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POTENT AND SELECTIVE HDAC6 MACROCYCLIC INHIBITORS

Abstract

The present disclosure is generally directed to macrocyclic oligoamides useful in the inhibition of HDAC6, and methods for treating diseases that are ameliorated by the inhibition of HDAC6.

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS [0001] This application claims the benefit of priority of U.S. Provisional Application No. 63/333,077, filed Apr. 20, 2022, and incorporated herein by reference in its entirety.

FIELD OF DISCLOSURE

[0002] The present disclosure is generally directed to small macrocyclic oligoamides that are potent inhibitors of histone deacetylase 6 (HDAC6) and methods of using them.

BACKGROUND

[0003] Histone deacetlyases (HDACs) are enzymes that deactylate lysine residues from histones as well as from several other nuclear, cytoplasmic and mitochondrial non-histone proteins. The role they play in regulating gene expression has made them therapeutic targets, for example as targets for antitumor agents, as they can induce various cellular effects such as apoptosis, cell cycle arrest, and inhibition of angiogenesis. Further, HDAC6 modulation has been found to promote neuroprotection in neurons as well as affect cellular response to oxidative stress. Thus, there is substantial interest in developing potent and selective therapeutics that modulate HDAC6 behavior.

SUMMARY

[0004] One aspect of the disclosure provides oligoamide compounds of formula (I): ##STR00001## [0005] or a pharmaceutically acceptable salt thereof, wherein [0006] L is C.sub.1-C.sub.6alkylene; [0007] R is —SH, —OH, —NH.sub.2, —CONH—OH, —CO.sub.2H, or —SO.sub.2NH.sub.2; [0008] R.sub.1 is hydrogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, hydroxy(C.sub.1-C.sub.6 alkyl), amino(C.sub.1-C.sub.6 alkyl), or benzyl; [0009] R.sub.2 is hydrogen or C.sub.1-C.sub.6 alkyl; or R.sub.1 and R.sub.2 together with the atoms to which they are attached, form a pyrrolidine ring optionally substituted with one or two R.sub.3; [0010] each R.sub.3 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy; [0011] X is C, CH, or CH.sub.2, and Y is C, CH, or CH.sub.2, where X and Y, together with the atoms to which they are attached, form a 10- to 20-member macrocycle, the macrocycle optionally substituted with one or more R.sub.4, and/or optionally fused with a phenyl, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic cycloalkyl, or bicyclic cycloalkyl moiety, each moiety optionally substituted with one or two R.sub.5, wherein [0012] each R.sub.4 is independently selected from the group consisting of halogen, —NO.sub.2, —CN, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, C.sub.1-C.sub.6 haloalkoxy, hydroxy(C.sub.1-C.sub.6 alkyl), hydroxy(C.sub.1-C.sub.6 alkoxy), alkoxy(C.sub.1-C.sub.6 alkyl), alkoxy(C.sub.1-C.sub.6 alkoxy), amino(C.sub.1-C.sub.6 alkyl), —CO.sub.2H, —CO.sub.2(C.sub.1-C.sub.6 alkyl), —CO(C.sub.1-C.sub.6 alkyl), carboxy(C.sub.1-C.sub.6 alkyl), —CONH.sub.2, —CONH(C.sub.1-C.sub.6 alkyl), —CON(C.sub.1-C.sub.6 alkyl).sub.2, —(C.sub.1-C.sub.6 alkyl)-CONH.sub.2,1H-imidazol-4-yl-methyl, or phenyl(C.sub.0-C.sub.1 alkyl) optionally substituted with one or more of halogens or —OH, or two R.sub.4 groups, together with the carbon to which they are attached, form a ═O, [0013] each R.sub.5 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy.

[0014] In another aspect, the present disclosure provides for a method of treating a disease that is ameliorated by the inhibition of histone deacetylase 6 (HDAC6), the method comprising administering to a subject in need of such treatment one or more compounds as otherwise described herein or a pharmaceutical composition as otherwise described herein.

[0015] In another aspect, the present disclosure provides for a method of inhibiting HDAC6, the method comprising administering one or more compounds as otherwise described herein or a pharmaceutical composition as otherwise described herein.

