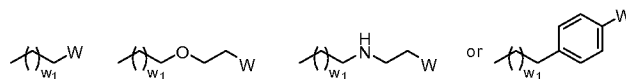
Formula VIC'

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

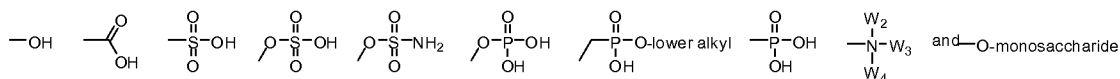
Y' is N or CR₃;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:

5



wherein W is selected from:

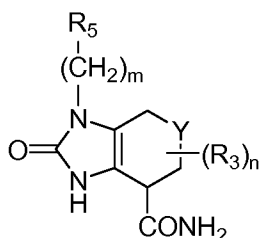


10

wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

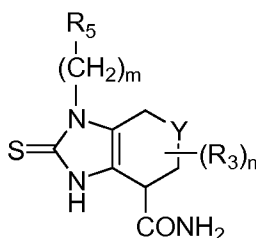
n is 0, 1, 2 or 3.

76. The compound of Claim 1 according to Formula VIIA, Formula VIIB, or Formula VIIC:

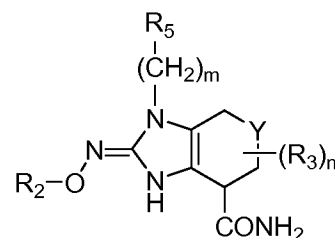


15

Formula VIIA



Formula VIIB



Formula VIIC

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y is O, S, NR₃ or CR₃R₃;

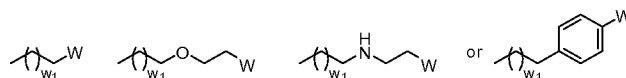
R_5 is hydrogen, halogen, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5;

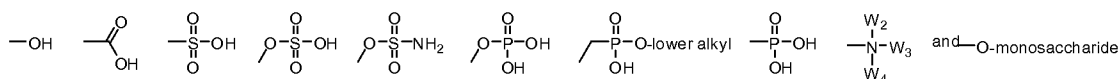
20

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:

25



wherein W is selected from:

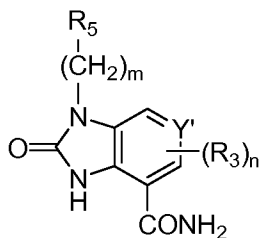


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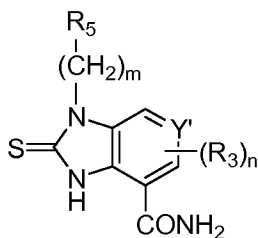
wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

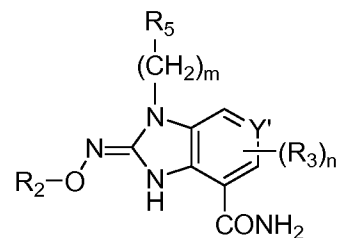
77. The compound of Claim 1 according to Formula VIIA', Formula VIIB', or Formula VIIC':



Formula VIIA'



Formula VIIIB'



Formula VIIC'

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

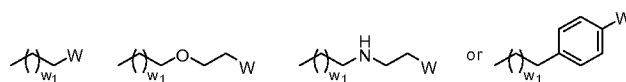
Y' is N or CR₃;

5 R₅ is hydrogen, halogen, -CN, -OH, or -NH₂;

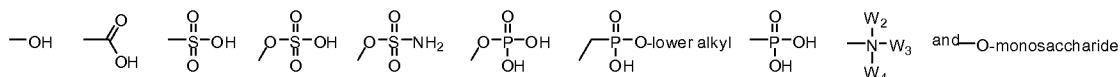
m is 1, 2, 3, 4 or 5;

each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:

10



wherein W is selected from:

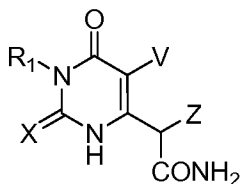


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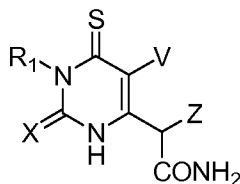
wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

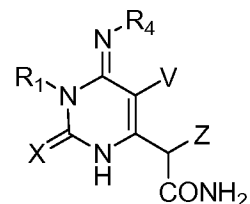
78. The compound of Claim 1 according to Formula VIIIA, Formula VIIIB, or Formula VIIC:



Formula VIIIA



Formula VIIIB

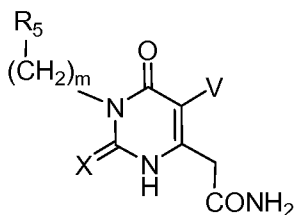


Formula VIIC

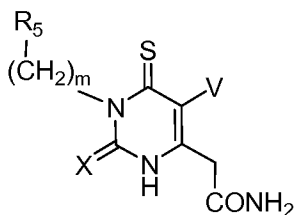
20

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof.

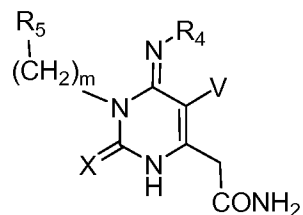
79. The compound of Claim 1 according to Formula IXA, Formula IXB, or Formula IXC:



Formula IXA



Formula IXB



Formula IXC

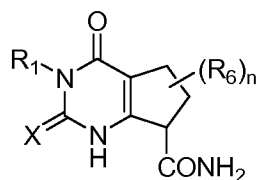
25

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

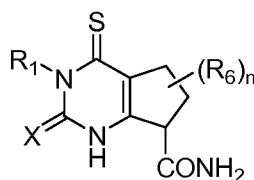
R₅ is hydrogen, halogen, -CN, -OH, or -NH₂; and

m is 1, 2, 3, 4 or 5.

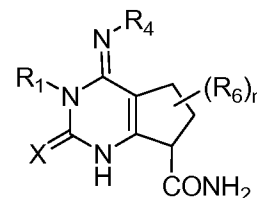
80. The compound of Claim 1 according to Formula XA, Formula XB or Formula XC:



Formula XA



Formula XB

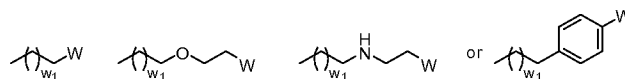


Formula XC

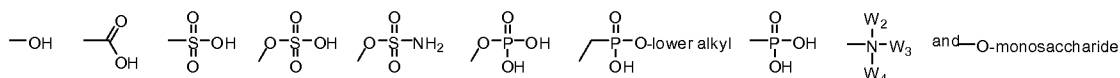
5 or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

each R_6 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:

10



wherein W is selected from:

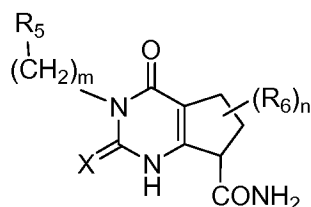


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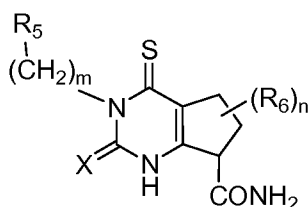
wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1 or 2.

