The present invention relates to pharmaceutical compositions containing these compounds. The present invention also relates to a method for preparing these compounds. The present invention also relates to a method of treating a mammalian disorder in which LSDI levels are elevated by administering these compounds and compositions to a patient in need thereof. The present invention also relates to a method for decreasing histone demethylase activity in a mammal comprising administering to the mammal an effective amount of these compounds and compositions.

Title: SUBSTITUTED-IZ/-BENZO[Z]-IMIDAZOLE SERIES COMPOUNDS AS LYSINE-SPECIFIC DEMETHYLASE 1 (LSDI) INHIBITORS

Abstract: The present invention provides compounds which are useful as inhibitors of lysine-specific demethylase 1 ("LSD1").
SUBSTITUTED- 1H-BENZO [D] IMIDAZOLE SERIES COMPOUNDS AS LYSINE-SPECIFIC DEMETHYLASE 1 (LSD1) INHIBITORS

Field of the Invention

[001] The present invention relates to substituted-1 H-benzo[d]imidazole series of compounds which are useful as inhibitors of lysine-specific demethylase 1 ("LSD1"). The present invention also relates to pharmaceutical compositions containing these compounds. The present invention also relates to a method for preparing these compounds. The present invention also relates to a method of treating a mammalian disorder in which LSD1 levels are elevated by administering these compounds and compositions to a patient in need thereof. The present invention also relates to a method for decreasing histone demethylase activity in a mammal comprising administering to the mammal an effective amount of these compounds and compositions.

Background of the Invention

[002] Over the past decade it has become clear that epigenetic changes, which alter gene activity without altering DNA sequence, collaborate with genetic mistakes to promote cancer development and progression (Tsai, H. C. and Baylin, S. B. Cell Res 2011, 21 (3), 502-17; and Fullgrabe, J., Kavanagh, E., and Joseph, B. Oncogene 2011). The regulation of the modifications on DNA and the proteins associated with DNA has become an area of intense interest and the enzymes involved in these processes have been suggested as a new class of protein targets for drug development. The major proteins associated with DNA are histone proteins. Histone tails are subject to a variety of posttranslational modifications, such as phosphorylation, acetylation, methylation, and ubiquitination, and these modifications, especially acetylation and methylation on lysine residues, play a major role in the regulation of gene expression, and are often dysregulated in cancer (Fullgrabe, J., Kavanagh, E., and Joseph, B. Oncogene 2011).

[003] Recently an enzyme called Lysine-Specific Demethylase 1 ("LSD1") was identified as the first histone demethylase that specifically catalyzes the oxidative demethylation of monomethylated and dimethylated histone H3 at lysine 4 (H3K4me1 and H3K4me2) and lysine 9 (H3K9me1 and H3K9me2) through a flavin adenine dinucleotide (FAD)-dependent reaction (Shi, Y., et al. Cell 2004, 119 (7), 941-53; and Metzger, E., et al. Nature 2005, 437 (7057), 436-9). LSD1 is a component of the corepressor of RE1 silencing transcription factor (CoREST) complex that is responsible for silencing neuronal-specific genes in nonneuronal cells (Gocke
and Yu, *PLOS One*, 2008, 3 (9), e3255 (1-12)). The active site of LSD1 shows a highly negatively charged substrate-binding cavity spacious enough to accommodate the N-terminal tail of histone H3. (Chen, Y., et al. *PNAS*, 2006, 103(38), 13956-13961. Further, an N-terminal SWIRM domain and an insertion in the core catalytic domain, termed the Tower Domain, were established as necessary structural motifs for enzymatic activity and interactions with cofactors such as CoREST. *Id.*

Several lines of evidence point to LSD1 as being a possible therapeutic target in cancer. LSD1 is reportedly over-expressed in a variety of tumors including neuroblastoma, estrogen receptor (ER)-negative breast, bladder, lung, and colorectal tumors (Schulte, J. H., et al. *Cancer Res* 2009, 69 (5), 2065-71; Lim, S., et al. *Carcinogenesis* 2010, 31 (3), 512-20; and Hayami, S., et al. *Int J Cancer* 2011, 128 (3), 574-86). Increased methylation of the permissive H3K4 mark by LSD1 inhibition has been shown to reactivate expression of tumor suppressor genes in cancer models (Huang, Y., et al. *Clin Cancer Res* 2009, 15 (23), 7217-28). In addition, LSD1 has been found to associate with estrogen and androgen receptors leading to the specific demethylation of the repressive H3K9 mark, thereby increasing target gene expression (Metzger, E., et al. *Nature* 2005, 437 (7057), 436-9; and Garcia-Bassets, I., et al. *Cell* 2007, 128 (3), 505-18). Thus, depending upon cofactors bound to LSD1, demethylation by LSD1 can contribute to cancer through both the permissive H3K4 and the repressive H3K9 mark. Therefore, the inhibition of LSD1 might be an effective strategy for re-expression of epigenetically silenced tumor suppressor genes as well as down regulation of important cancer pathways in a number of cancer types. Several LSD1 inhibitors have been reported, but they have shown poor selectivity and/or pharmacological properties, making further exploration of LSD1 biology difficult.

Monoamine oxidase (MAO) inhibitors such as tranylcypromine and pargyline have been reported as LSD1 inhibitors, and there have been several reports regarding attempts to discover derivatives with increased selectivity for LSD1 over MAO (Mimasu, S., et al. *Biochemistry* 2010, 49 (30), 6494-503; Binda, C., et al. *J Am Chem Soc* 2010, 132 (19), 6827-33; Culhane, J. C., et al. *J Am Chem Soc* 2006, 128 (14), 4536-7; Culhane, J. C., et al. *J Am Chem Soc* 2010, 132 (9), 3164-76; and Ueda, R., et al. *J Am Chem Soc* 2009, 131 (48), 17536-7). These compounds irreversibly inactivate LSD1 by covalent binding to the FAD cofactor. Polyamine derivatives have also been evaluated as LSD1 inhibitors, where compounds with activity in the µM range have been described (Huang, Y., et al. *Clin Cancer Res* 2009, 15 (23),...
7217-28; Sharma, S. K., et al. J Med Chem 2010, 53 (14), 5197-212; and Huang, Y., et al. Proc Natl Acad Sci USA 2007, 104 (19), 8023-8). In general, these and other reported LSD1 inhibitors are neither adequately selective nor potent enough to optimally interact with the crucial amino acid residues of the substrate-binding site present in LSD1.

[006] In summary, the LSD1 protein plays a key role in epigenetic and transcriptional regulation, and is frequently altered in mammalian cancers, thus making them an attractive target for therapeutic intervention. Despite advances in drug discovery directed to identifying inhibitors of LSD1 protein activity, there is still a scarcity of compounds that are both potent, efficacious, and selective inhibitors of LSD1. Furthermore, there is a scarcity of compounds effective in the treatment of cancer and other diseases associated with dysfunction in LSD1. These needs and other needs are satisfied by the present invention.

Summary of the Invention

[007] The present invention provides compounds and pharmaceutical compositions that are useful as inhibitors of lysine specific demethylase 1 ("LSD1"). In another embodiment, the present invention relates to a method for preparing the disclosed compounds. In another embodiment, the present invention relates to a method for treatment of a human disease in which LSD1 levels are elevated comprising administering to a patient in need thereof the disclosed pharmaceutical compositions.

[008] In one embodiment the disclosed compound is of Formula I

![Chemical Structure]

wherein:

- m is 0 or 1,
- n is 0 or 1,
- X is selected from the group consisting of -CH and -N;
- Y is selected from the group consisting of -NH, -NCH$_3$, -NCH$_2$CH$_3$, -O and -S;
Ri is selected from the group consisting of -H, -CH_3 and -CH_2CH_3;
R_2 and R_4 are independently selected from the group consisting of -H, -CH_3, -OH, -NH_2, halo, -CF_3, OCF_3, -OCH_3 and -CN;
R_3 is selected from the group consisting of -H, -CH_3, -OH, -NH_2, a halo, -CF_3, OCF_3, -OCH_3, CN, -CONHRs and -NHCORs;
R_5 is selected from the group consisting of -H, -CH_3, -CH_2CH_3, -C_1-3, a cycloalkyl and a halo;
R_6 is selected from the group consisting of -H and -CH_3;
R_7 is selected from the group consisting of -CH_3, -NH_2, -NCH_3, a C_6 alkyl, a C_6 cycloalkyl, a halo-C_6 alkyl, a cycloalkyl, a C_6 heterocycloalkyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, oxazinanyl, morpholinyl, hexahydrophrimidinyl, hexahydropyridazinyl and an optionally substituted moiety selected from the group consisting of:

and

R_8 is selected from the group consisting of -H, C_6 alkyl, C_5-6 cycloalkyl and C_5-6 heterocycloalkyl;
or a pharmaceutically acceptable salt, hydrochloric acid, sulphate, methanesulfonic acid or benzene sulfonic acid thereof.

[009] In another embodiment, the present invention relates to a method for preparing a disclosed compound or a pharmaceutically acceptable salt thereof.
In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound as an active agent in said composition and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method for the treatment of a disorder of uncontrolled cellular proliferation in a mammal, the method comprising the step of administering to the mammal an effective amount of a disclosed compound.

In another embodiment, the present invention relates to a method for treatment of a mammalian disorder in which lysine-specific demethylase 1 (LSD1) levels are elevated comprising administering to a patient in need thereof an effective amount of a disclosed compound.

In another embodiment, the present invention relates to a method for decreasing histone demethylase activity in a mammal, the method comprising the step of administering to the mammal an effective amount of a disclosed compound.

In another embodiment the present invention relates to a method for the treatment of a disorder in a human wherein the disorder is selected from the group consisting of breast cancer, prostate cancer, lung cancer, bladder cancer, acquired immune deficiency syndrome (AIDS), and liver disease caused by a Hepatitis C viral infection.

The disclosed embodiments are simply exemplary embodiments of the inventive concepts disclosed herein and should not be considered as limiting, unless so stated.

**Brief Description of the Figures**

Figure 1 is a graphical representation of the IC\textsubscript{50} values reported for the concentration of drug at which 50% inhibition was reached.

**Detailed Description of the Invention**

The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein
can be used in the practice or testing of the present invention, example methods and materials are now described.

[019] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein can be different from the actual publication dates, which can require independent confirmation.

A. Definitions

[020] As used herein, nomenclature for compounds, including organic compounds, can be given using common names, IUPAC, IUBMB, or CAS recommendations for nomenclature. When one or more stereochemical features are present, Cahn-Ingold-Prelog rules for stereochemistry can be employed to designate stereochemical priority, EIZ specification, and the like. One of skill in the art can readily ascertain the structure of a compound if given a name, either by systemic reduction of the compound structure using naming conventions, or by commercially available software, such as ChemDraw™ (Cambridgesoft Corporation, U.S.A.).

[021] 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. Thus, for example, reference to "a functional group," "an alkyl," or "a residue" includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[022] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also
understood that each unit between two particular units are also disclosed. For example, if 10 and
15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[023] References in the specification and concluding claims to parts by weight of a
particular element or component in a composition denotes the weight relationship between the
element or component and any other elements or components in the composition or article for
which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of
component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5,
and are present in such ratio regardless of whether additional components are contained in the
compound.

[024] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is
based on the total weight of the formulation or composition in which the component is included.

[025] As used herein, the terms "LSD1" and "lysine-specific demethylase 1" can be used
interchangeably and refer to a histone demethylase encoded by the KDM1 A gene. The KDM1 A
gene has a gene map locus of lp36.12 as described by the Entrez Gene cytogenetic band,
Ensembl cytogenetic band, and the HGNC cytogenetic band. The term LSD1 refers to a native
protein that has 852 amino acids with a molecular weight of about 92903 Da, and is a member of
the flavin monoamine oxidase family. The term LSD1 is inclusive of the protein, gene product
and/or gene referred to by such alternative designations as: LSD1, KDM1; RPT-184J9.1; AOF2;
BHC1 10; KIAA0601; LSD1; BRAF35-HDAC complex protein BHC1 10; FAD-binding protein
BRAF35-HDAC complex, 110 kDa subunit; amine oxidase (flavin containing) domain 2; lysine-
specific histone demethylase 1; lysine-specific histone demethylase 1A; flavin-containing amine
oxidase domain-containing protein 2; lysine (K)-specific demethylase 1; amine oxidase (flavin
containing) domain 2; and FAD-binding protein BRAF35-HDAC complex, 110 kDa subunit, as
used by those skilled in the art.

[026] As used herein, the term "histone demethylase" refers to that group of enzymes which
remove methyl groups from histone proteins. The term is inclusive of both histone lysine
demethylases, i.e. enzymes which remove methyl groups from lysine residues in histones, and
histone arginine demethylases, i.e. enzymes which remove methyl groups from arginine residues
in histones.
As used herein, the terms "optional" or "optionally" means that the subsequently
described event or circumstance can or can not occur, and that the description includes instances
where said event or circumstance occurs and instances where it does not.