[0016] In another aspect, the present disclosure provides for use of one or more compounds as otherwise described herein or a pharmaceutical composition as otherwise described herein for treating a disease that is ameliorated by the inhibition of HDAC6.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] The accompanying drawings are included to provide a further understanding of the methods and compositions of the disclosure, and are incorporated in and constitute a part of this specification. The drawings illustrate one or more embodiment(s) of the disclosure and, together with the description, serve to explain the principles and operation of the disclosure.

[0018] FIG. **1**. Design of potent and selective macrocyclic inhibitors of HDAC6. (A) Schematic description of hash-assembly of macrocycles in the HDAC6 active site. Starting from a two residue hydrogen-bonding motif extracted from PDB 6WJS, candidate macrocycles are identified by rapidly searching for closures across all hydrogen-bond containing hash tables, building the resulting macrocycles in the pocket, and discarding candidates that clash with HDAC6. This search embeds the starting two-residue motif in nearly 38,000 possible macrocycles in only 4 hours on a single CPU core. Candidate macrocycles are then docked into the HDAC6 active site using Rosetta™ GALigandDock and prioritized for synthesis based on the quality of the resulting interface. In total we identified 2,700 candidate macrocycles that contain the two residue motif but do not clash with the protein, and selected 11 for synthesis based on the computed HDAC binding energy. Ten of the eleven chemically synthesized macrocycles displayed IC50s against HDAC6 ranging from 1.5 nM to 70 nM. The most potent and selective of these macrocycles are shown in B-E: Column I, chemical structure colored by chemotype; Column II, predicted model of macrocycle bound to HDAC6; Column III, Concentration dependence of inhibition of HDAC6, HDACs 1 (closed square), 2 (closed triangle), 3 (closed inverted triangle), 4 (closed diamond), 5 (open circle), 7 (open square), 8 (open triangle), 9 (open inverted triangle), 11(open diamond). The macrocycles show selectivity for HDAC6 over other HDACs ranging from 100-fold to greater than 1000-fold. Enzymatic inhibition assay was performed by Reaction Biology.

DETAILED DESCRIPTION

[0019] The present disclosure is generally directed to small macrocyclic oligoamides that are potent inhibitors of histone deacetylase 6 (HDAC6). Thus one aspect of the disclosure provides oligoamide compounds of formula (I):

##STR00002## [0020] or a pharmaceutically acceptable salt thereof, wherein [0021] L is C.sub.1-C.sub.6 alkylene; [0022] R is —SH, —OH, —NH.sub.2, —CONH—OH, —CO.sub.2H, or —SO.sub.2NH.sub.2; [0023] R.sub.1 is hydrogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, hydroxy(C.sub.1-C.sub.6 alkyl), amino(C.sub.1-C.sub.6 alkyl), or benzyl; [0024] R.sub.2 is hydrogen or C.sub.1-C.sub.6 alkyl; or R.sub.1 and R.sub.2 together with the atoms to which they are attached, form a pyrrolidine ring optionally substituted with one or two R.sub.3; [0025] each R.sub.3 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy; [0026] X is C, CH, or CH.sub.2, and Y is C, CH, or CH.sub.2, where X and Y, together with the atoms to which they are attached, form a 10- to 20-member macrocycle, the macrocycle optionally substituted with one or more R.sub.4, and/or optionally fused with a phenyl, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic cycloalkyl, or bicyclic cycloalkyl moiety, each moiety optionally substituted with one or two R.sub.5, wherein [0027] each R.sub.4 is independently selected from the group consisting of halogen, —NO.sub.2, —CN, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH,