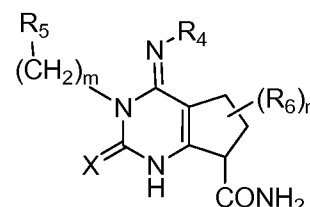
81. The compound of Claim 1 according to Formula XIA, Formula XIB or Formula XIC:



Formula XIA



Formula XIB



Formula XIC

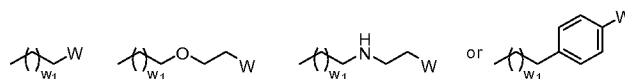
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

R_5 is hydrogen, halogen, -CN, -OH, or -NH₂;

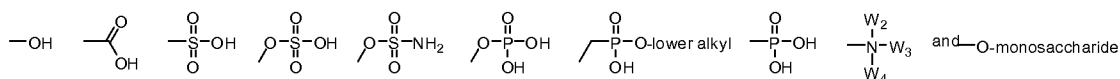
m is 1, 2, 3, 4 or 5;

25

each R_6 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



wherein W is selected from:

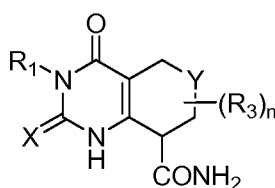


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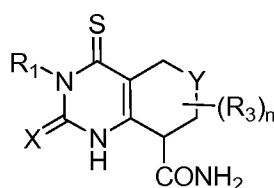
wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

5 n is 0, 1, 2 or 3.

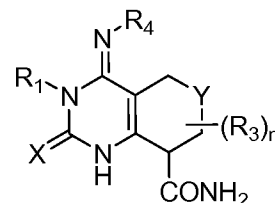
82. The compound of Claim 1 according to Formula XIA, Formula XIIB or Formula XIIC:



Formula XIA



Formula XIIB

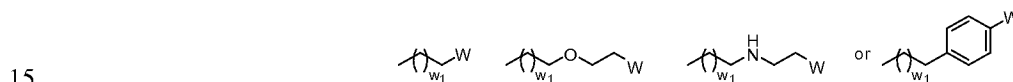


Formula XIIC

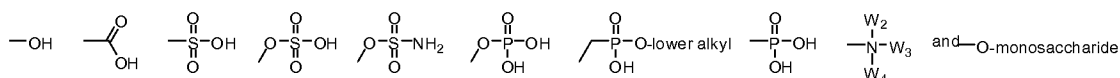
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

10 Y is O, S, NR_3 or CR_3R_3 ;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



wherein W is selected from:

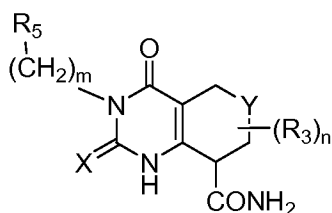


wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

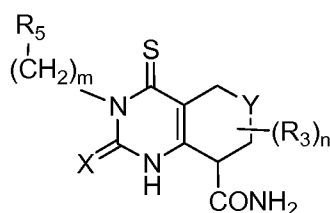
20

n is 0, 1, 2 or 3.

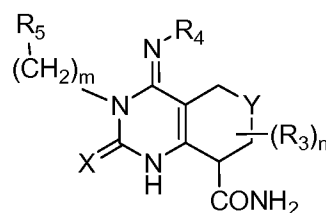
83. The compound of Claim 1 according to Formula XIII A, Formula XIII B or Formula XIII C:



Formula XIII A



Formula XIII B



Formula XIII C

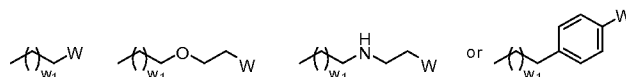
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y is O, S, NR_3 or CR_3R_3 ;

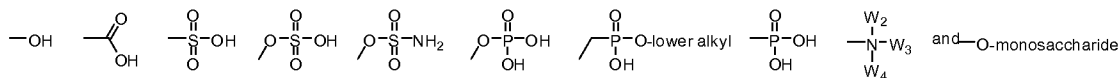
R_5 is hydrogen, halogen, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5;

30 each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



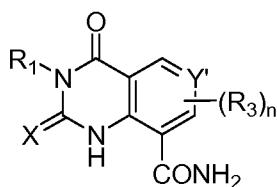
wherein W is selected from:



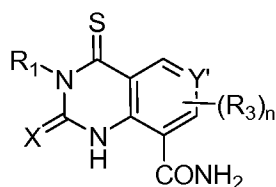
wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

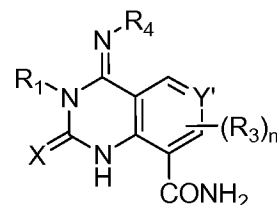
84. The compound of Claim 1 according to Formula XIIIA', Formula XIIB' or Formula XIIC':



Formula XIIIA'



Formula XIIB'

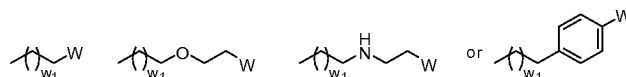


Formula XIIC'

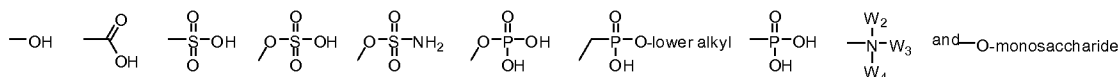
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y' is N or CR_3 ;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



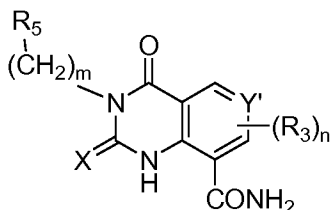
wherein W is selected from:



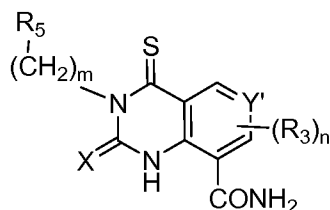
wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