As used herein, the term "subject" can be a vertebrate, such as a mammal, a fish, a
bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a
human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent.
The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as
fetuses, whether male or female, are intended to be covered. In one embodiment, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects. In some embodiments of the disclosed methods, the subject has been diagnosed with a need for treatment of a disorder of uncontrolled cellular proliferation associated with a histone lysine demethylase dysfunction prior to the administering step. In some embodiments of the disclosed method, the subject has been diagnosed with a need for inhibition of a histone lysine demethylase prior to the administering step.

As used herein, the term "treatment" refers to the medical management of a patient
with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or
disorder. This term includes active treatment, that is, treatment directed specifically toward the
improvement of a disease, pathological condition, or disorder, and also includes causal treatment,
that is, treatment directed toward removal of the cause of the associated disease, pathological
condition, or disorder. In addition, this term includes palliative treatment, that is, treatment
designed for the relief of symptoms rather than the curing of the disease, pathological condition,
or disorder; preventative treatment, that is, treatment directed to minimizing or partially or
completely inhibiting the development of the associated disease, pathological condition, or
disorder; and supportive treatment, that is, treatment employed to supplement another specific
therapy directed toward the improvement of the associated disease, pathological condition, or
disorder. In various embodiments, the term covers any treatment of a subject, including a
mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that
can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the
disease, i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the
disease. In one embodiment, the subject is a mammal such as a primate, and, in another
embodiment, the subject is a human. The term "subject" also includes domesticated animals
(e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, zebra fish etc.).

[030] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein. For example, "diagnosed with a disorder of uncontrolled cellular proliferation" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by a compound or composition that can inhibit a histone lysine demethylase. As a further example, "diagnosed with a need for inhibition of a histone demethylase" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition characterized by a histone demethylase dysfunction. Such a diagnosis can be in reference to a disorder, such as a disorder of uncontrolled cellular proliferation, cancer and the like, as discussed herein. For example, the term "diagnosed with a need for inhibition of histone demethylase activity" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by inhibition of histone demethylase activity.

For example, "diagnosed with a need for treatment of one or more disorders of uncontrolled cellular proliferation associated with a histone demethylase dysfunction" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have one or more disorders of uncontrolled cellular proliferation associated with a histone demethylase dysfunction.

[031] As used herein, the phrase "identified to be in need of treatment for a disorder," or the like, refers to selection of a subject based upon need for treatment of the disorder. For example, a subject can be identified as having a need for treatment of a disorder (e.g., a disorder related to a dysfunction of histone demethylase activity) based upon an earlier diagnosis by a person of skill and thereafter subjected to treatment for the disorder. It is contemplated that the identification can, in one embodiment, be performed by a person different from the person making the diagnosis. It is also contemplated, in another embodiment, that the administration can be performed by one who subsequently performed the administration.

[032] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those
skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, intraurethral administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various embodiments, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In various embodiments, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[033] The term "contacting" as used herein refers to bringing a disclosed compound and a cell, target receptor, or other biological entity together in such a manner that the compound can affect the activity of the target (e.g., receptor, cell, etc.), either directly; i.e., by interacting with the target itself, or indirectly; i.e., by interacting with another molecule, co-factor, factor, or protein on which the activity of the target is dependent.

[034] As used herein, the terms "effective amount" and "amount effective" refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side affects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of
any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In various embodiments, a preparation can be administered in a "prophylactically effective amount"; that is, an amount effective for prevention of a disease or condition.

[035] As used herein, "EC$_{50}$," is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% agonism or activation of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one embodiment, an EC50 can refer to the concentration of a substance that is required for 50% agonism or activation in vivo, as further defined elsewhere herein. In another embodiment, EC50 refers to the concentration of agonist or activator that provokes a response halfway between the baseline and maximum response.

[036] As used herein, "IC$_{50}$," is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. For example, an IC50 can refer to the concentration of a substance that is required for 50% inhibition in vivo or the inhibition is measured in vitro, as further defined elsewhere herein. Alternatively, IC50 refers to the half maximal (50%) inhibitory concentration (IC) of a substance The inhibition can be measured in a cell-line such as AN3 CA, BT-20, BT-549, HCT 116, HER218, MCF7, MDA-MB-231, MDA-MB-235, MDA-MB-435S, MDA-MB-468, PANC-1, PC-3, SK-N-MC, T-47D, and U-87 MG. In another embodiment, the inhibition is measured in a cell-line, e.g. HEK-293 or HeLa, transfected with a mutant or wild-type mammalian histone demethylase, e.g. LSD1.

[037] The term "pharmacologically acceptable" describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[038] The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[039] As used herein, the term "pharmacologically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for
reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[040] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad embodiment, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic
compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain embodiments, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0041] The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, s-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can be cyclic or acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (e.g., from one to four) carbon atoms.

[0042] For example, a "C1-C3 alkyl" group can be selected from methyl, ethyl, n-propyl, i-propyl, and cyclopropyl, or from a subset thereof. In certain embodiments, the "C1-C3 alkyl" group can be optionally further substituted. As a further example, a "C1-C4 alkyl" group can be selected from methyl, ethyl, n-propyl, i-propyl, cyclopropyl, n-butyl, i-butyl, s-butyl, t-butyl, and cyclobutyl, or from a subset thereof. In certain embodiments, the "C1-C4 alkyl" group can be optionally further substituted. As a further example, a "C1-C6 alkyl" group can be selected from methyl, ethyl, n-propyl, i-propyl, cyclopropyl, n-butyl, i-butyl, s-butyl, t-butyl, cyclobutyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, neopentyl, cyclopentyl, n-hexyl, i-hexyl, 3-methylpentane, 2,3-dimethylbutane, neohexane, and cyclohexane, or from a subset thereof. In certain embodiments, the "C1-C6 alkyl" group can be optionally further substituted. As a further example, a "C1-C8 alkyl" group can be selected from methyl, ethyl, n-propyl, i-propyl, cyclopropyl, n-butyl, i-butyl, s-butyl, t-butyl, cyclobutyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, neopentyl, cyclopentyl, n-hexyl, i-hexyl, 3-methylpentane, 2,3-dimethylbutane, neohexane,
cyclohexane, heptane, cycloheptane, octane, and cyclooctane, or from a subset thereof. In certain embodiments, the "C1-C8 alkyl" group can be optionally further substituted. As a further example, a "CI -CI 2 alkyl" group can be selected from methyl, ethyl, n-propyl, i-propyl, cyclopropyl, n-butyl, i-butyl, s-butyl, t-butyl, cyclobutyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, neopentyl, cyclopentyl, n-hexyl, i-hexyl, 3-methylpentane, 2,3-dimethylbutane, neohexane, cyclohexane, heptane, cycloheptane, octane, cyclooctane, nonane, cyclononane, decane, cyclodecane, undecane, cycloundecane, dodecane, and cyclododecane, or from a subset thereof. In certain embodiments, the "CI -CI 2 alkyl" group can be optionally further substituted.

[043] Throughout the specification "alkyl" is generally used to refer to both unsubstiuted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" or "haloalkyl" specifically refers to an alkyl group that is substituted with one or more halide, e.g., fluorine, chlorine, bromine, or iodine. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "alkylamino" specifically refers to an alkyl group that is substituted with one or more amino groups, as described below, and the like. When "alkyl" is used in one instance and a specific term such as "alkylalcohol" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "alkylalcohol" and the like.

[044] This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, e.g., an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, e.g., a "halogenated alkoxy," a particular substituted alkenyl can be, e.g., an "alkenylalcohol," and the like. Again, the practice of using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is not meant to imply that the general term does not also include the specific term.

[045] The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term "heterocycloalkyl" is a type of cycloalkyl group as defined above, and is included within the meaning of the term "cycloalkyl," where at least one of the carbon atoms of the ring is replaced
with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, nitrile, sulfonamide, or thiol as described herein.

[046] The term "aryl" as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, phenoxybenzene, and the like. The term "aryl" also includes "heteroaryl," which is defined as a group that contains an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Likewise, the term "non-heteroaryl," which is also included in the term "aryl," defines a group that contains an aromatic group that does not contain a heteroatom. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, ary1, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, nitrile, sulfonamide, or thiol as described herein. The term "biaryl" is a specific type of aryl group and is included in the definition of "aryl." Biaryl refers to two aryl groups that are bound together via a fused ring structure, as in naphthalene, or are attached via one or more carbon-carbon bonds, as in biphenyl.

[047] The terms "halogen," "halide," and "halo," as used herein, refer to the halogens fluorine, chlorine, bromine, and iodine. It is also contemplated that, in various embodiments, halogen can be selected from fluoro, chloro, bromo, and iodo. For example, halogen can be selected from fluoro, chloro, and bromo. As a further example, halogen can be selected from fluoro and chloro. As a further example, halogen can be selected from chloro and bromo. As a further example, halogen can be selected from bromo and iodo. As a further example, halogen can be selected from chloro, bromo, and iodo. In one embodiment, halogen can be fluoro. In another embodiment, halogen can be chloro. In another embodiment, halogen is bromo. In another embodiment, halogen is iodo.

[048] It is also contemplated that, in certain embodiments, pseudohalogens (e.g. triflate, mesylate, tosylate, brosylate, etc.) can be used in place of halogens. For example, in certain embodiments, halogen can be replaced by pseudohalogen. As a further example, pseudohalogen
can be selected from triflate, mesylate, tosylate, and brosylate. In one embodiment, pseudohalogen is triflate. In another embodiment, pseudohalogen is mesylate. In another embodiment, pseudohalogen is tosylate. In another embodiment, pseudohalogen is brosylate.

The term "heterocycle," as used herein refers to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Heterocycle includes azetidine, dioxane, furan, imidazole, isothiazole, isoxazole, morpholine, oxazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, piperazine, piperidine, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, tetrahydrofuran, tetrahydropyran, tetrazine, including 1,2,4,5-tetrazine, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, thia diazole, including 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, thiazole, thiophene, triazine, including 1,3,5-triazine and 1,2,4-triazine, triazole, including 1,2,3-triazole, 1,3,4-triazole, and the like.

"R^1," "R^2," "R^3," "R^n," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (i.e., attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. In is also contemplated that, in certain embodiments,
unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[052] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; -(CH)_2=CHOR; -(CH)_2=C(O)OR; -(CH)_2=C(0)NR; -(CH)_2=CH(OOCR); -(CH)_2=CH(OMR); -(CH)_2=C(O)NR; -(CH)_2=C(0)OH, or -(CH)_2=C(O)OR, which may be substituted with R°; -(CH)_2=CH(0)Ph which may be substituted with R°; -(CH)_2=C(0)Ph, which may be substituted with R°; -(CH)_2=S(0)Ph which may be substituted with R°; -N0 which may be substituted with R°; -N0 hydrogen; -N0 aliphatic; -N0 aryl; -N0 aromatic ring; or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[053] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, -(CH)_2=CHR; -(haloR°); -(CH)_2=CHOR; -(CH)_2=CH(OMR); -(CH)_2=C(O)OR; -(CH)_2=C(O)NR; -(CH)_2=C(O)OH, or -(CH)_2=C(O)OR, which may be substituted with R°; -(CH)_2=C(0)OH, or -(CH)_2=C(O)OR, which may be substituted with R°; -(CH)_2=CH(0)Ph which may be substituted with R°; -(CH)_2=C(0)Ph, which may be substituted with R°; -(CH)_2=S(0)Ph which may be substituted with R°; -N0 which may be substituted with R°; -N0 hydrogen; -N0 aliphatic; -N0 aryl; -N0 aromatic ring; or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

-17-
"halo" is substituted only with one or more halogens, and is independently selected from Ci_4 aliphatic, -CH_2Ph, -O(CH_2)_0-iPh, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R^ transfers =0 and =S.

[054] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =0, =S, =NNR^*, =NNHC(0)R^*, =NNHC(0)OR^*, =NNHC(0)OR^*, =NNHC(0)_2R^*, =NOR^*, =N(0(CR_2)_2)=0, or -S(C(R_2)_2)_2S^*, wherein each independent occurrence of R^* is selected from hydrogen, Ci_6 aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: -O(CR_2)_2=0, wherein each independent occurrence of R^* is selected from hydrogen, Ci_6 aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[055] Suitable substituents on the aliphatic group of R^ include halogen, -R^*, -(haloR^*), -OH, -OR^*, -O(haloR^*), -CN, -C(0)OH, -C(0)OR^*, -NH_2, -NHR^*, -NR^*, or -N0_2, wherein each R^* is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently Ci_4 aliphatic, -CH_2Ph, -O(CH_2)_0-iPh, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[056] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include -R^, -NR^, -C(0)R^, -C(0)OR^, -C(0)C(0)R^, -C(0)CH_2C(0)R^, -S(0)_2R^, -S(0)_2NR^, -C(S)NR^, -C(NH)NR^, or -N(R^)S(0)_2R^; wherein each R^ is independently hydrogen, Ci_6 aliphatic which may be substituted as defined below, unsubstituted -OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and, notwithstanding the definition above, two independent occurrences of R^ transfers form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^*$, -(halo$R^*$), -OH, -OR*, -O(halo$R'$), -CN, -C(0)OH, -C(0)OR*, -NH$_2$, -NHR*, -NR$_2^*$, or -N0$_2$, wherein each $R^*$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently $C_{1-4}$ aliphatic, -CH$_2$Ph, -O(CH$_2$)$_0-i$Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers. Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, e.g., each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labelled or isotopically-substituted compounds identical to those described, 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 typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as $^2$H, $^3$H, $^{13}$C, $^{14}$C, $^{15}$N, $^{18}$O, $^{17}$O, $^{35}$S, $^{18}$F and $^{36}$Cl, respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which
radioactive isotopes such as 3H and 14C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H, and carbon-14, i.e., 14C, 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 labelled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[061] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvate or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

[062] The term "co-crystal" means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrates or solvates, see e.g. "Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?" Almarsson, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

[063] It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an α-hydrogen can exist in an equilibrium of the keto form and the enol form.
Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. Unless stated to the contrary, the invention includes all such possible tautomers.