C.sub.1-C.sub.6 alkoxy, C.sub.1-C.sub.6 haloalkoxy, hydroxy(C.sub.1-C.sub.6 alkyl), hydroxy(C.sub.1-C.sub.6 alkoxy), alkoxy(C.sub.1-C.sub.6 alkyl), alkoxy(C.sub.1-C.sub.6 alkoxy), amino(C.sub.1-C.sub.6 alkyl), —CO.sub.2H, —CO.sub.2(C.sub.1-C.sub.6 alkyl), —CO(C.sub.1-C.sub.6 alkyl), carboxy(C.sub.1-C.sub.6 alkyl), —CONH.sub.2, —CONH(C.sub.1-C.sub.6 alkyl), —CON(C.sub.1-C.sub.6 alkyl).sub.2, —(C.sub.1-C.sub.6 alkyl)-CONH.sub.2,1H-imidazol-4-yl-methyl, or phenyl(C.sub.0-C.sub.1 alkyl) optionally substituted with one or more of halogens or —OH, or two R.sub.4 groups, together with the carbon to which they are attached, form a ═O, [0028] each R.sub.5 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy.

[0029] As provided above, X and Y, together with the atoms to which they are attached, form a 10- to 20-member macrocycle. In certain embodiments, the macrocycle is a 15- to 20-member macrocycle. The macrocycle may include heteroatoms, such as N, O, and S, at any available position on the macrocycle (i.e., instead of a carbon atom). The macrolide may be optionally substituted with one or more R.sub.4 at any available atom, provided that the chemical valance is satisfied. In certain embodiments, the macrocycle may be optionally fused with a phenyl, monocyclic heteroaryl (e.g., triazole), monocyclic heterocyclyl, monocyclic cycloalkyl (e.g., cyclohexane) or bicyclic cycloalkyl moiety, provided that the chemical valance is satisfied.

[0030] In one embodiment, X and Y, together with the atoms to which they are attached, form a 10- to 20-member macrocycle optionally fused with a cyclohexane, pyrrolidine, benzene, and/or tetrahydroisoquinoline, and optionally substituted with one or more R.sub.4.

[0031] In one embodiment, X and Y, together with the atoms to which they are attached, form a 10- to 20-member macrocycle optionally fused with a cyclohexane, and optionally substituted with one or more R.sub.4.

[0032] In one embodiment, X and Y, together with the atoms to which they are attached, form a 10- to 20-member macrocycle optionally fused with a triazole, and optionally substituted with one or more R.sub.4.

[0033] In certain embodiments, the macrocycle is substituted with at least two R.sub.4 groups. For example, in certain embodiments, two R.sub.4 groups, together with the carbon to which they are attached, form ═O. In other embodiments, two R.sub.4 groups are each halogen (e.g., fluoro).

[0034] In certain embodiments, the

##STR00003##

portion of the macrocycle includes one or more of the following moieties, with the attachment from left to right or right to left:

##STR00004## ##STR00005## ##STR00006##

[0035] In certain embodiments, these moieties are optionally substituted with one or more R.sub.4.

Therapeutics Applications

[0036] The compounds of the disclosure are capable of inhibiting histone deacetylase 6 (HDAC6). Inhibition of HDAC6 may be either in vivo and/or in vitro. Accordingly, the disclosure provides methods for treating diseases that are ameliorated by the inhibition of HDAC6 providing to a patient in need of such treatment a therapeutically effective amount of either a compound of the disclosure (e.g., compounds formula (I)), or a pharmaceutical composition comprising one or more of compounds of the disclosure.

[0037] In certain embodiments, the diseases that are ameliorated by the inhibition of HDAC6 by the compounds of the present disclosure include neurodegenerative disorders. Examples include, but are not limited to, Alzheimer's disease, Parkinson's disease, Huntington's disease, Lewy body disease, Charcot-Marie-Tooth (CMT) disease, Rett Syndrome, progressive supranuclear palsy, amyotrophic lateral sclerosis, and frontotemporal dementia. In certain embodiments, the neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, or Huntington's disease.

[0038] In certain embodiments, the diseases that are ameliorated by the inhibition of HDAC6 by

the compounds of the present disclosure include cancer. In certain embodiments, the cancer is lymphoproliferative cancer. Examples of lymphoproliferative cancer include, but are not limited to, multiple myeloma, Hodgkin's lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, anaplastic cell lymphoma, chronic lymphocytic leukemia, peripheral T cell lymphoma, cutaneous T cell lymphoma. In certain embodiments, the cancer is ovarian cancer, breast cancer, bladder cancer, pancreatic cancer, esophageal cancer, colorectal cancer, stomach cancer, lung cancer, and liver cancer.