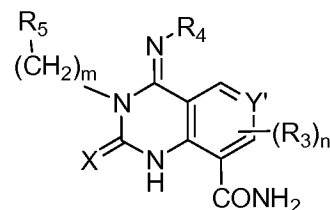
85. The compound of Claim 1 according to Formula XIIIA', Formula XIIB' or Formula XIIC':



Formula XIIIA'



Formula XIIB'



Formula XIIC'

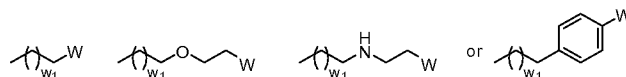
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y' is N or CR_3 ;

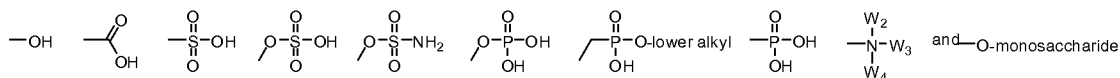
R_5 is hydrogen, halogen, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5;

each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



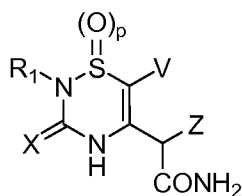
wherein W is selected from:



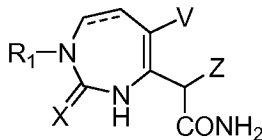
wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

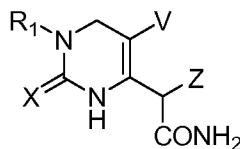
86. The compound of Claim 1 according to Formula XIVA, Formula XIVB, Formula XIVC or Formula XIVD:



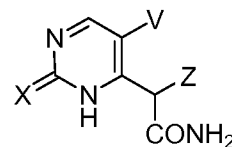
Formula XIVA



Formula XIVB



Formula XIVC



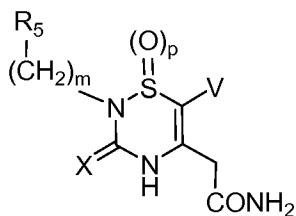
Formula XIVD

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

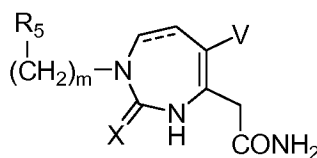
p is 1 or 2; and

---- represents CH₂-CH₂ or CH=CH.

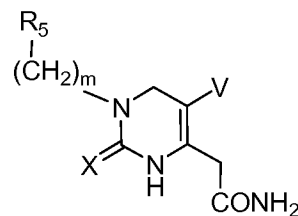
87. The compound of Claim 1 according to Formula XVA, Formula XVB or Formula XVC:



Formula XVA



Formula XVB



Formula XVC

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

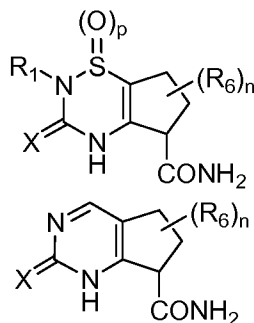
p is 1 or 2;

---- represents CH₂-CH₂ or CH=CH;

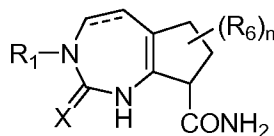
R₅ is hydrogen, halogen, -CN, -OH, or -NH₂; and

m is 1, 2, 3, 4 or 5.

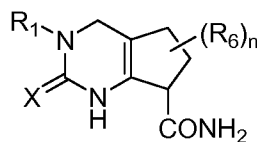
88. The compound of Claim 1 according to Formula XVIA, Formula XVIB, Formula XVIC or Formula XVID:



Formula XVIIA



Formula XVIIIB



Formula XVIIIC

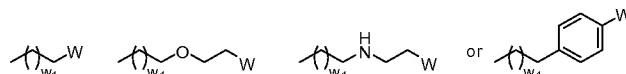
Formula XVIIID

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

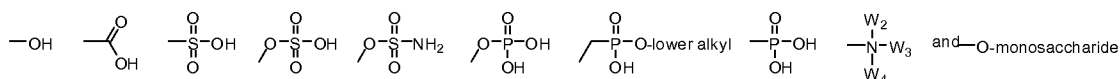
5 p is 1 or 2;

---- represents $\text{CH}_2\text{-CH}_2$ or CH=CH ;

each R_6 is independently hydrogen, halogen, $-\text{CN}$, $-\text{L-OH}$, $-\text{L-NH}_2$, a water solubilizing group, or a substituted or unsubstituted group selected from $-\text{L-alkyl}$, L-alkenyl , L-alkynyl , $-\text{L-cycloalkyl}$, L-cycloalkenyl , $-\text{L-heterocycloalkyl}$, $-\text{L-haloalkyl}$, $-\text{L-alkoxy}$, $-\text{L-alkylamine}$, $-\text{L-dialkylamine}$, $-\text{L-aryl}$ and $-\text{L-heteroaryl}$,
 10 wherein L is a bond, $-\text{C(O)-}$, $-\text{S(O)}$, or $-\text{S(O)}_2$ and wherein the water solubilizing group is:



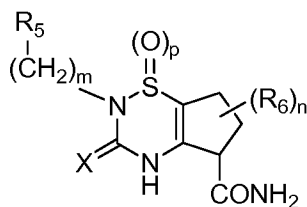
wherein W is selected from:



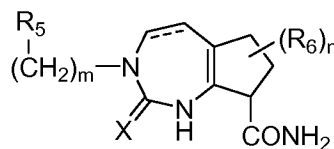
15 wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1 or 2.

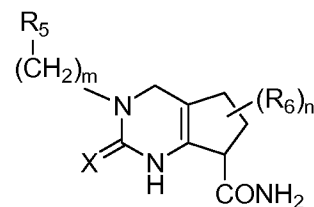
89. The compound of Claim 1 according to Formula XVIIA, Formula XVIIIB or Formula XVIIIC:



Formula XVIIIA



Formula XVIIIB



Formula XVIIIC

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

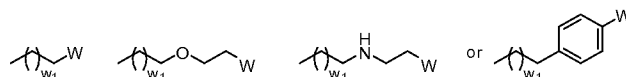
p is 1 or 2;

---- represents $\text{CH}_2\text{-CH}_2$ or CH=CH ;

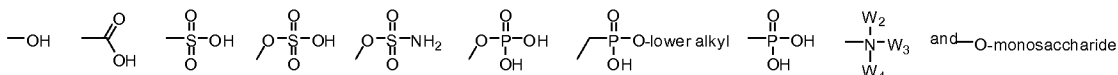
25 R_5 is hydrogen, halogen, $-\text{CN}$, $-\text{OH}$, or $-\text{NH}_2$; and

m is 1, 2, 3, 4 or 5.