It is known that chemical substances form solids which are present in different states of order which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

In some embodiments, a structure of a compound can be represented by a formula:

\[
\begin{align*}
\text{R}^n
\end{align*}
\]

which is understood to be equivalent to a formula:

\[
\begin{align*}
\text{R}^{n(a)} \text{R}^{n(b)} \text{R}^{n(c)} \text{R}^{n(d)}
\end{align*}
\]

wherein \( n \) is typically an integer. That is, \( R^m \) is understood to represent five independent substituents, \( R^{n(a)}, R^{n(b)}, R^{n(c)}, R^{n(d)}, R^{n(e)} \). By "independent substituents," it is meant that each R substituent can be independently defined. For example, if in one instance \( R^{n(b)} \) is halogen, then \( R^{n(b)} \) is not necessarily halogen in that instance.

Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Sigma-Aldrich Chemical Co., (Milwaukee, WL), Acros Organics (Morris Plains, NJ), Fisher Scientific (Pittsburgh, PA.), or Sigma (St. Louis, MO.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry,
Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds can not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all embodiments of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is
understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

B. Compounds

[071] In one embodiment, the present invention relates to compounds that are useful as inhibitors of lysine specific demethylase 1 ("LSD1"). In another embodiment the compounds of the invention are useful in the treatment of mammalian disorders in which LSD1 levels are elevated.

[072] It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

1. Structure

[073] In one embodiment, the present invention provides for a compound having the structure represented by Formula I:

```
\[
\text{structure image}
\]
```

wherein:

- m is 0 or 1,
- n is 0 or 1,
- X is selected from the group consisting of -CH and -N;
- Y is selected from the group consisting of -NH, -NCH₃, -NCH₂CH₃, -O and -S;
- Rᵢ is selected from the group consisting of -H, -CH₃ and -CH₂CH₃;
- R₂ and R₄ are independently selected from the group consisting of -H, -CH₃, -OH, -NH₂, halo, -CF₃, OCF₃, -OCH₃ and -CN;
- R₃ is selected from the group consisting of -H, -CH₃, -OH, -NH₂, a halo, -CF₃, OCF₃, -OCH₃, CN, -CONHRₛ and -NHCORₛ;
- R₅ is selected from the group consisting of -H, -CH₃, -CH₂CH₃, -C₁₋₃, a cycloalkyl and a halo;
R₁ is selected from the group consisting of -H and -CH₃;
R₂ is selected from the group consisting of -CH₃, -NH₂, -NCH₃, a C₆H alkyl, a C₆C cycloalkyl, a halo-C₆ alkyl, a cycloalkyl, a C₆H heterocycloalkyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, oxazolidinyl, pyrazolidinyl, piperazinyl, oxazinanyl, morpholiny, hexahydroprimidinyl, hexahydropyrindazinyl and an optionally substituted moiety selected from the group consisting of:

\[
\text{Formula I}
\]

R₃ is selected from the group consisting of -H, C₆H alkyl, C₆C cycloalkyl and C₆H heterocycloalkyl;

or a pharmaceutically acceptable salt, hydrochloric acid, sulphate, methanesulfonic acid or benzene sulfonic acid thereof.

2. Example Compounds

[074] In one embodiment, the present invention provides a compound of Formula I that can be present as:
or a pharmaceutically acceptable salt, hydrochloric acid, sulphate, methanesulfonic acid or benzene sulfonic acid thereof.

In one embodiment, the disclosed compound exhibits inhibition of a histone demethylase.

In another embodiment, the histone demethylase is a member of the lysine-specific (LSD) family of histone demethylases. In another embodiment, the histone demethylase is LSD1.

[075] In another embodiment, the compound inhibits histone demethylase with an IC$_{50}$ of less than about 1.0x10$^{-4}$ M, less than about 1.0x10$^{-5}$ M, less than about 1.0x10$^{-6}$ M, less than about 1.0x10$^{-7}$ M, less than about 1.0x10$^{-8}$ M, and less than about 1.0x10$^{-9}$ M. In another embodiment, the compound inhibits LSD with an IC$_{50}$ of less than about 1.0x10$^{-4}$ M, less than
about 1.0x10⁻³ M, less than about 1.0x10⁻⁶ M, less than about 1.0x10⁻⁷ M, less than about 1.0x10⁻⁸ M, and less than about 1.0x10⁻⁹ M. In another embodiment, the compound LSD₁ with an IC₅₀ of less than about 1.0x10⁻⁴ M, less than about 1.0x10⁻⁵ M, less than about 1.0x10⁻⁶ M, less than about 1.0x10⁻⁷ M, less than about 1.0x10⁻⁸ M, and less than about 1.0x10⁻⁹ M.

[076] It is contemplated that one or more compounds can optionally be omitted from the disclosed invention.

3. Inhibition of Histone Demethylase Activity

[077] In one embodiment, the present invention provides for compounds that exhibit inhibition of LSD protein activity. In a preferred embodiment, the disclosed compounds exhibit selective inhibition of LSD₁ protein activity. In a more preferred embodiment, the disclosed compounds exhibit binding to the LSD₁ substrate ATP and LSD₁ peptide substrate binding sites. In another embodiment, the disclosed compounds exhibit inhibition of LSD-mediated demethylation of histone 3 (H3) at the Lys4 position. In another embodiment, the disclosed compounds exhibit inhibition LSD-mediated demethylation of H3K3ml and H3K4me2. In another embodiment, the disclosed compounds exhibit inhibition LSD-mediated demethylation of H3K9me2 and H3K9mel.

[078] In one embodiment, the disclosed compounds exhibit disruption of of LSD interaction with a complexes comprising one or more of HDAC1/2, CoREST, CtBPI, BRAF35 and BHC80 proteins. In a preferred embodiment the disclosed compounds disrupt binding of LSD₁ to one or more proteins selected from HDAC1/2, CoREST, CtBPI, BRAF35 and BHC80 proteins. In another embodiment, the disclosed compounds disrupt binding of LSD2 to one or more proteins selected from G9a, NSD3, HDAC1/2, CoREST, CtBPI, BRAF35 and BHC80 proteins.

[079] Inhibition of LSD activity can be determined by a variety of both in vitro and in vivo methods known to one skilled in the art. For example, enzymatic activity can be determined in in vitro enzyme assay systems. In various embodiments, the enzymatic activity of LSD₁ can be determined in a spectrophotometric assay. Briefly, the assay is based on the multistep enzymatic reaction in which LSD₁ first produces H₂O₂ during the demethylation of lysine 4 on a peptide corresponding to the first 21 amino acids of the N-terminal tail of histone H3. In the presence of horseradish peroxidase, the H₂O₂ produced reacts with ADHP to produce the highly fluorescent compound resorufin that can be analyzed with an excitation wavelength of 530-540 nm and an emission wavelength of 585-595 nm. The assay requires a source of LSD₁ enzyme, either
purified from natural sources (e.g. a tissue or cultured cells), isolated as a recombinantly expressed protein, or as an unpurified protein in whole cell extracts. In one embodiment, the disclosed compounds exhibit inhibition of LSD protein activity with an IC\textsubscript{50} in an EMSA assay of less than about 300 mM, less than about 100 mM, less than about 50 mM, less than about 10 mM, less than about 1 mM, less than about 500 nM, or of less than about 100 nM. In another embodiment, the disclosed compounds exhibit inhibition of LSD1 protein activity with an IC\textsubscript{50} in an EMSA assay of less than about 300 mM, less than about 100 mM, less than about 50 mM, less than about 10 mM, less than about 1 mM, less than about 500 nM, or of less than about 100 nM. In another embodiment, the disclosed compounds exhibit inhibition of LSD2 protein activity with an IC\textsubscript{50} in an EMSA assay of less than about 300 mM, less than about 100 mM, less than about 50 mM, less than about 10 mM, less than about 1 mM, less than about 500 nM, or of less than about 100 nM.

[080] In one embodiment, the disclosed compounds are selective for LSD. In another embodiment, selective inhibition of LSD activity is determined using an enzyme assay. In another embodiment, the compound inhibits LSD activity in an enzyme assay with an IC\textsubscript{50} less than the IC\textsubscript{50} for MAO A and/or MAO B. That is, a disclosed compound can have selectivity for the LSD protein vis-a-vis MAO A and/or MAO B. For example, in one embodiment, a disclosed compound can inhibit LSD with an IC\textsubscript{50} of about 5-fold less than that for MAO A, of about 10-fold less than that for MAO A, of about 20-fold less than that for MAO A, of about 30-fold less than that for MAO A, of about 50-fold less than that for MAO A, of about 100-fold less than that for MAO A, of about 250-fold less than that for MAO A, of about 500-fold less than that for MAO A, of about 1000-fold less than that for MAO A, and more than about 1000-fold less than that for MAO A. In another embodiment, a disclosed compound can inhibit LSD with an IC\textsubscript{50} of about 5-fold less than that for MAO B, of about 10-fold less than that for MAO B, of about 20-fold less than that for MAO B, of about 30-fold less than that for MAO B, of about 50-fold less than that for MAO B, of about 100-fold less than that for MAO B, of about 250-fold less than that for MAO B, of about 500-fold less than that for MAO B, of about 1000-fold less than that for MAO B, and more than about 1000-fold less than that for MAO B.

[081] In another embodiment, the disclosed compounds are selective for LSD1. In a preferred embodiment, selective inhibition of LSD1 activity is determined using an enzyme assay. In various further embodiments, the compound inhibits LSD1 activity in an enzyme assay with an
IC$_{50}$ less than the IC$_{50}$ for one or more of LSD2, MAO A, and MAO B. That is, a disclosed compound can have selectivity for the LSD1 protein vis-a-vis one or more of LSD2, MAO A, and MAO B. For example, in one embodiment, a disclosed compound can inhibit LSD1 with an IC$_{50}$ of about 5-fold less than that for LSD2, of about 10-fold less than that for LSD2, of about 20-fold less than that for LSD2, of about 30-fold less than that for LSD2, or of about 50-fold less than that for LSD2. In another embodiment, a disclosed compound can inhibit LSD1 with an IC$_{50}$ of about 5-fold less than that for MAO A, of about 10-fold less than that for MAO A, of about 20-fold less than that for MAO A, of about 30-fold less than that for MAO A, of about 50-fold less than that for MAO A, of about 100-fold less than that for MAO A, of about 250-fold less than that for MAO A, of about 500-fold less than that for MAO A, of about 1000-fold less than that for MAO A. In another embodiment, a disclosed compound can inhibit LSD1 with an IC$_{50}$ of about 5-fold less than that for MAO B, of about 10-fold less than that for MAO B, of about 20-fold less than that for MAO B, of about 30-fold less than that for MAO B, of about 50-fold less than that for MAO B, of about 100-fold less than that for MAO B, of about 250-fold less than that for MAO B, of about 500-fold less than that for MAO B, of about 1000-fold less than that for MAO B, and more than about 1000-fold less than that for MAO B.

[082] In one embodiment, the disclosed compounds and products of disclosed methods of making inhibit cell growth. In another embodiment, the disclosed compounds and products of disclosed methods inhibit cell growth in an in vitro assay system. In another embodiment, the in vitro assay system makes use of a cell-line derived from a from cancer or tumor selected from breast cancer, ovarian cancer, testicular cancer, lung cancer, liver cancer, prostate cancer, pancreatic cancer and a sarcoma. In another embodiment, the cell-line is derived from a human source. In another embodiment, the disclosed compounds inhibit cell growth in a cell with a persistently active LSD protein. In another embodiment, the cell-line has an activated LSD protein. In another embodiment, the cell-line is selected from AN3 CA, BT-20, BT-549, HCT 116, HER218, MCF7, MDA-MB-231, MDA-MB-235, MDA-MB-435S, MDA-MB-468, PANCA-1, PC-3, SK-N-MC, T-47D, and U-87 MG. In one embodiment, the disclosed compounds exhibit inhibition of cell growth activity in an in vitro cell-based assay with an IC$_{50}$ of less than about 500 mM, of less than about 250 mM, less than about 100 mM, less than...
about 50 mM, less than about 10 mM, less than about 1 mM, less than about 500 nM, of less than about 100 nM, or of less than about 1 nM.