[0039] In certain embodiments, the diseases that are ameliorated by the inhibition of HDAC6 by the compounds of the present disclosure include heart diseases. Examples include, but are not limited to, diastolic dysfunction, coronary heart disease, cardiomyopathy, endocarditis, congenital cardiovascular defects, congestive heart failure, dilated cardiomyopathy, hypertropic cardiomyopathy, valvular heart disease, myocardial infarction, congestive heart failure, diastolic/systolic heart failure, atrial arrhythmia, ventricular arrhythmia, cardiac valve disease, and ischemia.

[0040] In certain embodiments, the disease that is ameliorated by the inhibition of HDAC6 by the compounds of the present disclosure includes sepsis-induced inflammation.

[0041] In certain embodiments, the diseases that are ameliorated by the inhibition of HDAC6 by the compounds of the present disclosure include kidney diseases.

Pharmaceutical Compositions

[0042] In another aspect, the present disclosure provides compositions comprising one or more of compounds as described above with respect to formula (I) and an appropriate carrier, excipient or diluent. The exact nature of the carrier, excipient or diluent will depend upon the desired use for the composition, and may range from being suitable or acceptable for veterinary uses to being suitable or acceptable for human use. The composition may optionally include one or more additional compounds. In certain embodiments, the composition may include one or more antibiotic compounds.

[0043] When used to treat or prevent such diseases, the compounds described herein may be administered singly, as mixtures of one or more compounds or in mixture or combination with other agents useful for treating such diseases and/or the symptoms associated with such diseases. The compounds may also be administered in mixture or in combination with agents useful to treat other disorders or maladies. The compounds may be administered in the form of compounds per se, or as pharmaceutical compositions comprising a compound.

[0044] Pharmaceutical compositions comprising the compound(s) may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making levigating, emulsifying, encapsulating, entrapping or lyophilization processes. The compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically.

[0045] The compounds may be formulated in the pharmaceutical composition per se, or in the form of a hydrate, solvate, N-oxide or pharmaceutically acceptable salt. Typically, such salts are more soluble in aqueous solutions than the corresponding free acids and bases, but salts having lower solubility than the corresponding free acids and bases may also be formed.

[0046] Pharmaceutical compositions may take a form suitable for virtually any mode of administration, including, for example, topical, ocular, oral, buccal, systemic, nasal, injection, transdermal, rectal, vaginal, etc., or a form suitable for administration by inhalation or insufflation.

[0047] For topical administration, the compound(s) may be formulated as solutions, gels, ointments, creams, suspensions, etc. Systemic formulations include those designed for administration by injection, e.g., subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal oral or pulmonary administration.

[0048] Useful injectable preparations include sterile suspensions, solutions or emulsions of the active compound(s) in aqueous or oily vehicles. The compositions may also contain formulating agents, such as suspending, stabilizing and/or dispersing agent. The formulations for injection may be presented in unit dosage form, e.g., in ampules or in multidose containers, and may contain added preservatives. Alternatively, the injectable formulation may be provided in powder form for reconstitution with a suitable vehicle, including but not limited to sterile pyrogen free water, buffer, dextrose solution, etc., before use. To this end, the active compound(s) may be dried by any technique, such as lyophilization, and reconstituted prior to use.
[0049] For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation.
[0050] For oral administration, the pharmaceutical compositions may take the form of, for example, lozenges, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulfate). The tablets may be coated by several methods, for example, sugars, films or enteric coatings.
[0051] Liquid preparations for oral administration may take the form of, for example, elixirs, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol, cremophore™ or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, preservatives, flavoring, coloring and sweetening agents as appropriate.
[0052] Preparations for oral administration may be suitably formulated to give controlled release of the compound. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner. For rectal and vaginal routes of administration, the compound(s) may be formulated as solutions (for retention enemas) suppositories or ointments containing conventional suppository bases such as cocoa butter or other glycerides.
[0053] For nasal administration or administration by inhalation or insufflation, the compound(s) can be conveniently delivered in the form of an aerosol spray from pressurized packs or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, fluorocarbons, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges for use in an inhaler or insufflator (for example capsules and cartridges comprised of gelatin) may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.
[0054] For ocular administration, the compound(s) may be formulated as a solution, emulsion, suspension, etc. suitable for administration to the eye. A variety of vehicles are suitable for administering compounds to the eye.
[0055] For prolonged delivery, the compound(s) can be formulated as a depot preparation for administration by implantation or intramuscular injection. The compound(s) may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, e.g., as a sparingly soluble salt. Alternatively, transdermal delivery systems manufactured as an adhesive disc or patch which slowly releases the compound(s) for percutaneous absorption may be used. To this end, permeation enhancers may be used to facilitate transdermal penetration of the compound(s).