each R_6 is independently hydrogen, halogen, $-\text{CN}$, $-\text{L-OH}$, $-\text{L-NH}_2$, a water solubilizing group, or a substituted or unsubstituted group selected from $-\text{L-alkyl}$, L-alkenyl , L-alkynyl , $-\text{L-cycloalkyl}$, L-cycloalkenyl , $-\text{L-heterocycloalkyl}$, $-\text{L-haloalkyl}$, $-\text{L-alkoxy}$, $-\text{L-alkylamine}$, $-\text{L-dialkylamine}$, $-\text{L-aryl}$ and $-\text{L-heteroaryl}$,
 30 wherein L is a bond, $-\text{C(O)-}$, $-\text{S(O)}$, or $-\text{S(O)}_2$ and wherein the water solubilizing group is:



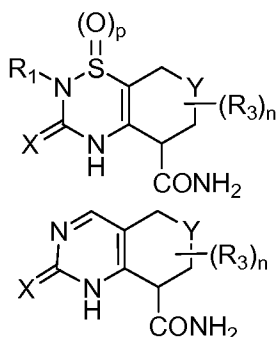
wherein W is selected from:



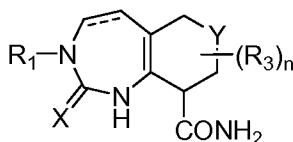
wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

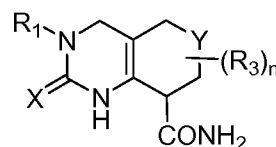
90. The compound of Claim 1 according to Formula XVIII A, Formula XVIII B, Formula XVIII C or Formula XVIII D:



Formula XVIII A



Formula XVIII B



Formula XVIII C

Formula XVIII D

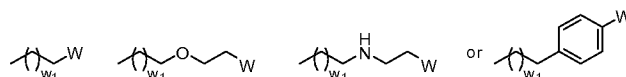
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

p is 1 or 2;

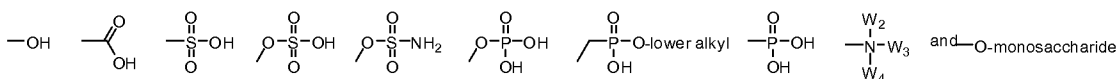
--- represents $\text{CH}_2\text{-CH}_2$ or CH=CH ;

Y is O, S, NR_3 or CR_3R_3 ;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L- NH_2 , a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



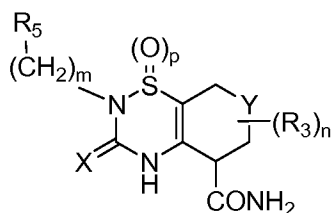
wherein W is selected from:



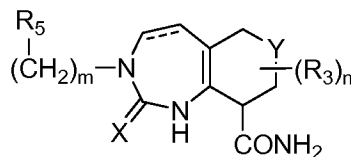
wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

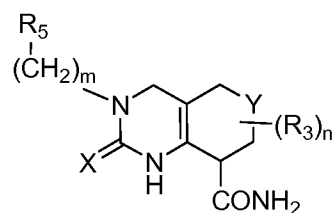
91. The compound of Claim 1 according to Formula XIX A, Formula XIX B or Formula XIX C:



Formula XIXA



Formula XIXB



Formula XIXC

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

p is 1 or 2;

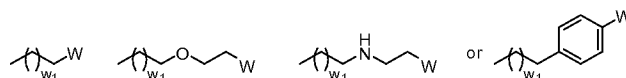
5 ---- represents CH₂-CH₂ or CH=CH;

Y is O, S, NR₃ or CR₃R₃;

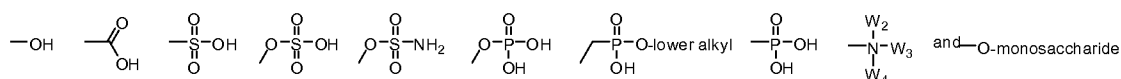
R₅ is hydrogen, halogen, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5;

10 each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



wherein W is selected from:



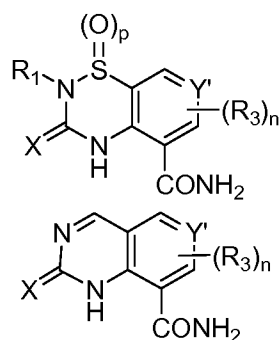
15

wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

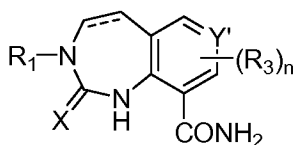
20

n is 0, 1, 2 or 3.

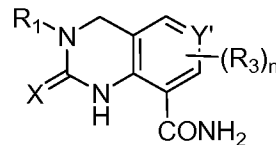
92. The compound of Claim 1 according to Formula XVIII A', Formula XVIII B', Formula XVIII C' or Formula XVIII D':



Formula XVIII A'



Formula XVIII B'



Formula XVIII C'

Formula XVIII D'

25

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

p is 1 or 2;

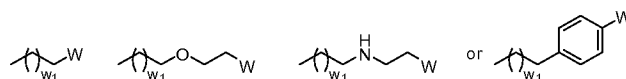
---- represents CH₂-CH₂ or CH=CH;

Y' is N or CR₃;

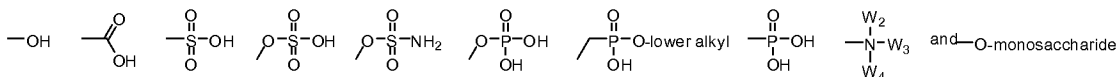
30

each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-

heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



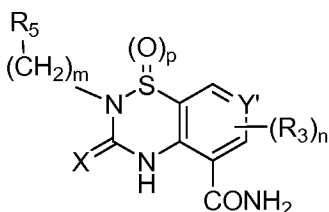
wherein W is selected from:



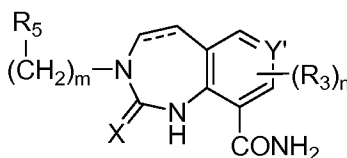
wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

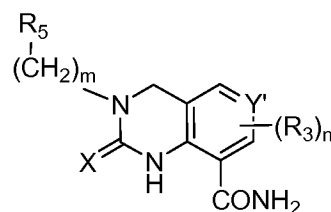
93. The compound of Claim 1 according to Formula XIXA', Formula XIXB' or Formula XIXC':