[083] In one embodiment, the disclosed compounds and products of disclosed methods of making inhibit cell migration. In another embodiment, the disclosed compounds and products of disclosed methods inhibit cell migration in an in vitro assay system. In another embodiment, the in vitro assay system makes use of a cell-line derived from a from cancer or tumor selected from breast cancer, ovarian cancer, testicular cancer, lung cancer, liver cancer, prostate cancer, pancreatic cancer and a sarcoma. In another embodiment, the cell-line is derived from a human source. In another embodiment, the disclosed compounds inhibit cell growth in a cell with a persistently active LSD protein. In another embodiment, the cell-line has an activated LSD protein. In another embodiment, the cell-line is selected from AN3 CA, BT-20, BT-549, HCT 116, HER218, MCF7, MDA-MB-231, MDA-MB-235, MDA-MB-435S, MDA-MB-468, PANC-1, PC-3, SK-N-MC, T-47D, and U-87 MG. In one embodiment, the disclosed compounds exhibit inhibition of cell migration in an in vitro cell-based assay with an IC_{50} of less than about 300 mM, less than about 100 mM, less than about 50 mM, less than about 10 mM, less than about 1 mM, less than about 500 nM, or of less than about 100 nM.

C. Methods of Making the Compounds

[084] In one aspect, the invention relates to methods of making compounds useful as inhibitors of LSD. In a further aspect, the products of disclosed methods of making are modulators of LSD activity. In a yet further aspect, the products of disclosed methods of making bind to a STAT protein and negatively modulate LSD activity. The compounds can, in one aspect, exhibit subtype selectivity. In a still further aspect, the products of disclosed methods of making exhibit selectivity for the LSD1 member of the LSD protein family. In an even further aspect, the products of the disclosed methods of making exhibit selectivity for the LSD2 member of the LSD protein family.

[085] In one aspect, the invention relates to methods of making compounds useful as inhibitors of histone demethylase, which can be useful in the treatment of disorders of uncontrolled cellular proliferation. In a further aspect, the histone demethylase is LSD1. In a yet further aspect, the histone demethylase is LSD2.

[086] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the
literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

[087] Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, in addition to other standard manipulations known in the literature or to one skilled in the art. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

[088] In one aspect, the disclosed compounds comprise the products of the synthetic methods described herein. In a further aspect, the disclosed compounds comprise a compound produced by a synthetic method described herein. In a still further aspect, the invention comprises a pharmaceutical composition comprising a therapeutically effective amount of the product of the disclosed methods and a pharmaceutically acceptable carrier. In a still further aspect, the invention comprises a method for manufacturing a medicament comprising combining at least one compound of any of disclosed compounds or at least one product of the disclosed methods with a pharmaceutically acceptable carrier or diluent.

General Synthesis of compounds of Formula I.

[089] A mixture of 2-chloro-5- substituted-lH-benzo[d]imidazole (1.5 mmol) and substituted aromatic 2-aminophenol (1.5 mmol) was dissolved in anhydrous tetrahydrofuran (3 mL) and then the reaction mixture was heated via microwave irradiation to 150 °C for 5 h. The cooled crude product mixture was boiled with diluted hydrochloric acid for 10 minutes and cooled and filtered. The filtered solid was then washed with dilute sodium hydroxide solution, then with water and dried. The resulting crude material was purified by flash column chromatography (3% MeOH/CH₂Cl₂) affording the compound 4-substituted-2-((5-substituted-lH-benzo[d]imidazol-2-yl)amino)phenol as a solid.

General Synthesis of pharmaceutically acceptable salts of Formula I.

[090] To a stirred suspension of 4-substituted-2-((5-substituted-lH-benzo[d]imidazol-2-yl)amino)phenol in a suitable solvent including, but not limited to, methanol, ethanol, acetone, acetonitrile, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, ethylacetate 2-propanol, toluene, diethylether) and a required quantity of water was dissolved various inorganic or organic acids including, but not limited to benzenesulfonic, benzoic, camphorsulfonic, citric,
ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, either by heating or at room temperature until clear. The resulting contents were cooled to obtain the precipitated salts. The resulting product was filtered and washed with cold solvents and dried to obtain the pharmaceutical salt of interest for the compounds provided in the Formula I.

[091] It is contemplated that each disclosed methods can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step, manipulation, and/or component can be optionally omitted from the invention. It is understood that a disclosed methods can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed methods of using.

D. Pharmaceutical Compositions

[092] In one embodiment, the present invention provides for pharmaceutical compositions comprising a therapeutically effective amount of the disclosed compounds. In another embodiment, the present invention provides for pharmaceutical compositions comprising a therapeutically effective amount of the disclosed compounds and a pharmaceutically acceptable carrier.

[093] The disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[094] As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (-ic and -ous), ferric,
ferrous, lithium, magnesium, manganese (-ic and -ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethlenediamine, diethyamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[095] As used herein, the term "pharmaceutically acceptable non-toxic acids", includes inorganic acids, organic acids, and salts prepared therefrom, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and its anion tosylate and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, methanesulfonic, phosphoric, p-toluenesulfonic, tosylate, sulfuric, and tartaric acids.

[096] In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, and/or pharmaceutically acceptable salt(s) thereof, can also be administered by controlled release means and/or delivery devices. The compositions can
be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[097] Thus, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[098] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[099] In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets can be coated by standard aqueous or nonaqueous techniques

[0100] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[0101] The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a
pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[0102] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[0103] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[0104] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[0105] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose
suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

[0106] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

[0107] In the treatment conditions which require inhibition or negative modulation of LSD protein activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day and can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably 0.5 to 100 mg/kg per day. A suitable dosage level can be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5.0 or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the from of tablets containing 1.0 to 1000 miligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900 and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage of the patient to be treated. The compound can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosing regimen can be adjusted to provide the optimal therapeutic response.

[0108] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the type and severity of the particular disease undergoing therapy.

E. Method of Using the Compounds and Compositions

[0109] The disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the
aforementioned diseases, disorders and conditions for which compounds of Formula I or II or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound is preferred. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound will be more efficacious than either as a single agent.

[0110] The pharmaceutical compositions and methods of the present invention can further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

[0111] The compounds disclosed herein are useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of disorders wherein the patient or subject would benefit from inhibition or negative modulation of a LSD protein. In one embodiment, a treatment can include selective inhibition of LSD to an extent effective to affect histone demethylation activity. Thus, a disorder can be associated with histone demethylation activity, for example dysfunctional epigenetic regulation of genes in a cancer cell. In one embodiment, provided is a method of treating or preventing a disorder in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[0112] Also provided is a method for the treatment of one or more disorders, for which LSD inhibition is predicted to be beneficial, in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[0113] In one embodiment, provided is a method for treating a disorder of uncontrolled cellular proliferation, comprising: administering to a subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject. In another embodiment, provided is a
method for treating or preventing a neurodegenerative disorder, comprising: administering to a
subject at least one disclosed compound; at least one disclosed pharmaceutical composition;
and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the
subject. In another embodiment, provided is a method for treating or preventing acquired
immune deficiency syndrome ("AIDS"). In another embodiment, provided is a method for
treating or preventing AIDS by controlling reactivation of latent human immunodeficiency virus
1 ("HIV"). In another embodiment, provided is a method for treating or preventing a symptom
of Hepatitis C virus infection. In another embodiment, provided is a method for treating or
preventing liver disease in an individual infected with the Hepatitis C virus. Also provided is a
method for the treatment of a disorder in a mammal comprising the step of administering to the
mammal at least one disclosed compound, composition, or medicament.

[0114] The invention is directed at the use of described chemical compositions to treat diseases
or disorders in patients (preferably human) wherein LSD inhibition would be predicted to have a
therapeutic effect, such as disorders of uncontrolled cellular proliferation (e.g. cancers) and
neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and Parkinson's
disease, by administering one or more disclosed compounds or products.

[0115] The compounds disclosed herein are useful for treating, preventing, ameliorating,
controlling or reducing the risk of a variety of disorders of uncontrolled cellular proliferation. In
one embodiment, the disorder of uncontrolled cellular proliferation is associated with a histone
demethylase dysfunction. In another embodiment, the histone demethylase dysfunction is
disregulation of the LSD. In a still another embodiment, the histone demethylase dysfunction is
disregulation of the LSD1. In another embodiment, the histone demethylase dysfunction is
disregulation of the LSD2.

[0116] Also provided is a method of use of a disclosed compound, composition, or medicament.
In one embodiment, the method of use is directed to the treatment of a disorder. In another
embodiment, the disclosed compounds can be used as single agents or in combination with one
or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the
aforementioned diseases, disorders and conditions for which the compound or the other drugs
have utility, where the combination of drugs together are safer or more effective than either drug
alone. The other drug(s) can be administered by a route and in an amount commonly used
therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed
compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound is preferred. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound can be more efficacious than either as a single agent.

[0117] Examples of disorders associated with a histone demethylase dysfunction include a disorder of uncontrolled cellular proliferation. In another embodiment, the disorder of uncontrolled cellular proliferation is cancer. In another embodiment, the cancer is a leukemia. In another embodiment, the cancer is a sarcoma. In another embodiment, the cancer is a solid tumor. In another embodiment, the cancer is a lymphoma.

[0118] It is understood that cancer refers to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. The cancer may be multi-drug resistant (MDR) or drug-sensitive. Examples of cancer include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include breast cancer, estrogen receptor-negative breast cancer, triple negative breast cancer, prostate cancer, colon cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, cervical cancer, ovarian cancer, peritoneal cancer, liver cancer, e.g., hepatic carcinoma, bladder cancer, colorectal cancer, endometrial carcinoma, kidney cancer, and thyroid cancer.

[0119] In various embodiments, further examples of cancers are basal cell carcinoma, biliary tract cancer; bone cancer including Ewing's sarcoma; brain and central nervous system ("CNS") cancer; choriocarcinoma; connective tissue cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer; intra-epithelial neoplasm; larynx cancer; lymphoma including Hodgkin's and Non-Hodgkin's lymphoma; melanoma; myeloma; neuroblastoma; oral cavity cancer (e.g., lip, tongue, mouth, and pharynx); retinoblastoma; rhabdomyosarcoma; rectal cancer; cancer of the respiratory system; sarcoma; skin cancer; stomach cancer; testicular cancer; uterine cancer; cancer of the urinary system, as well as other carcinomas and sarcomas.

[0120] In another embodiment, the cancer is a hematological cancer. In another embodiment, the hematological cancer is selected from acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia.
(JMML), Hodgkin lymphoma, Non-Hodgkin lymphoma, multiple myeloma, solitary myeloma, localized myeloma, and extramedullary myeloma. In another embodiment, the cancer is selected from chronic lymphocytic leukemia, small lymphocytic lymphoma, B-cell non-Hodgkin lymphoma, and large B-cell lymphoma.

[0121] In another embodiment, the cancer is a cancer of the brain. In another embodiment, the cancer of the brain is selected from a glioma, medulloblastoma, primitive neuroectodermal tumor (PNET), acoustic neuroma, glioma, meningioma, pituitary adenoma, schwannoma, CNS lymphoma, primitive neuroectodermal tumor, craniopharyngioma, chordoma, medulloblastoma, cerebral neuroblastoma, central neurocytoma, pineocytoma, pineoblastoma, atypical teratoid rhabdoid tumor, chondrosarcoma, chordoma, choroid plexus carcinoma, choroid plexus papilloma, craniopharyngioma, dysembryoplastic neuroepithelial tumor, gangliocytoma, germinoma, hemangioblastoma, hemangiopericytoma, and metastatic brain tumor. In another embodiment, the glioma is selected from ependymoma, astrocytoma, oligodendroglioma, and oligoastrocytoma. In another embodiment, the glioma is selected from juvenile pilocytic astrocytoma, subependymal giant cell astrocytoma, ganglioglioma, subependymoma, pleomorphic xanthoastrocytoma, anaplastic astrocytoma, glioblastoma multiforme, brain stem glioma, oligodendroglioma, ependymoma, oligoastrocytoma, cerebellar astrocytoma, desmoplastic infantile astrocytoma, subependymal giant cell astrocytoma, diffuse astrocytoma, mixed glioma, optic glioma, gliomatosis cerebri, multifocal gliomatous tumor, multicentric glioblastoma multiforme tumor, paraganglioma, and ganglioglioma.