[0056] Alternatively, other pharmaceutical delivery systems may be employed. Liposomes and emulsions are examples of delivery vehicles that may be used to deliver compound(s). Certain organic solvents such as dimethyl sulfoxide (DMSO) may also be employed, although usually at the cost of greater toxicity.

[0057] The pharmaceutical compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the compound(s). The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

[0058] The compound(s) described herein, or compositions thereof, will generally be used in an amount effective to achieve the intended result, for example in an amount effective to treat or prevent the particular disease being treated. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated and/or eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient may still be afflicted with the underlying disorder. Therapeutic benefit also generally includes halting or slowing the progression of the disease, regardless of whether improvement is realized.

[0059] The amount of compound(s) administered will depend upon a variety of factors, including, for example, the particular indication being treated, the mode of administration, whether the desired benefit is prophylactic or therapeutic, the severity of the indication being treated and the age and weight of the patient, the bioavailability of the particular compound(s) the conversation rate and efficiency into active drug compound under the selected route of administration, etc.

[0060] Determination of an effective dosage of compound(s) for a particular use and mode of administration is well within the capabilities of those skilled in the art. Effective dosages may be estimated initially from in vitro activity and metabolism assays. For example, an initial dosage of compound for use in animals may be formulated to achieve a circulating blood or serum concentration of the metabolite active compound that is at or above an IC.sub.50 of the particular compound as measured in as in vitro assay. Calculating dosages to achieve such circulating blood or serum concentrations taking into account the bioavailability of the particular compound via the desired route of administration is well within the capabilities of skilled artisans. Initial dosages of compound can also be estimated from in vivo data, such as animal models. Animal models may be used for testing the efficacy of the active metabolites to treat or prevent the various diseases described above. Animal models suitable for testing the bioavailability and/or metabolism of compounds into active metabolites can be used. Such information can be adapted to determine dosages of particular compounds suitable for human administration.

[0061] Dosage amounts will typically be in the range of from about 0.0001 mg/kg/day, 0.001 mg/kg/day or 0.01 mg/kg/day to about 100 mg/kg/day, but may be higher or lower, depending upon, among other factors, the activity of the active compound, the bioavailability of the compound, its metabolism kinetics and other pharmacokinetic properties, the mode of administration and various other factors, discussed above. Dosage amount and interval may be adjusted individually to provide plasma levels of the compound(s) and/or active metabolite compound(s) which are sufficient to maintain therapeutic or prophylactic effect. For example, the compounds may be administered once per week, several times per week (e.g., every other day), once per day or multiple times per day, depending upon, among other things, the mode of administration, the specific indication being treated and the judgment of the prescribing physician. In cases of local administration or selective uptake, such as local topical administration, the effective local concentration of compound(s) and/or active metabolite compound(s) may not be related to plasma concentration. Skilled artisans will be able to optimize effective dosages without undue experimentation.

Definitions

[0062] The following terms and expressions used herein have the indicated meanings.