Formula XIXA'



Formula XIXB'



Formula XIXC'

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

p is 1 or 2;

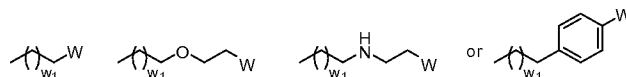
--- represents CH₂-CH₂ or CH=CH;

Y' is N or CR₃;

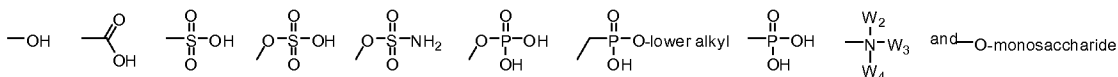
R₅ is hydrogen, halogen, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5;

each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



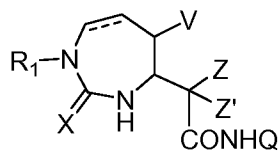
wherein W is selected from:



wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

94. A compound of Formula XX:



Formula XX

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

R₁ is hydrogen, halogen, -CN, -L-OH, -L-NH₂, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl,

wherein L is a bond, -C(O)-, -S(O)-, or -S(O)₂;

X is O, S or N-O-R²,

wherein R² is hydrogen or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, mercaptoalkyl, haloalkyl, and carboxyalkyl;

V, Z and Z' are each independently H, F, Cl, Br, I, -CN, -L-OH, -L-NH₂, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl,

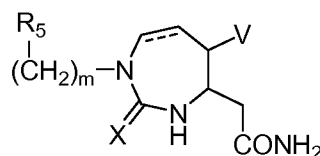
wherein L is a bond, -C(O)-, -S(O)-, or -S(O)₂-,

or when taken together V and Z form a saturated or unsaturated, substituted or unsubstituted 5-7 member ring which incorporates 0, 1 or 2 heteroatoms selected from O, S and N;

Q is hydrogen or hydroxyl; and

---- represents CH₂-CH₂ or CH=CH.

95. The compound of Claim 94 according to Formula XXA:



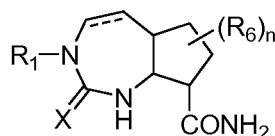
Formula XXA

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

R₅ is H, F, Cl, Br, I, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5.

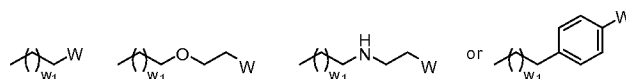
96. The compound of Claim 94 according to Formula XXB:



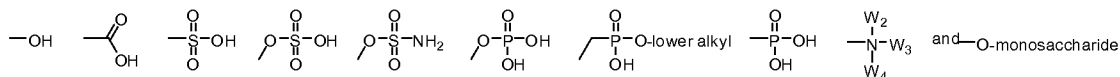
Formula XXB

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

each R₆ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O)-, or -S(O)₂ and wherein the water solubilizing group is:



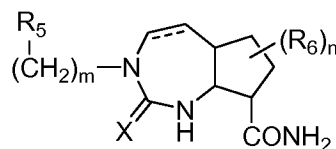
wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1 or 2.

97. The compound of Claim 94 according to Formula XXC:



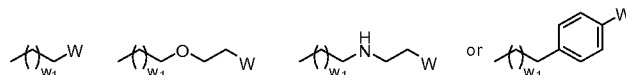
Formula XXC

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

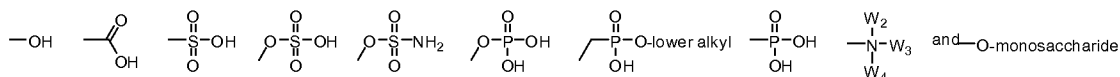
R_5 is hydrogen, halogen, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5;

each R_6 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O)-, or -S(O)₂ and wherein the water solubilizing group is:



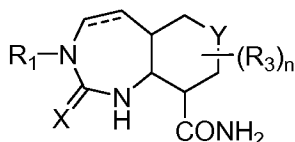
wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

98. The compound of Claim 94 according to Formula XXD:

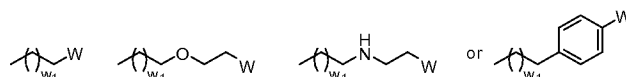


Formula XXD

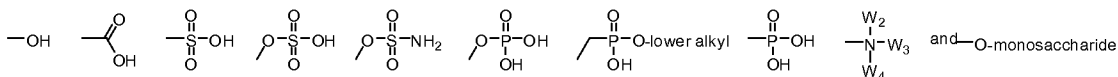
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y is O, S, NR₃ or CR₃R₃;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O)-, or -S(O)₂ and wherein the water solubilizing group is:



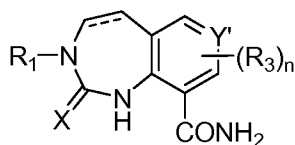
wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

99. The compound of Claim 94 according to Formula XXE:

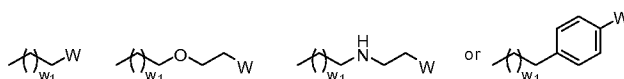


Formula XXE

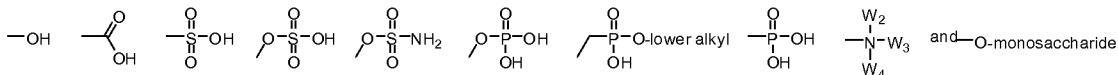
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y' is N or CR_3 ;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



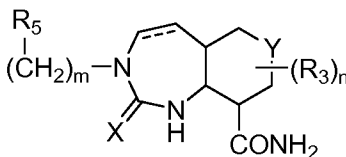
wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

100. The compound of Claim 94 according to Formula XXF:



Formula XXF

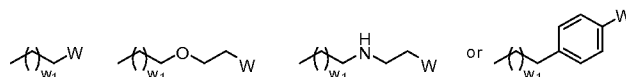
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y is O, S, NR_3 or CR_3R_3 ;

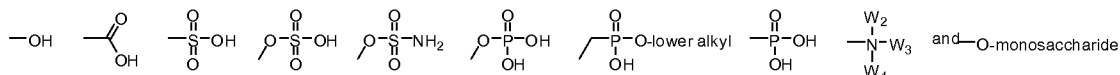
R_5 is hydrogen, halogen, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



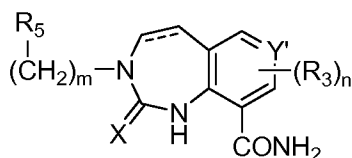
wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