[0122] In one embodiment, the cancer can be a cancer selected from cancers of the blood, brain, genitourinary tract, gastrointestinal tract, colon, rectum, breast, kidney, lymphatic system, stomach, lung, pancreas, and skin. In another embodiment, the cancer is selected from prostate cancer, glioblastoma multiforme, endometrial cancer, breast cancer, and colon cancer. In another embodiment, the cancer is selected from a cancer of the breast, ovary, prostate, head, neck, and kidney. In another embodiment, the cancer is selected from cancers of the blood, brain, genitourinary tract, gastrointestinal tract, colon, rectum, breast, liver, kidney, lymphatic system, stomach, lung, pancreas, and skin. In another embodiment, the cancer is selected from a cancer of the lung and liver. In another embodiment, the cancer is selected from a cancer of the breast, ovary, testes and prostate. In another embodiment, the cancer is a cancer of the breast.
another embodiment, the cancer is a cancer of the ovary. In another embodiment, the cancer is a cancer of the prostate. In another embodiment, the cancer is a cancer of the testes.

[0123] In various embodiments, disorders associated with a histone demethylase dysfunction include neurodegenerative disorders. In another embodiment, the neurodegenerative disease is selected from Alzheimer's disease, Parkinson's disease, and Huntington's disease.

[0124] The compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein. The compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents.

[0125] The present invention is further directed to administration of a LSD inhibitor for improving treatment outcomes in the context of disorders of uncontrolled cellular proliferation, including cancer. That is, in one embodiment, the invention relates to a cotherapeutic method comprising the step of administering to a mammal an effective amount and dosage of at least one compound of the invention in connection with cancer therapy.

[0126] In another embodiment, administration improves treatment outcomes in the context of cancer therapy. Administration in connection with cancer therapy can be continuous or intermittent. Administration need not be simultaneous with therapy and can be before, during, and/or after therapy. For example, cancer therapy can be provided within 1, 2, 3, 4, 5, 6, 7 days before or after administration of the compound. As another example, cancer therapy can be provided within 1, 2, 3, or 4 weeks before or after administration of the compound. As another example, cognitive or behavioral therapy can be provided before or after administration within a period of time of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 half-lives of the administered compound.

[0127] In one embodiment, the disclosed compounds can be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which disclosed compounds or the other drugs can have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) can be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and a disclosed
compound is preferred. However, the combination therapy can also include therapies in which a disclosed compound and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the disclosed compounds and the other active ingredients can be used in lower doses than when each is used singly.

[0128] Accordingly, the pharmaceutical compositions include those that contain one or more other active ingredients, in addition to a compound of the present invention.

[0129] The above combinations include combinations of a disclosed compound not only with one other active compound, but also with two or more other active compounds. Likewise, disclosed compounds can be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which disclosed compounds are useful. Such other drugs can be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to a disclosed compound is preferred. Accordingly, the pharmaceutical compositions include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

[0130] The weight ratio of a disclosed compound to the second active ingredient can be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of a disclosed compound to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[0131] In such combinations a disclosed compound and other active agents can be administered separately or in conjunction. In addition, the administration of one element can be prior to, concurrent to, or subsequent to the administration of other agent(s).

[0132] Accordingly, the subject compounds can be used alone or in combination with other agents which are known to be beneficial in the subject indications or other drugs that affect
receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the disclosed compounds. The subject compound and the other agent can be coadministered, either in concomitant therapy or in a fixed combination.


Vumon®, X, Xeloda®, Zanosar®, Zevalin™, Zinecard®, Zoladex®, Zoledronic acid, Zolinza, Zometa…®, Hydrocort Acetate®
Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Anastrozole, Altretamine, ALIMTA, Adriamycin
Hexadrol, Factor, Folinic
Fludarabine, Evista
Vumon®, X, Xeloda®, Z, Zanosar®, Zevalin™, Zinecard®, Zoladex®, Zoledronic acid, Zolinza, Zometa®

[0136] In one embodiment, the compound can be employed in combination with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, NSAID's including ibuprofen, vitamin E, and anti-amyloid antibodies. In another embodiment, the subject compound can be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbital, alonimid, alprazolam, amisulpride, amitriptyline, amobarbital, amoxapine, aripiprazole, bentazepam, benzoctamine, brotizolam, bupropion, buspirone, butabarbital, butalbital, caprure, carbocloal, chloral betaine, chloral hydrate, clomipramine, clonazepam, cloperidone, clorazepate, chlordiazepoxide, clorethate, chlorpromazine, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, dipalproex, diphenhydramine, doxepin, estazolam, etchlorvynol, etomidate, fenobam, flunitrazepam, flupentixol, fluphenazine, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, haloperidol, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, meprobamal, meprophen, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, olanzapine, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, quiuiapine, reclazepam, risperidone, roletamide, secobarbital, sertraline, suproclon, temazepam, thioridazine, thiorthoxtene, trazolactone, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, ziprasidone, zolazepam, Zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound can be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

[0137] In the treatment of conditions which require inhibition or negative modulation of LSD, an appropriate dosage level will generally be about 0.01 to 1000 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level can be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day,
or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosage regimen can be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0138] Thus, in one embodiment, the invention relates to methods for inhibiting or negatively modulating LSD in at least one cell, comprising the step of contacting the at least one cell with at least one compound of the invention, in an amount effective to modulate or activate LSD activity response, e.g. LSD1 or LSD2, in the at least one cell. In another embodiment, the cell is mammalian, for example human. In another embodiment, the cell has been isolated from a subject prior to the contacting step. In another embodiment, contacting is via administration to a subject.

2. Kits

[0139] In one embodiment, the invention relates to a kit comprising at least one compound having a structure represented by Formula I or II, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, and one or more of:

(a) at least one agent known to increase histone demethylase activity;
(b) at least one agent known to decrease histone demethylase activity;
(c) at least one agent known to treat a disorder of uncontrolled cellular proliferation;
(d) at least one agent known to treat a neurodegenerative disorder;
(e) instructions for treating a neurodegenerative disorder; or
(f) instructions for treating a disorder associated with uncontrolled cellular proliferation.
In another embodiment, the compound of the kit is compound represented by Formula I. In another embodiment, the compound of the kit is compound represented by Formula II.

In another embodiment, the compound of the kit is a disclosed compound or a product of a disclosed method of making a compound.

In another embodiment, the at least one compound or the at least one product and the at least one agent are co-formulated. In another embodiment, the at least one compound or the at least one product and the at least one agent are co-packaged.

In another embodiment, the histone demethylase is a lysine-specific histone demethylase. In another embodiment, the lysine-specific histone demethylase is LSD1.

In another embodiment, the at least one agent is a hormone therapy agent. In another embodiment, the hormone therapy agent is selected from one or more of the group consisting of leuprolide, tamoxifen, raloxifene, megestrol, fulvestrant, triptorelin, medroxyprogesterone, letrozole, anastrozole, exemestane, bicalutamide, goserelin, histrelin, fluoxymesterone, estramustine, flutamide, toremifene, degarelix, nilutamide, abarelix, and testolactone, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

In another embodiment, the at least one agent is a chemotherapeutic agent. In another embodiment, the chemotherapeutic agent is selected from one or more of the group consisting of an alkylating agent, an antimetabolite agent, an antineoplastic antibiotic agent, a mitotic inhibitor agent, a mTOR inhibitor agent or other chemotherapeutic agent.

In another embodiment, the antineoplastic antibiotic agent is selected from one or more of the group consisting of doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plicamycin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

In another embodiment, the antimetabolite agent is selected from one or more of the group consisting of gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, flouxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

In another embodiment, the alkylating agent is selected from one or more of the group consisting of carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan,
carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0149] In another embodiment, the mitotic inhibitor agent is selected from one or more of the group consisting of irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etopside, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0150] In another embodiment, the mTor inhibitor agent is selected from one or more of the group consisting of everolimus, siroliumus, and temsirolimus, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0151] In another embodiment, the disorder of uncontrolled cellular proliferation is associated with a histone demethylase dysfunction. In another embodiment, the disorder of uncontrolled cellular proliferation is a cancer. In another embodiment, cancer is a leukemia. In another embodiment, the cancer is a sarcoma. In another embodiment, cancer is a solid tumor. In another embodiment, the cancer is a lymphoma. In another embodiment, the cancer is selected from chronic lymphocytic leukemia, small lymphocytic lymphoma, B-cell non-Hodgkin lymphoma, and large B-cell lymphoma. In another embodiment, the cancer is selected from cancers of the blood, brain, genitourinary tract, gastrointestinal tract, colon, rectum, breast, livery, kidney, lymphatic system, stomach, lung, pancreas, and skin. In another embodiment, the cancer is selected from a cancer of the lung and liver. In another embodiment, the cancer is selected from a cancer of the breast, ovary, testes and prostate. In another embodiment, the cancer is a cancer of the breast. In various embodiment, the cancer is a cancer of the ovary. In another embodiment, the cancer is a cancer of the prostate. In another embodiment, the cancer is a cancer of the testes.

3. Non-Medical Uses

[0152] Also provided are the uses of the disclosed compounds and products as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of histone demethylase activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents that inhibit histone demethylase activity.
F. Experimental

[0153] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

[0154] Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein.

[0155] The following exemplary compounds of the invention were synthesized. The Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way. The Examples are typically depicted in free base form, according to the IUPAC naming convention. However, some of the Examples were obtained or isolated in salt form.

[0156] As indicated, some of the Examples were obtained as racemic mixtures of one or more enantiomers or diastereomers. The compounds may be separated by one skilled in the art to isolate individual enantiomers. Separation can be carried out by the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. A racemic or diastereomeric mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases.

1. General Chemical Materials and Methods

[0157] All analytical or anhydrous grade reagents were purchased from commercial sources and were used without further purification. Solvents were of analytical or anhydrous grade (Sigma-Aldrich). Specialty chemicals and building blocks obtained from several suppliers were of the highest offered purity (always ≥ 95%).
NMR spectroscopy was performed on a Varian Unity 400 instrument with a 5 mm broadband probe and using standard pulse sequences. Chemical shifts (δ) are reported in parts-per-million (ppm) downfield from solvent references. Coupling constants (J-values) are expressed in Hz.

Mass spectrometry was performed on a Finnigan LCQ Duo LCMS ion trap electrospray (ESI) mass spectrometer. All samples were analyzed by positive ESI-MS and the mass-to-charge ratio (m/z) of the protonated molecular ion is reported.

Microwave-assisted reactions were performed on a Biotage Initiator 2.5 at various powers.

Hydrogenation reactions were performed on a standard Parr hydrogenation apparatus. Reactions were monitored either by HPLC or TLC. When monitored by TLC, reactions were analyzed on Baker flexible-backed plates coated with 200 µm of silica gel containing a fluorescent indicator. Preparative TLC was performed on 20 cm x 20 cm Analtech Uniplates coated with a 1000 or 2000 µm silica gel layer containing a fluorescent (UV 254) indicator. Elution mixtures are reported as v:v. Spot visualization was achieved using UV light.

Flash chromatography was performed on a Teledyne Isco CombiFlash RF 200 using appropriately sized Redisep Rf Gold or Standard normal-phase silica or reversed-phase C-18 columns. Crude compounds were adsorbed on silica gel, 70-230 mesh 40 Å (for normal phase) or Celite 503 (for reversed-phase) and loaded into solid cartridges. Elution mixtures are reported as v:v.

2. Molecular Modeling and Virtual Screening Methods

All computational studies employed PDB ID 2Z5U for the structural coordinates of LSD1. Virtual docking methods ICM, Glide and GOLD programs were implemented. The protein structure was prepared by 3D protonation, deletion of water molecules and energy minimization using the ICM force field and distance-dependent dielectric potential with an RMS gradient of 0.1; heavy atoms in the protein were kept fixed, and histidine residues were considered as neutral. Virtual screening calculations utilized default parameters (unless explicitly specified otherwise) with ICM and Glide scores as scoring functions respectively. In both cases, FAD was defined as the ligand and an active site region was defined by a sphere of radius 12 Å around the bound FAD in complex with LSD1.
Confirmation of the accuracy and efficiency of the applied docking protocol used the FAD cofactor adenine dinucleotide fragment, and the flavin fragment, and known LSD1 inhibitors (decoy set) as positive controls. Two separate docking runs were carried out with ICM and the Glide docking program; GOLD docking was employed for re-scoring.

The compound database was prepared using Ligprep 2.1.23 (Schrodinger, LLC, New York, New York). Two rounds of VS, including HTVS and standard precision (SP) docking, were adopted. The top 10000 compounds ranked by Glide were stored and submitted for additional docking experiments using ICM docking. The final set of 2000 hits was selected based on ICM scores and individual compounds were visually inspected to check the docking poses and interactions between ligands and LSD1. GOLD consensus scoring functions were employed further to re-score these 2000 hits selected from Glide and ICM. Finally, 121 compounds were purchased (if available) or synthesized for LSD1 inhibition studies.