[0063] Throughout this specification, unless the context requires otherwise, the word “comprise” and “include” and variations (e.g., “comprises,” “comprising,” “includes,” “including”) will be understood to imply the inclusion of a stated component, feature, element, or step or group of components, features, elements or steps but not the exclusion of any other integer or step or group of integers or steps.
[0064] 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.
[0065] Terms used herein may be preceded and/or followed by a single dash, “—”, or a double dash, “═”, to indicate the bond order of the bond between the named substituent and its parent moiety; a single dash indicates a single bond and a double dash indicates a double bond. In the absence of a single or double dash it is understood that a single bond is formed between the substituent and its parent moiety; further, substituents are intended to be read “left to right” unless a dash indicates otherwise. For example, C.sub.1-C.sub.6alkoxycarbonyloxy and —OC(O)C.sub.1-C.sub.6alkyl indicate the same functionality; similarly arylalkyl and -alkylaryl indicate the same functionality.
[0066] The term “alkenyl” as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons, unless otherwise specified, and containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, 3-decenyl, and 3,7-dimethylocta-2,6-dienyl.
[0067] The term “alkoxy” as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.
[0068] The term “alkyl” as used herein, means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms unless otherwise specified. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl. When an “alkyl” group is a linking group between two other moieties, then it may also be a straight or branched chain; examples include, but are not limited to —CH.sub.2—, —CH.sub.2CH.sub.2—, —CH.sub.2CH.sub.2CHC(CH.sub.3)—, and —CH.sub.2CH(CH.sub.2CH.sub.3)CH.sub.2—.
[0069] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., —(CH.sub.2).sub.n—, wherein n is a positive integer, preferably from one to six, from one to four, from one to three, from one to two, or from two to three. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group. An alkylene chain also may be substituted at one or more positions with an aliphatic group or a substituted aliphatic group.
[0070] The term “alkynyl” as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.
[0071] The term “aryl,” as used herein, means a phenyl (i.e., monocyclic aryl), or a bicyclic ring system containing at least one phenyl ring or an aromatic bicyclic ring containing only carbon atoms in the aromatic bicyclic ring system. The bicyclic aryl can be azulenyl, naphthyl, or a phenyl fused to a monocyclic cycloalkyl, a monocyclic cycloalkenyl, or a monocyclic heterocyclyl. The bicyclic aryl is attached to the parent molecular moiety through any carbon atom contained within the phenyl portion of the bicyclic system, or any carbon atom with the napthyl or azulenyl ring. The fused monocyclic cycloalkyl or monocyclic heterocyclyl portions of the bicyclic aryl are

optionally substituted with one or two oxo and/or thioxo groups. Representative examples of the bicyclic aryls include, but are not limited to, azulenyl, naphthyl, dihydroinden-1-yl, dihydroinden-2-yl, dihydroinden-3-yl, dihydroinden-4-yl, 2,3-dihydroindol-4-yl, 2,3-dihydroindol-5-yl, 2,3-dihydroindol-6-yl, 2,3-dihydroindol-7-yl, inden-1-yl, inden-2-yl, inden-3-yl, inden-4-yl, dihydronaphthalen-2-yl, dihydronaphthalen-3-yl, dihydronaphthalen-4-yl, dihydronaphthalen-1-yl, 5,6,7,8-tetrahydronaphthalen-1-yl, 5,6,7,8-tetrahydronaphthalen-2-yl, 2,3-dihydrobenzofuran-4-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 2,3-dihydrobenzofuran-7-yl, benzo[d][1,3]dioxol-4-yl, benzo[d][1,3]dioxol-5-yl, 2H-chromen-2-on-5-yl, 2H-chromen-2-on-6-yl, 2H-chromen-2-on-7-yl, 2H-chromen-2-on-8-yl, isoindoline-1,3-dion-4-yl, isoindoline-1,3-dion-5-yl, inden-1-on-4-yl, inden-1-on-5-yl, inden-1-on-6-yl, inden-1-on-7-yl, 2,3-dihydrobenzo[b][1,4]dioxan-5-yl, 2,3-dihydrobenzo[b][1,4]dioxan-6-yl, 2H-benzo[b][1,4]oxazin3(4H)-on-5-yl, 2H-benzo[b][1,4]oxazin3(4H)-on-6-yl, 2H-benzo[b][1,4]oxazin3(4H)-on-7-yl, 2H-benzo[b][1,4]oxazin3(4H)-on-8-yl, benzo[d]oxazin-2(3H)-on-5-yl, benzo[d]oxazin-2(3H)-on-6-yl, benzo[d]oxazin-2(3H)-on-7-yl, benzo[d]oxazin-2(3H)-on-8-yl, quinazolin-4(3H)-on-5-yl, quinazolin-4(3H)-on-6-yl, quinazolin-4(3H)-on-7-yl, quinazolin-4(3H)-on-8-yl, quinoxalin-2(1H)-on-5-yl, quinoxalin-2(1H)-on-6-yl, quinoxalin-2(1H)-on-7-yl, quinoxalin-2(1H)-on-8-yl, benzo[d]thiazol-2(3H)-on-4-yl, benzo[d]thiazol-2(3H)-on-5-yl, benzo[d]thiazol-2(3H)-on-6-yl, and, benzo[d]thiazol-2(3H)-on-7-yl. In certain embodiments, the bicyclic aryl is (i) naphthyl or (ii) a phenyl ring fused to either a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, or a 5 or 6 membered monocyclic heterocyclyl.