101. The compound of Claim 94 according to Formula XXG:

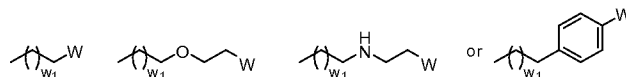


Formula XXG

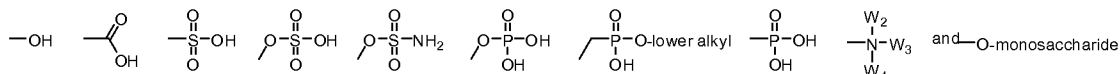
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y' is N or CR_3 ;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



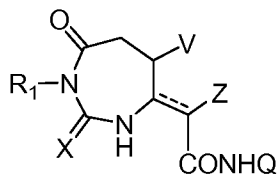
wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

102. A compound of Formula XXI:



Formula XXI

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

R_1 is hydrogen, halogen, -CN, -L-OH, -L-NH₂, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl,

wherein L is a bond, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$;

X is O, S or $\text{N}-\text{O}-\text{R}^2$,

wherein R^2 is hydrogen or a substituted or unsubstituted group selected from alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, heteroaryl, mercaptoalkyl, haloalkyl, and carboxyalkyl;

V and Z are each independently H, F, Cl, Br, I, $-\text{CN}$, $-\text{L}-\text{OH}$, $-\text{L}-\text{NH}_2$, or a substituted or unsubstituted group selected from $-\text{L}-\text{alkyl}$, $\text{L}-\text{alkenyl}$, $\text{L}-\text{alkynyl}$, $-\text{L}-\text{cycloalkyl}$, $\text{L}-\text{cycloalkenyl}$, $-\text{L}-\text{heterocycloalkyl}$, $-\text{L}-\text{haloalkyl}$, $-\text{L}-\text{alkoxy}$, $-\text{L}-\text{alkylamine}$, $-\text{L}-\text{dialkylamine}$, $-\text{L}-\text{aryl}$ and $-\text{L}-\text{heteroaryl}$,

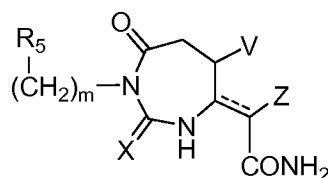
wherein L is a bond, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$,

or when taken together V and Z form an unsaturated or partially unsaturated, substituted or unsubstituted 5-7 member ring which incorporates 0, 1 or 2 heteroatoms selected from O, S and N; and

Q is hydrogen or hydroxyl; and

--- represents CH_2-CH_2 or $\text{CH}=\text{CH}$.

103. The compound of Claim 102 according to Formula XXIA:



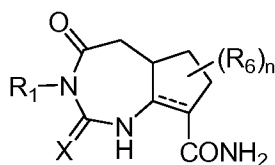
Formula XXIA

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

R_5 is H, F, Cl, Br, I, $-\text{CN}$, $-\text{OH}$, or $-\text{NH}_2$;

m is 1, 2, 3, 4 or 5.

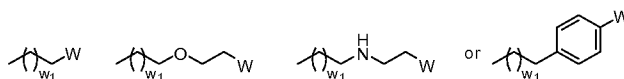
104. The compound of Claim 102 according to Formula XXIB:



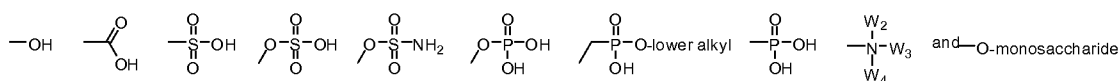
Formula XXIB

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

each R_6 is independently hydrogen, halogen, $-\text{CN}$, $-\text{L}-\text{OH}$, $-\text{L}-\text{NH}_2$, a water solubilizing group, or a substituted or unsubstituted group selected from $-\text{L}-\text{alkyl}$, $\text{L}-\text{alkenyl}$, $\text{L}-\text{alkynyl}$, $-\text{L}-\text{cycloalkyl}$, $\text{L}-\text{cycloalkenyl}$, $-\text{L}-\text{heterocycloalkyl}$, $-\text{L}-\text{haloalkyl}$, $-\text{L}-\text{alkoxy}$, $-\text{L}-\text{alkylamine}$, $-\text{L}-\text{dialkylamine}$, $-\text{L}-\text{aryl}$ and $-\text{L}-\text{heteroaryl}$, wherein L is a bond, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2$ and wherein the water solubilizing group is:



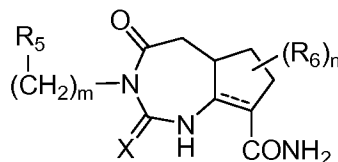
wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1 or 2.

105. The compound of Claim 102 according to Formula XXIC:



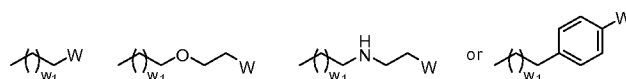
Formula XXIC

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

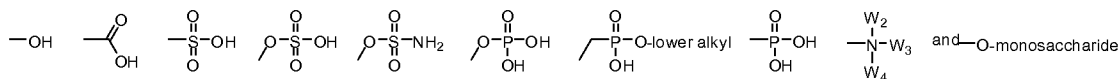
5 R₅ is hydrogen, halogen, -CN, -OH, or -NH₂;

m is 1, 2, 3, 4 or 5;

each R₆ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



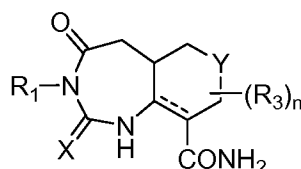
wherein W is selected from:



wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

106. The compound of Claim 102 according to Formula XXID:

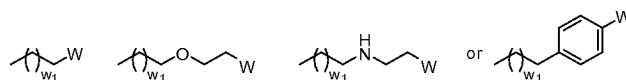


Formula XXID

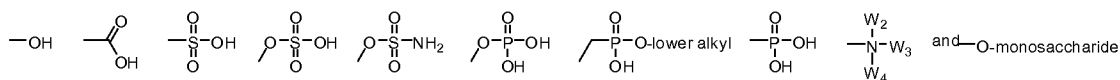
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y is O, S, NR₃ or CR₃R₃;

each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



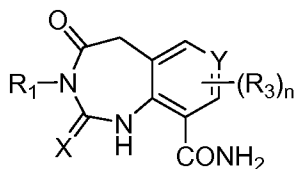
wherein W is selected from:



wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

107. The compound of Claim 102 according to Formula XXIE:

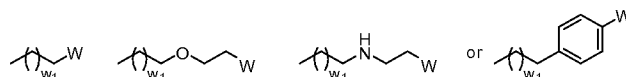


Formula XXIE

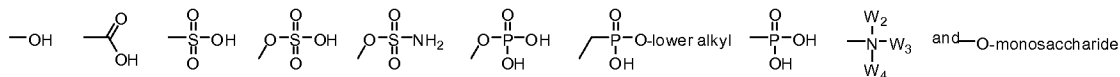
5 or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y' is N or CR₃;

each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



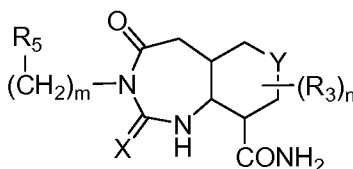
wherein W is selected from:



15 wherein W₁ is 0, 1, 2 or 3; W₂ and W₃ are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W₂ and W₃ form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W₄ is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

108. The compound of Claim 102 according to Formula XXIF:



Formula XXIF

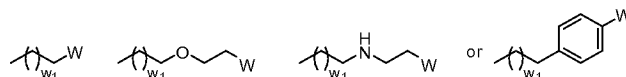
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

Y is O, S, NR₃ or CR₃R₃;

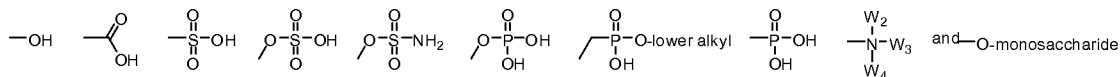
R₅ is hydrogen, halogen, -CN, -OH, or -NH₂;

25 m is 1, 2, 3, 4 or 5;

each R₃ is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:



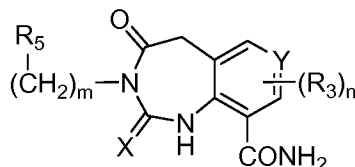
wherein W is selected from:



wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

5 n is 0, 1, 2 or 3.

109. The compound of Claim 102 according to Formula XXIG:



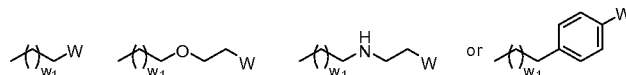
Formula XXIG

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof, wherein:

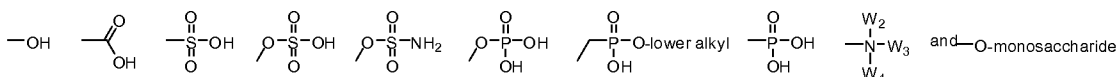
10 Y' is N or CR_3 ;

each R_3 is independently hydrogen, halogen, -CN, -L-OH, -L-NH₂, a water solubilizing group, or a substituted or unsubstituted group selected from -L-alkyl, L-alkenyl, L-alkynyl, -L-cycloalkyl, L-cycloalkenyl, -L-heterocycloalkyl, -L-haloalkyl, -L-alkoxy, -L-alkylamine, -L-dialkylamine, -L-aryl and -L-heteroaryl, wherein L is a bond, -C(O)-, -S(O), or -S(O)₂ and wherein the water solubilizing group is:

15



wherein W is selected from:

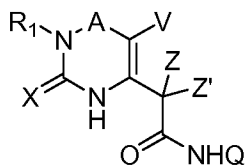


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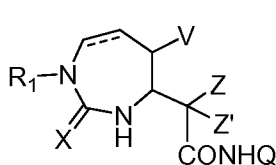
wherein W_1 is 0, 1, 2 or 3; W_2 and W_3 are each independently hydrogen or methyl or, when taken together with the nitrogen to which they are attached, W_2 and W_3 form a five or six membered ring that optionally contains an oxygen atom or a second nitrogen atom; and W_4 is an electron pair or an oxygen atom; and

n is 0, 1, 2 or 3.

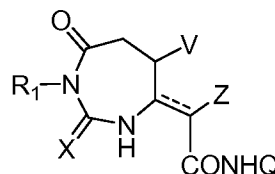
110. A pharmaceutical composition comprising a compound of Formula I, Formula XX or Formula XXI:



Formula I



Formula XX

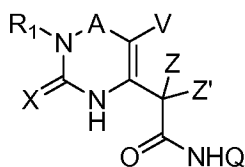


Formula XXI

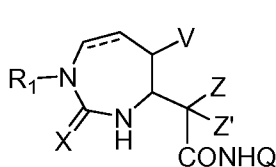
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or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof.

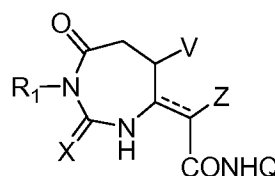
111. A method for treating a patient suffering from a sirtuin mediated disorder, comprising administering to said individual an effective amount of a composition comprising a compound of Formula I, Formula XX or Formula XXI:



Formula I



Formula XX



Formula XXI

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or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof.

112. The method of Claim **111**, wherein said compound Formula I, Formula XX or Formula XXI is administered in combination with an additional cancer therapy.

113. The method of Claim **112**, wherein said additional cancer therapy is selected from surgery, radiation therapy, or administration of at least one chemotherapeutic agent.

5 114. The method of Claim **113**, wherein said additional cancer therapy is co-administration of at least one chemotherapeutic agent.

115. The method of Claim **113**, wherein said additional cancer therapy is surgery.

116. The method of Claim **115**, wherein administration of said compound of Formula I, Formula XX or Formula XXI occurs after surgery.

10 117. The method of Claim **111**, wherein said sirtuin mediated disorder is selected from the group consisting of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorder, neurological disorders, fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases and malignant diseases.

15 118. The method of Claim **111**, wherein said sirtuin mediated disorder is selected from the group consisting of diseases or disorders related to aging or stress (including increasing radiosensitivity and/or chemosensitivity), diabetes, obesity (including stimulation of appetite or weight gain), neurodegenerative diseases, cardiovascular disease, blood clotting disorders, stroke, ischemia, inflammation, flushing, infections including viral infections (e.g. herpes, HIV, adenovirus, and HTLV-1 associated malignant and benign disorders), autoimmune disorders (e.g., systemic lupus erythematosus, scleroderma, and arthritis, in
20 which autoimmune cells should be removed), fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, tumors, leukemias, neoplasms, carcinomas, metabolic diseases, malignant diseases, stimulation of appetite, and/or stimulation of weight gain.

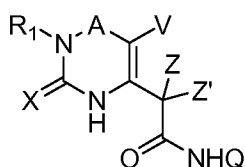
119. The method of Claim **111**, wherein said sirtuin mediated disorder is a hyperproliferative disease.