3. MD Simulation Methods

All simulations were performed using the AMBER ff99SB force field (Hornak, V., et al. Proteins 2006, 65 (3), 712-25) for LSD1, the general Amber force field ("gaff; see Wang, J., et al JComput Chem 2004, 25 (9), 1157-74) for compound 12, and the TIP3P (Jorgensen, W. L., Journal of Chemical Physics 1982, (77), 4156-4163) model for water was employed. The simulations approximated long-range electrostatic interactions using the particle-mesh Ewald method (PME) procedure (Essmann, U., et al. Journal of Chemical Physics 1995, (103), 8577-8593; Darden, T., et al. Journal of Chemical Physics 1993, (98), 10089-10092). Using LEaP the binding modes generated from ICM docking in complex with LSD1 were solvated to neutral charge and the complexes were first minimized with PMEMD (Case, D. A., et al. AMBER11, San Francisco, 2010). Following minimization, 200 ps of unrestrained molecular dynamics simulation using a non-bonded interaction cutoff of 9Å was run for both binding modes with a constant pressure periodic boundary maintaining 1 atm of pressure and isotropic position scaling with a relaxation time of 2 ps. SHAKE was used to constrain bonds involving hydrogen and Langevin dynamics were used to regulate temperature (Case, D. A., et al. AMBER11, San Francisco, 2010), maintaining 300 K. Relative free energies of binding for comparisons between the two binding modes were predicted using MMPBSA.py with 100 snapshots at 1-ps intervals starting either at 1ps or 10lps into the trajectory.
4. Virtual Screening Results

The first crystal structures of LSD1 elucidating critical architectural features were later by Stavropoulos et al. (Nat Struct Mol Biol 2006, 13(7):626-32; Protein Data Bank or PDB ID 2H94; see http://www.wwpdb.org/), Yang et al. (Mol Cell 2006, 23 (3), 377-87; PDB ID 2IW5), and Chen et al. (Proc Natl Acad Sci USA 2006, 103 (38), 13956-61; PDB ID 2HKO). These 2.9 Å, 2.57 Å, and 2.8 Å structures, respectively, show a highly negatively charged substrate-binding cavity spacious enough to accommodate the N-terminal tail of histone H3. Further, an N-terminal SWIRM domain and an insertion in the core catalytic domain, termed the Tower Domain, were established as necessary structural motifs for enzymatic activity and interactions with cofactors such as CoREST. For the studies described herein, the structure, PDB ID 2Z5U, was used with bound LSD1 inhibitor tranylcypromine for computational studies, including virtual screening, docking, and molecular dynamics (Mimasu, S., et al. Biochem Biophys Res Commun 2008, 366 (1), 15-22). In order to evaluate the chemical space outside of tranylcypromine and polyamine derivatives, HTVS was used with an in-house library. The library was curated from publicly available vendor libraries, totaling approximately 13 million compounds, using custom filters developed in-house. Compounds were filtered based on Lipinski's rule of five, with exceptions occurring in only 62,000 compounds. Further, structurally redundant compounds were removed such that the resulting library contained a diverse, yet manageable set of about 2 million compounds. Prior to screening, compounds were prepared using the LigPrep module of the Schrodinger Suite as well as ICM's inbuilt preparation of three-dimensional (3D) ligands such that physiologically relevant protonation states were used.

Prepared ligands were then docked against three different sites on LSD1; the FAD site located in the amine oxidase domain, and the adenine dinucleotide and flavin fragments of this pocket. The docking protocols used by both ICM and Glide were run with the FAD, adenine dinucleotide, flavin fragments, and known LSD1 inhibitors to check for accuracy. In addition to the docking algorithm rankings, visual inspection of the docking results were used to evaluate binding position, suitable pose, and orientation. Taken together, the scoring functions from ICM and Glide were able to correctly identify known inhibitors within the top 2% of the decoy set used. GOLD was used to re-score and the GOLD fitness function produced similar enrichments.
A virtual screen was set up against the FAD-binding pocket of LSD1 using the established docking protocol and the 2 million-compound database. The top 10,000 compounds were selected from both ICM and Glide scoring functions for further analysis. A few identical compounds were scored similarly between the two algorithms; this redundancy was filtered out. Furthermore, visual inspection was performed to filter out similar compounds and to increase the diversity of the final selection. Visual analysis also allowed identification of key interactions within the FAD-binding pocket of LSD1. These include hydrogen bonding with Ser289, Arg310 and Arg316, van der Waals interactions with Val590 and Leu625, and π interactions with Trp756. Moreover, compounds with hydroxyl and hydrophobic electron withdrawing groups seemed to show increased enrichment in the initial docking results. The FAD-binding pocket of LSD1 is a deep and narrow crevice in the interior of the protein and is surrounded by hydrophobic amino acid residues. Thus the hydrophobic character of the compounds may play an important role in the random walk of the compound into the active site.

Based on the selection criteria discussed above, 121 structurally distinct compounds were procured and submitted for biochemical screening against LSD1. The biochemical assay, as described in the experimental section, measures \( \text{H2O2} \) produced from the oxidative demethylation of a peptide substrate. From the 121 compounds, a series of related compounds, which showed potent activity in the biochemical assay, were identified. Structures for the series are presented in Table 1.

Table 1.

<table>
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<tr>
<th>No.</th>
<th>Structure</th>
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</table>
In a further aspect, the compounds produced exhibit inhibition of a histone demethylase. In a still further aspect, the histone demethylase is a member of the lysine-specific ("LSD") family of histone demethylases. In yet another aspect, the histone demethylase is LSD1. In an even further aspect, the histone demethylase is LSD2. In a still further aspect, the compound produced exhibits inhibition of cell viability.

In a further aspect, the compounds produced exhibit inhibition with an IC$_{50}$ of less than about 1.0 x 10$^{-4}$ M. In a still further aspect, the compound produced exhibits inhibition with an IC$_{50}$ of less than about 1.0 x 10$^{-5}$ M. In a yet further aspect, the compound produced exhibits inhibition with an IC$_{50}$ of less than about 1.0 x 10$^{-6}$ M. In an even further aspect, the compound produced exhibits inhibition with an IC$_{50}$ of less than about 1.0 x 10$^{-7}$ M. In a still further aspect, the compound produced exhibits inhibition with an IC$_{50}$ of less than about 1.0 x 10$^{-8}$ M. In a yet further aspect, the compound produced exhibits inhibition with an IC$_{50}$ of less than about 1.0 x 10$^{-9}$ M.

5. Example Method of Preparation

SCHEME 1. PREPARATION OF 4-CHLORO-2-((5-(MORPHOLINOSULFONYL)-1H-BENZO[D]IMIDAZOL-2-YL)AMINO)PHENOL (COMPOUND 1)
**PREPARATION OF 2-CHLORO-1H-BENZO[D]IMIDAZOL-5-AMINE**

[0174] PROCEDURE: 2-chloro-5-nitro-1H-benzo[d]imidazole (200 mg, 1.012 mmol) is slurried with ethanol (6 mL), water (2 mL), and dimethylformamide (0.5 mL). Iron (283 mg, 5.06 mmol), and ammonium chloride (271 mg, 5.06 mmol) were added and the reaction mixture was heated to reflux for 30 min. The crude mixture was filtered and the resulting filtrate was concentrated and the compound was purified by flash column chromatography (2% CH₂OH/CH₂Cl₂) afforded the title compound 2-chloro-1H-benzo[d]imidazol-5-amine (150 mg, 0.877 mmol, 87% yield) as a solid. Proton nuclear magnetic resonance ("¹H NMR") (400 MHz, DMSO-d₆): δ 7.14 (d, 1H, J = 8.4 Hz), 6.56 (s, 1H), 6.49 (d, 1H, J = 8.8 Hz), 4.92 (bs, 2H).

**PREPARATION OF 2-CHLORO-1H-BENZO[D]IMIDAZOLE-5-SULFONYL CHLORIDE.**

[0175] PROCEDURE: 2-chloro-1H-benzo[d]imidazol-5-amine (100 mg, 0.597 mmol) was dissolved in acetonitrile (10 ml) and after cooling to -10 °C, acetic acid (0.600 ml) and hydrochloric acid, 37% (0.400 ml) were added. To the mixture was added a solution of Sodium nitrite (53.5 mg, 0.776 mmol) in water (0.4 mL). After stirring at -10 °C for 30 min, SO₂ gas was bubbled in over 10 minutes and a solution of copper (II) chloride (104 mg, 0.776 mmol) in water (0.4 mL) was added drop wise. The mixture was allowed to warm to room temperature and stir for 16 h. The reaction mixture was diluted with water and extracted with ethyl acetate (25 mL). The organic layer was washed with saturated sodium bicarbonate, dried over sodium
sulfate, filtered and evaporated to dryness to give the product 2-chloro-lH-benzo[d]imidazole-5-sulfonyl chloride (77 mg, 0.301 mmol, 50.4 % yield) as a syrup. The product was used for further reaction without purification.

**PREPARATION OF 4-((2-CHLORO-1H-BENZO[D]IMIDAZOL-5-YL)SULFONYL)MORPHOLINE.**

[0176] PROCEDURE: morpholine (10.41 mg, 0.119 mmol) was added to the 2-chloro-lH-benzo[d]imidazole-5-sulfonyl chloride (25 mg, 0.100 mmol) in presence of potassiumcarbonate (27.5 mg, 0.199 mmol) in tetrahydrofuran (10 mL) at room temperature and the reaction mixture was stirred for 12 h at room temperature. The reaction was monitored by thin layer chromatography, after completion of the reaction, Solvent was removed by vacuum and then compound was purified by column chromatography (5% methanol/dichloromethane) afforded the product 4-((2-chloro-lH-benzo[d]imidazol-5-yl)sulfonyl)morpholine (13 mg, 0.041 mmol, 41.1 % yield) as a solid. 1HNMR (400 MHz, CDC13): δ 7.88 (s, 1H), 7.57-7.54 (m, 2H), 3.67 (m, 4H), 2.93 (m, 4H).

**PREPARATION OF 4-CHLORO-2-((5-(MORPHOLINOSULFONYL)-1H-BENZO[D]IMIDAZOL-2-YL)AMINO)PHENOL (COMPOUND 1).**

[0177] PROCEDURE: A mixture of 4-((2-chloro-lH-benzo[d]imidazol-5-yl)sulfonyl)morpholine (10 mg, 0.033 mmol) and 2-amino-4-chlorophenol (4.76 mg, 0.033 mmol) was dissolved in anhydrous THF (2 mL) and then the reaction mixture was heated via microwave irradiation to 150 °C for 5 h. The cooled crude product mixture was boiled with diluted hydrochloric acid and filtered. The filtered solid was then washed with dilute sodium hydroxide solution, then with water and dried. The resulting crude material was purified by flash column chromatography (5% CH₃OH/CH₂Cl₂) afforded the title compound 4-chloro-2-((5-(morpholinosulfonfonyl)-lH-benzo[d]imidazol-2-yl)amino)phenol (5.6 mg, 0.013 mmol, 40.5 % yield) as a solid. 1HNMR (400 MHz, CDC13): δ 7.65 (s, 1H), 7.47 (m, 1H), 7.44 (d, 1H, J = 8.4
Hz), 7.35 (d, 1H, J = 8.0 Hz), 6.91 (d, 1H, J = 9.2 Hz), 6.84 (d, 1H, J = 8.0 Hz), 3.70 (m, 4H), 2.95 (m, 4H). ESI-MS: 409.08 [M+H]+.

**PREPARATION OF 4-CHLORO-2-((5-((4-METHYLPIPERAZIN-1-YL)-SULFONYL)-1H-BENZO[D]IMIDAZOL-2-YL)AMINO)PHENOL (2)**

[0178] PROCEDURE Step 1: 1-methylpiperazine (29.6 mg, 0.296 mmol) was added to a solution of 2-((5-chloro-2-methoxyphenyl)amino)-1H-benzo[d]imidazole-5-sulfonyl chloride (100 mg, 0.269 mmol) in THF (10 mL) at 20 °C and the reaction mixture was stirred for 10 min, and then Zinc dust (35.1 mg, 0.537 mmol) was added to the reaction mixture and stirred at room temperature for 12 h. Reaction mixture was monitored by TLC, after completion of the reaction, reaction mixture was filtered, the filtrate was concentrated and the residue was purified by column chromatography (5% methanol/DCM) to obtained the product N-(5-chloro-2-methoxyphenyl)-5-((4-methylpiperazin-1-yl)sulfonyl)-1H-benzo[d]imidazol-2-amine (45 mg, 0.098 mmol, 36.5 % yield) as a solid. 1H NMR (400 MHz, CDC13): δ 8.22 (d, 1H, J = 2.4 Hz), 7.67 (s, 1H), 7.41 (dd, 1H, J = 1.6 & 8.8 Hz), 7.32 (d, 1H, J = 8.4 hz), 6.83 (dd, 1H, J = 2.4 & 8.4 Hz), 6.64 (d, 1H, J = 9.2 Hz), 3.69 (s, 3H), 3.01 (m, 4H), 2.50 (m, 4H), 2.25 (s, 3H).

[0179] PROCEDURE Step 2: A solution of N-(5-chloro-2-methoxyphenyl)-5-((4-methylpiperazin-1-yl)sulfonyl)-1H-benzo[d]imidazol-2-amine (45 mg, 0.103 mmol) in anhydrous DCM (3 mL) was added to BBr3 (1.0 M in DCM, 0.344 mL) at -78 °C, then stirred at r.t. for overnight. Reaction mixture was monitored by TLC, after completion of the reaction, the resulting dark brown solution was quenched with NaHCO3. Reaction mixture was extracted with DCM and dried, the residue was purified by column chromatography (5% methanol/DCM)
to obtain the product 4-chloro-2-((5-((4-methylpiperazin-1-yl)sulfonyl)-1H-benzo[d]imidazol-2-yl)amino)phenol (2) (16 mg, 0.037 mmol, 35.6 % yield) as a solid. 1H NMR (400 MHz, CD30D): δ 8.14 (d, 1H, J = 2.4 Hz), 7.74 (s, 1H), 7.49 (m, 2H), 6.88 (dd, 1H, J = 2.4 & 8.4 Hz), 6.82 (d, 1H, J = 8.8 Hz), 3.02 (m, 4H), 2.50 (m, 4H), 2.24 (s, 3H).

ESI-MS: 422.0 [M+H]+.

6. General Biochemical and Cell Materials and Methods

[0180] LSD1 activity was determined using a LSD1 Inhibitor Screening Assay Kit (Cayman Chemical Item Number 700120) purchased from Cayman Chemical Company (Ann Arbor, Michigan). Recombinant (expressed in baculovirus infected BTI insect cells) monoamine oxidase A and monoamine oxidase B (Catalog No. M73 16 and M7441, respectively) were purchased from Sigma-Aldrich Co. LLC. (St. Louis, Missouri). MAO-GloTM Assay Kit was purchased from Promega Corporation (Madison, Wisconsin). ATPlite™ Luminescence Assay System (e.g. Catalog No. V1401) was purchased from PerkinElmer Inc. (Waltham, Massachusetts).

7. Cell Culture

[0181] Cancer cell lines were obtained from ATCC. Cells were cultured according to the procedures provided. Cell-lines used included those shown in Table 2 below. In addition to the supplements indicated in Table 2, media were also supplemented with 1% penicillin/streptomycin (100 IU/mL pencillin and 100 µg/mL streptomycin). Cells were cultured at 37 °C and 5% CO₂. ATCC is the American Type Culture Collection (Manassas, Virginia).

<table>
<thead>
<tr>
<th>Cell-line</th>
<th>ATCC® Number</th>
<th>Organ/tissue/pathology*</th>
<th>Culture Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN3 CA</td>
<td>HTB-1 11™</td>
<td>Uterine / endometrium / adenocarcinoma</td>
<td>Eagle's Minimum Essential Medium supplemented with 10% FCS**</td>
</tr>
<tr>
<td>BT-20</td>
<td>HTB-19™</td>
<td>Breast / carcinoma</td>
<td>Eagle's Minimum Essential Medium supplemented with 10% FCS</td>
</tr>
<tr>
<td>Cell-line</td>
<td>ATCC® Number</td>
<td>Organ/tissue/pathology*</td>
<td>Culture Media</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>BT-549</td>
<td>HTB-122™</td>
<td>Breast / ductal carcinoma</td>
<td>RPMI-1640 Medium supplemented with 0.023 IU/ml insulin and 10% FCS</td>
</tr>
<tr>
<td>HCT 116</td>
<td>CCL-247™</td>
<td>Colon / colorectal carcinoma</td>
<td>McCoy’s 5a Medium</td>
</tr>
<tr>
<td>HER218***</td>
<td>Not applicable</td>
<td>Breast / adenocarcinoma</td>
<td>RPMI-1640 Medium supplemented and 10% FCS</td>
</tr>
<tr>
<td>MCF7</td>
<td>HTB-22™</td>
<td>Breast / adenocarcinoma</td>
<td>Eagle’s Minimum Essential Medium supplemented with 0.01 mg/ml bovine insulin and 10% FCS.</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>HTB-26™</td>
<td>Breast / adenocarcinoma</td>
<td>Leibovitz’s L-15 Medium supplemented with 10% FCS</td>
</tr>
<tr>
<td>MDA-MB-435S</td>
<td>HTB-129™</td>
<td>Pleural effusion; likely melanoma</td>
<td>Leibovitz’s L-15 Medium supplemented with 0.01 mg/ml bovine insulin, •0.01 mg/ml glutathione, and 10% FCS.</td>
</tr>
<tr>
<td>MDA-MB-468</td>
<td>HTB-132™</td>
<td>Breast / adenocarcinoma</td>
<td>Leibovitz’s L-15 Medium supplemented with 10% FCS</td>
</tr>
<tr>
<td>PANC-1</td>
<td>CRL-1469™</td>
<td>Pancreas / duct / epithelioid carcinoma</td>
<td>Dulbecco’s Modified Eagle’s Medium supplemented with 10% FCS</td>
</tr>
<tr>
<td>PC-3</td>
<td>CRL-1435™</td>
<td>Prostate adenocarcinoma</td>
<td>F-12K Medium supplemented with 10% FCS</td>
</tr>
<tr>
<td>Cell-line</td>
<td>ATCC® Number</td>
<td>Organ/tissue/pathology*</td>
<td>Culture Media</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>SK-N-MC</td>
<td>HTB-10™</td>
<td>Brain / neuroepithelioma</td>
<td>Eagle's Minimum Essential Medium supplemented with 10% FCS</td>
</tr>
<tr>
<td>T-47D</td>
<td>HTB-133™</td>
<td>Breast / ductal carcinoma</td>
<td>RPMI-1640 Medium supplemented with 0.2 units/ml bovine insulin and 10% FCS</td>
</tr>
<tr>
<td>U-87 MG</td>
<td>HTB-14™</td>
<td>Brain / glioblastoma, astrocytoma</td>
<td>Eagle's Minimum Essential Medium supplemented with 10% FCS</td>
</tr>
</tbody>
</table>

* All organ/tissue sources were of human origin.

** FCS is Fetal Calf Serum


8. **Lsd1 Histone Demethylase Assay**

[0182] The primary assay for compound inhibitory activity was the LSD1 Inhibitor Screening Assay Kit (Cayman Chemical Company, Ann Arbor, Michigan; Cayman Chemical Item Number 700120). Briefly, test compounds were diluted to 20X the desired test concentration in 100% DMSO and 2.5 μL of the diluted drug sample was added to a black 384-well plate. The LSD1 enzyme stock was diluted 17-fold with assay buffer and 40 μM of the diluted LSD1 enzyme was added to the appropriate wells. The reaction mixture comprised horseradish peroxidase, dimethyl K4 peptide (corresponding to the first 21 amino acids of the N-terminal tail of histone H3), and 10-acetyl-3,7-dihydroxyphenoxazine was then added to wells. Generation of resorufin (generated by reacting with H₂O₂ produced in the reaction) was analyzed on an Envision microplate reader with an excitation wavelength of 530nm and an emission wavelength of 595nm.

9. **Monoamine Oxidase ("Mao")Assay**

[0183] Inhibition of monoamine oxidase activity was carried using the MAO-Glo™ Assay Kit according to the manufacturer's suggested protocol. Briefly, 6.25 μL of test compound was
added to each well of a 384-well plate. Enzyme (either MAO A or B) was added (12.5 µL in 2x buffer containing 1 µg protein) and allowed to incubate for 5 minutes. Finally, 6.25 µL of 4x MAO substrate was added to each well. Following a one hour incubation, 25 µL of Luciferin detection reagent was added to each well, and incubated for 20 minutes. Luminescence was then measured on an Envision microplate reader.

10. Cell Viability Assay

[0184] Cell viability was determined using ATPlite™ Luminescence Assay System (PerkinElmer Inc., Waltham, Massachusetts) using the various cell-lines described above and in Table 2. Briefly, cells were seeded in 96-well plates and then treated with different concentrations of inhibitor (0.1% final DMSO concentration). After 96-hours of incubation, ATPlite detection reagent was added directly to the culture well. Luminescence was read 5 minutes later on an Envision microplate reader.

11. Real-Time PCR

[0185] Briefly, T-47D cells were seeded in 96-well plates and treated with concentrations of inhibitors as indicated. Cell lysates, Reverse transcription, and single color syber green real time PCR was performed using the Cells-to-Ct kit (Life Technologies). Transcript levels of heme oxygenase (HMOX) were normalized to hypoxanthine phosphoribosyltransferase (HPRT) and β-actin. The primers used in real-time PCR are shown below in Table 3.

<table>
<thead>
<tr>
<th>Primer Designation</th>
<th>Amplification Target</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMOX_F</td>
<td>Heme oxygenase</td>
<td>AACTTTCAAGGGCCAGGT</td>
</tr>
<tr>
<td>HMOX_R</td>
<td>Heme oxygenase</td>
<td>GTAGACAGGGCGAAGACTG</td>
</tr>
<tr>
<td>HPRT_F</td>
<td>Hypoxanthine</td>
<td>TGCTGAGGATTTGGAAAGG</td>
</tr>
<tr>
<td>HPRT_R</td>
<td>Hypoxanthine</td>
<td>CCTTGAGCACACAGGGCTAC</td>
</tr>
<tr>
<td>B-Actin_F</td>
<td>β-actin</td>
<td>CTGGAACGGTGAAAGGTGACA</td>
</tr>
<tr>
<td>B-Actin_R</td>
<td>β-actin</td>
<td>AAGGGACTTCTGTAACAACGCA</td>
</tr>
</tbody>
</table>
[0186] The ASCII text file "Sequence.txt" created on December 10, 2013, having the size of 2
KB, is incorporated by reference into the specification.

12. IC50 Calculation

[0187] IC50 values are determined using GraphPad Prism 5 software. The data were entered as
an X-Y plot into the software as percent inhibition for each concentration of the drug. The
concentration values of the drug were log transformed and the nonlinear regression was carried
out using the "sigmoidal dose-response (variable slope)" option within the GraphPad software to
model the data and calculate IC50 values. The IC50 values reported are the concentration of drug
at which 50% inhibition was reached (Figure 1, Compound 2).

13. Prophetic In Vivo Anti-Tumor Effects: Cell-line Xenograft Model

[0188] The following example of the in vivo effect of the disclosed compounds are prophetic.
Generally agents which modulate the regulation of chromatin, including histone demethylase
inhibitors, display efficacy in preclinical models of cancer. In vivo effects of the compounds
described in the preceding examples are expected to be shown in various animal models of
cancer known to the skilled person, such as tumor xenograft models. These models are typically
conducted in rodent, most often in mouse, but may be conducted in other animal species as is
convenient to the study goals. Compounds, products, and compositions disclosed herein are
expected to show in vivo effects in various animal models of cancer known to the skilled person,
such as mouse tumor xenograft models.

[0189] In vivo effects of compounds can be assessed with in a mouse tumor xenograft study, one
possible study protocol is described herein. Briefly, cells (2 to 5 x 10^6 in 100 mL culture media)
were implanted subcutaneously, e.g. by subcutaneous injection, in the right hind flank of athymic
nu/nu nude mice (5 to 6 weeks old, 18-22 g). For test compounds of the present invention, a
typical cell-line used for the tumor xenograft study would be AN3 CA or BT-20. Other suitable
cell-lines for these studies are BT-549, HCT 116, HER218, MCF7, MDA-MB-231, MDA-MB-
The cells are cultured prior to harvesting for this protocol as described herein.

[0190] Following implantation, the tumors are allowed to grow to about 100 mm^3, typically
about 6-18 days post-implantation, before the animals are randomized into treatment groups (e.g.
vehicle, positive control and various dose levels of the test compound); the number of animals
per group is typically 8-12. Day 1 of study corresponds to the day that the animals receive their
first dose. The efficacy of a test compound can be determined in studies of various length dependent upon the goals of the study. Typical study periods are for 14, 21 and 28-days. The dosing frequency (e.g. whether animals are dosed with test compound daily, every other day, every third day or other frequencies) is determined for each study depending upon the toxicity and potency of the test compound. A typical study design would involve dosing daily (M-F) with the test compound with recovery on the weekend. Throughout the study, tumor volumes and body weights are measured twice a week. At the end of the study the animals are euthanized and the tumors harvested and frozen for further analysis. Alternatively, tumors may be processed immediately for analysis, e.g. fixed in buffered-formalin, paraffin embedded, and sectioned for hematoxylin/eosin staining and further immunohistochemical analysis for desired oncology markers.  

[0191] For example, compounds having a structure represented by a formula having a structure represented by Formula I and II, or a pharmaceutically acceptable salt, solvate, polymorph, hydrate and the stereochemically isomeric form thereof, are expected to show such in vivo effects.