25 120. The method of Claim **111**, wherein said sirtuin mediated disorder is a proliferative disease selected from psoriasis, restenosis, autoimmune disease, or atherosclerosis.

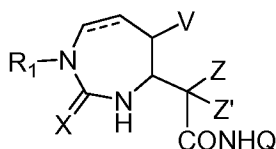
121. The method of Claim **111**, wherein said sirtuin mediated disorder is cancer, tumors, leukemias, neoplasms, or carcinomas.

30 122. The method of Claim **121**, wherein said cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, leukemia, myeloid leukemia, glioblastoma, follicular lymphoma, pre-B acute leukemia, chronic lymphocytic B-leukemia, mesothelioma or small cell line cancer.

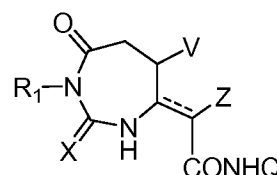
123. A method for degrading, inhibiting the growth of or killing cancer cells comprising contacting the cells with an amount of a composition effective to degrade, inhibit the growth of or kill cancer cells, the composition comprising a compound of Formula I, Formula XX or Formula XXI:



Formula I



Formula XX

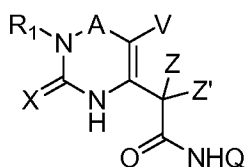


Formula XXI

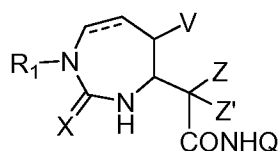
or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof.

124. The method of Claim **123**, wherein said cancer cells comprise brain, breast, lung, ovarian, pancreatic, prostate, renal, or colorectal cancer cells.

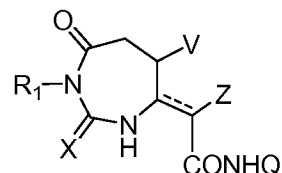
40 125. A method of inhibiting tumor size increase, reducing the size of a tumor, reducing tumor proliferation or preventing tumor proliferation in an individual comprising administering to said individual an effective amount of a composition to inhibit tumor size increase, reduce the size of a tumor, reduce tumor proliferation or prevent tumor proliferation, the composition comprising a compound of Formula I, Formula XX or Formula XXI:



Formula I



Formula XX



Formula XXI

or a pharmaceutically acceptable salt, prodrug, solvate, polymorph, tautomer or isomer thereof.

126. The method of Claim **125**, for inhibiting tumor size increase or reducing the size of a tumor wherein said tumor occurs in the brain, breast, lung, ovaries, pancreas, prostate, kidney, colon or rectum.
127. The method of Claim **125**, wherein said compound of Formula I, Formula XX or Formula XXI is administered in combination with an additional cancer therapy.
128. The method of Claim **127**, wherein said additional cancer therapy is selected from surgery, radiation therapy, or administration of at least one chemotherapeutic agent.
129. The method of Claim **128**, wherein said additional cancer therapy is co-administration of at least one chemotherapeutic agent.
130. The method of Claim **128**, wherein said additional cancer therapy is surgery.
131. The method of Claim **130**, wherein administration of said compound of Formula I, Formula XX or Formula XXI occurs after surgery.
132. The method of Claim **125**, for inhibiting tumor size increase.
133. The method of Claim **125**, for reducing the size of a tumor.
134. The method of Claim **125**, for reducing tumor proliferation.
135. The method of Claim **125**, for preventing tumor proliferation.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/79298

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/33; C07D 213/00 (2009.01)

USPC - 514/385-386

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)

USPC- 514/385-386

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/387, 393 (text search-see search terms below)

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

PubWEST (USPT, PGPB, EPAB, JPAB), Google Patent/Scholar

Search terms: histone deacetylase, sirtuin, hydroxypyrimidine, oxoimidazolidine, tetrahydro pyrimidone, carboxamide, cancer, solubility

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/0250784 A1 (Anandan et al.) 10 November 2005 (10.11.2005) para [0014], [0016]-[0017], [0030], [0032]-[0034], [0037]-[0043], [0096], [0105], [0114]-[0115], [0292], [0297], [0314], [0343]-[0444]	1-71, 110-135
Y	US 2006/0014768 A1 (Kawasaki et al.) 19 January 2006 (19.01.2006) para [0009], [0030], [0038], [0041], [0043], [0130]-[0131]	1-71, 110-135
Y	US 2007/0135438 A1 (Payne et al.) 14 June 2007 (14.06.2007) para [0007], [0014]-[0015], [0018]-[0020], [0048], [0050]-[0051], [0158]	11, 15-21, 33, 56, 62

☐ 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

09 February 2009 (09.02.2009)

Date of mailing of the international search report

17 FEB 2009

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/79298

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

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

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

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

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

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying 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.: 1-135, limited to compounds of formula IIA (namely claims 1-71 and 110-135).

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/79298

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Inventions 1-88, claims 1-135, drawn to compounds of formula I, as further defined by formulae IIA, IIB, IIC, IIIA, IIIB, IIIC, VA, VB, VC, VIA, VIB, VIC, VIA', VIB', VIC', VIIA, VIIB, VIIC, VIIA', VIIB', VIIC', VIIIA, VIIBB, VIIBC, IXA, IXB, IXC, XA, XB, XC, XIA, XIB, XIC, XIIA, XIIIB, XIIIC, XIII A, XIIIB, XIIIC, XIIA', XIIB', XIIIC', XIII A', XIIIB', XIIIC', XIVA, XIVB, XIVC, XIVD, XVA, XVB, XVC, XVIA, XVIB, XVIC, XVID, XVIIA, XVIIIB, XVIIIC, XVIII A, XVIIIB, XVIIIC, XVIII D, XIX A, XIXB, XIXC, XVIII A', XVIIIB', XVIIIC', XVIII D', XIX A', XIXB', XIXC', XXA, XXB, XXC, XXD, XXE, XXF, XXG, XXI, XXIA, XXIB, XXIC, XXID, XXIE, XXIF, and XXIG.

The inventions listed as Inventions 1-88 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The various formulae as defined above as inventions 1-88 do not share any special technical feature other than the broad genus as characterized by Formula I, which encompasses a very broad range of subgenera. The compounds of the various formulae as defined above do not share any significant structural element and cannot be considered as having the same or corresponding technical feature. The various formulae represent compounds which would be expected to exhibit different chemical and pharmacological properties.

Thus, the inventions listed as Inventions 1-88 do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

In this case the first named invention and first named species that will be searched without additional fees is Group I represented by claims 1-135, limited to compounds of formula IIA.