14. Prophetic In Vivo Anti-Tumor Effects: Tumor Graft Model

[0193] Briefly, tissue samples will be collected from informed, consented patients at Huntsman Cancer Hospital/University of Utah under an approved IRB protocol. Samples will be collected and de-identified by the Huntsman Cancer Institute Tissue Resource and Application Core facility before being obtained for implantation. It is anticipated that all primary tumors will be from individuals that had not received chemotherapy prior to tissue collection, and and all metastatic effusions will be from individuals that had been treated with chemotherapy, hormone therapy, and/or radiation therapy. The University of Utah Institutional Animal Care and Use Committee will review and approve all mouse experiments. It is anticipated that a minimum of three mice per experimental group will be used, and only female mice will be used for studies involving breast cancer tumors. A single fragment of fresh or frozen tumor (~8 mm3), or about 10^6 cells in matrigel, is implanted into cleared inguinal mammary fat pads of 3-4 week old female NOD/SCID mice. At the same, interscapular estrogen pellets are subcutaneously implanted in mice with ER+ tumors. Tumor growth is measured weekly using calipers. When tumors reach about 150-2,000 mm^3, the mice are euthanized, and tissue fragments are re-transplanted into another cohort of mice, frozen for later use, and/or analyzed for histology, gene expression, and DNA copy number. Tumor volumes are calculated using the formula 0.5 × length × (width)^2. For experiments to determine estrogen dependence, ER+ tumors are implanted into mice as described above, in the presence or absence of intrascapular estrogen pellets and with or without a concurrent surgical procedure to remove the ovaries, which is performed according to standard methods.

[0194] Freshly harvested tumor tissues from patients or mice are cut into ~8 mm3 pieces and stored in liquid nitrogen, in a solution of 95% FBS and 5% DMSO for later implantation. Alternatively, the tissue is digested with collagenase solution (1 mg/ml collagenase [Type IV, Sigma] in RPMI 1640 supplemented with 2.5% FBS, 10 mM HEPES, 10 μg/mL penicillin-streptomycin) at 37°C for 40-60 min, while shaking at 250 rpm. Digested tissue is strained to remove debris and washed in human breast epithelial cell (HBEC) medium (DMEM F/12 supplemented with 10 mM HEPES, 5% FBS, 1 mg/mL BSA, 0.5 μg/mL hydrocortisone, 50 μg/mL Gentamycin, 1 μg/mL ITS-X100) three times. The pellet is resuspended in freezing medium (5% FBS and 10% DMSO in HBEC medium) and stored in liquid nitrogen.

[0195] To assess the effect of a disclosed compound, tumors in mice are allowed to grow to about 100 mm^3, typically about 6-18 days post-implantation, before the animals are randomized
into treatment groups (e.g. vehicle, positive control and various dose levels of the test compound); the number of animals per group is typically 8-12. Day 1 of study corresponds to the day that the animals receive their first dose. The efficacy of a test compound can be determined in studies of various length dependent upon the goals of the study. Typical study periods are for 14, 21 and 28-days. The dosing frequency (e.g. whether animals are dosed with test compound daily, every other day, every third day or other frequencies) is determined for each study depending upon the toxicity and potency of the test compound. A typical study design would involve dosing daily (M-F) with the test compound with recovery on the weekend. Throughout the study, tumor volumes and body weights are measured twice a week. At the end of the study the animals are euthanized and the tumors harvested and frozen for further analysis. Alternatively, tumors may be processed immediately for analysis, e.g. fixed in buffered-formalin, paraffin embedded, and sectioned for hematoxylin/eosin staining and further immunohistochemical analysis for desired oncology markers.

[0196] For example, compounds having a structure represented by a formula having a structure represented by Formula I and II, or a pharmaceutically acceptable salt, solvate, polymorph, hydrate and the stereochemically isomeric form thereof, are expected to show such in vivo effects.

15. Prophetic Pharmaceutical Composition Examples

[0197] "Active ingredient" as used throughout these examples relates to one or more compounds having a structure represented by Formula I and II, or a pharmaceutically acceptable salt, solvate, polymorph, hydrate and the stereochemically isomeric form thereof. The following examples of the formulation of the compounds of the present invention in tablets, suspension, injectables and ointments are prophetic.

[0198] Typical examples of recipes for the formulation of the invention are as given below. Various other dosage forms can be applied herein such as a filled gelatin capsule, liquid emulsion/suspension, ointments, suppositories or chewable tablet form employing the disclosed compounds in desired dosage amounts in accordance with the present invention. Various conventional techniques for preparing suitable dosage forms can be used to prepare the prophetic pharmaceutical compositions, such as those disclosed herein and in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.) and Martindale The Extra Pharmacopoeia (London The Pharmaceutical Press).
The disclosure of this reference is hereby incorporated herein by reference.

a. Pharmaceutical Composition for Oral Administration

A tablet can be prepared as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>10 to 500 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>100 mg</td>
</tr>
<tr>
<td>Crystalline cellulose</td>
<td>60 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td>Starch (e.g. potato starch)</td>
<td>Amount necessary to yield total weight indicated below</td>
</tr>
<tr>
<td>Total (per capsule)</td>
<td>1000 mg</td>
</tr>
</tbody>
</table>

Alternatively, about 100 mg of a disclosed compound, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (e.g. from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate are used per tablet. The mixture of active component, lactose and starch is granulated with a 5% solution (m/m) of the PVP in water. After drying, the granules are mixed with magnesium stearate for 5 min. This mixture is moulded using a customary tablet press (e.g. tablet format: diameter 8 mm, curvature radius 12 mm). The moulding force applied is typically about 15 kN.

Alternatively, a disclosed compound can be administered in a suspension formulated for oral use. For example, about 100-5000 mg of the desired disclosed compound, 1000 mg of ethanol (96%), 400 mg of xanthan gum, and 99 g of water are combined with stirring. A single dose of about 10-500 mg of the desired disclosed compound according can be provided by 10 ml of oral suspension.

In these Examples, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds. In some circumstances it may be desirable to use a capsule, e.g. a filled gelatin capsule, instead of a tablet form. The choice of tablet or capsule will depend, in part, upon physicochemical characteristics of the particular disclosed compound used.
Examples of alternative useful carriers for making oral preparations are lactose, sucrose, starch, talc, magnesium stearate, crystalline cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, glycerin, sodium alginate, gum arabic, etc. These alternative carriers can be substituted for those given above as required for desired dissolution, absorption, and manufacturing characteristics.

The amount of a disclosed compound per tablet for use in a pharmaceutical composition for human use is determined from both toxicological and pharmacokinetic data obtained in suitable animal models, e.g. rat and at least one non-rodent species, and adjusted based upon human clinical trial data. For example, it could be appropriate that a disclosed compound is present at a level of about 10 to 1000 mg per tablet dosage unit.

b. Pharmaceutical Composition for Injectable Use

A parenteral composition can be prepared as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>10 to 500 mg</td>
</tr>
<tr>
<td>Sodium carbonate</td>
<td>560 mg*</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>80 mg*</td>
</tr>
<tr>
<td>Distilled, sterile water</td>
<td>Quantity sufficient to prepare total volume indicated below.</td>
</tr>
<tr>
<td>Total (per capsule)</td>
<td>10 ml per ampule</td>
</tr>
</tbody>
</table>

*Amount adjusted as required to maintain physiological pH in the context of the amount of active ingredient, and form of active ingredient, e.g. a particular salt form of the active ingredient.

Alternatively, a pharmaceutical composition for intravenous injection can be used, with composition comprising about 100-5000 mg of a disclosed compound, 15 g polyethyleneglycol 400 and 250 g water in saline with optionally up to about 15% Cremophor EL, and optionally up to 15% ethyl alcohol, and optionally up to 2 equivalents of a pharmaceutically suitable acid such as citric acid or hydrochloric acid are used. The preparation of such an injectable composition can be accomplished as follows: The disclosed compound and the polyethyleneglycol 400 are dissolved in the water with stirring. The solution is sterile filtered (pore size 0.22 µm) and filled
into heat sterilized infusion bottles under aseptic conditions. The infusion bottles are sealed with rubber seals.

[0208] In a further example, a pharmaceutical composition for intravenous injection can be used, with composition comprising about 10-500 mg of a disclosed compound, standard saline solution, optionally with up to 15% by weight of Cremophor EL, and optionally up to 15% by weight of ethyl alcohol, and optionally up to 2 equivalents of a pharmaceutically suitable acid such as citric acid or hydrochloric acid. Preparation can be accomplished as follows: a desired disclosed compound is dissolved in the saline solution with stirring. Optionally Cremophor EL, ethyl alcohol or acid are added. The solution is sterile filtered (pore size 0.22 µm) and filled into heat sterilized infusion bottles under aseptic conditions. The infusion bottles are sealed with rubber seals.

[0209] In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

[0210] The amount of a disclosed compound per ampule for use in a pharmaceutical composition for human use is determined from both toxicological and pharmacokinetic data obtained in suitable animal models, e.g. rat and at least one non-rodent species, and adjusted based upon human clinical trial data. For example, it could be appropriate that a disclosed compound is present at a level of about 10 to 1000 mg per tablet dosage unit.

[0211] Carriers suitable for parenteral preparations are, for example, water, physiological saline solution, etc. which can be used with tris(hydroxymethyl)aminomethane, sodium carbonate, sodium hydroxide or the like serving as a solubilizer or pH adjusting agent. The parenteral preparations contain preferably 50 to 1000 mg of a disclosed compound per dosage unit.

[0212] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.
[0213] The disclosed embodiments and examples are simply exemplary embodiments and examples of the inventive concepts disclosed herein and should not be considered as limiting, unless so stated.
What is claimed is:

1. A compound of Formula I

\[ \text{Yielding formula image} \]

wherein:

- \( m \) is 0 or 1,
- \( n \) is 0 or 1,
- \( X \) is selected from the group consisting of -CH and -N;
- \( Y \) is selected from the group consisting of -NH, -NCH\(_3\), -NCH\(_2\)CH\(_3\), -O and -S;
- \( R_i \) is selected from the group consisting of -H, -CH\(_3\) and -CH\(_2\)CH\(_3\);
- \( R_2 \) and \( R_4 \) are independently selected from the group consisting of -H, -CH\(_3\), -OH, -NH\(_2\), halo, -CF\(_3\), OCF\(_3\), -OCH\(_3\) and -CN;
- \( R_3 \) is selected from the group consisting of -H, -CH\(_3\), -OH, -NH\(_2\), a halo, -CF\(_3\), OCF\(_3\), -OCH\(_3\), CN, -CONHR\(_s\) and -NHCOR\(_s\);
- \( R_5 \) is selected from the group consisting of -H, -CH\(_3\), -CH\(_2\)CH\(_3\), -C\(_1\)-, a cycloalkyl and a halo;
- \( R_6 \) is selected from the group consisting of -H and -CH\(_3\);
- \( R_7 \) is selected from the group consisting of -CH\(_3\), -NH\(_2\), -NCH\(_3\), a Ci\(_6\)-alkyl, a Ci\(_6\)-cycloalkyl, a halo-Ci\(_6\)-alkyl, a cycloalkyl, a Ci\(_6\)-heterocycloalkyl, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, azepanyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperazinyl, oxazinanyl, morpholinyl, hexahydrophymidinyl, hexahydropyridazinyl and an optionally substituted moiety selected from the group consisting of:
R₈ is selected from the group consisting of -H, C₁₆ alkyl, C₃-6 cycloalkyl and C₃-6 heterocycloalkyl;
or a pharmaceutically acceptable salt, hydrochloric acid, sulphate, methanesulfonic acid or benzene sulfonic acid thereof.

2. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 as an active agent in said composition and a pharmaceutically acceptable carrier.

3. A method for the treatment of a disorder of uncontrolled cellular proliferation in a mammal, the method comprising the step of administering to the mammal an effective amount of a compound of claim 1.

4. A method for treatment of a mammalian disorder in which lysine-specific demethylase 1 (LSD1) levels are elevated comprising administering to a patient in need thereof an effective amount of a compound of claim 1.

5. A method for decreasing histone demethylase activity in a mammal, the method comprising the step of administering to the mammal an effective amount of a compound of claim 1.

6. A compound selected from the group consisting of:
or a pharmaceutically acceptable salt, hydrochloric acid, sulphate, methanesulfonic acid or benzene sulfinic acid thereof.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 6 as an active agent in said composition and a pharmaceutically acceptable carrier.
8. A method for the treatment of a disorder of uncontrolled cellular proliferation in a mammal, the method comprising the step of administering to the mammal an effective amount of a compound of claim 6.

9. A method for treatment of a mammalian disorder in which lysine-specific demethylase 1 (LSD1) levels are elevated comprising administering to a patient in need thereof an effective amount of a compound of claim 6.

10. A method for decreasing histone demethylase activity in a mammal, the method comprising the step of administering to the mammal an effective amount of a compound of claim 6.

11. A compound having a structure represented by a formula:

![Chemical Structure](image)

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 11 as an active agent in said composition and a pharmaceutically acceptable carrier.

13. A method for the treatment of a disorder of uncontrolled cellular proliferation in a mammal, the method comprising the step of administering to the mammal an effective amount of a compound of claim 11.

14. A method for treatment of a mammalian disorder in which lysine-specific demethylase 1 (LSD1) levels are elevated comprising administering to a patient in need thereof an effective amount of a compound of claim 11.

15. A method for decreasing histone demethylase activity in a mammal, the method comprising the step of administering to the mammal an effective amount of a compound of claim 11.