[0072] The terms “cyano” and “nitrile” as used herein, mean a —CN group.

[0073] The term “cycloalkyl” as used herein, means a monocyclic or a bicyclic cycloalkyl ring system. Monocyclic ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups can be saturated or unsaturated, but not aromatic. In certain embodiments, cycloalkyl groups are fully saturated. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems are bridged monocyclic rings or fused bicyclic rings. Bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form —(CH.sub.2).sub.w—, where w is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. Fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. The bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. In certain embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl.

[0074] The term “halo” or “halogen” as used herein, means —Cl, —Br, —I or —F.

[0075] The terms “haloalkyl” and “haloalkoxy” refer to an alkyl or alkoxy group, as the case may be, which is substituted with one or more halogen atoms.

[0076] The term “heteroaryl,” as used herein, means a monocyclic heteroaryl or a bicyclic ring system containing at least one heteroaromatic ring. The monocyclic heteroaryl can be a 5 or 6 membered ring. The 5 membered ring consists of two double bonds and one, two, three or four nitrogen atoms and optionally one oxygen or sulfur atom. The 6 membered ring consists of three double bonds and one, two, three or four nitrogen atoms. The 5 or 6 membered heteroaryl is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heteroaryl. Representative examples of monocyclic heteroaryl include, but are not

limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and triazinyl. The bicyclic heteroaryl consists of a monocyclic heteroaryl fused to a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. When the bicyclic heteroaryl contains a fused cycloalkyl, cycloalkenyl, or heterocyclyl ring, then the bicyclic heteroaryl group is connected to the parent molecular moiety through any carbon or nitrogen atom contained within the monocyclic heteroaryl portion of the bicyclic ring system. When the bicyclic heteroaryl is a monocyclic heteroaryl fused to a benzo ring, then the bicyclic heteroaryl group is connected to the parent molecular moiety through any carbon atom or nitrogen atom within the bicyclic ring system. Representative examples of bicyclic heteroaryl include, but are not limited to, benzimidazolyl, benzofuranyl, benzothienyl, benzoxadiazolyl, benzoxathiadiazolyl, benzothiazolyl, cinnolinyl, 5,6-dihydroquinolin-2-yl, 5,6-dihydroisoquinolin-1-yl, furopyridinyl, indazolyl, indolyl, isoquinolinyl, naphthyridinyl, quinolinyl, purinyl, 5,6,7,8-tetrahydroquinolin-2-yl, 5,6,7,8-tetrahydroquinolin-3-yl, 5,6,7,8-tetrahydroquinolin-4-yl, 5,6,7,8-tetrahydroisoquinolin-1-yl, thienopyridinyl, 4,5,6,7-tetrahydrobenzo[c][1,2,5]oxadiazolyl, and 6,7-dihydrobenzo[c][1,2,5]oxadiazol-4(5H)-onyl. In certain embodiments, the fused bicyclic heteroaryl is a 5 or 6 membered monocyclic heteroaryl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl. The heteroaryl may be optionally substituted with one or two oxo groups.

[0077] The terms “heterocyclyl” and “heterocycloalkyl” as used herein, mean a monocyclic heterocycle or a bicyclic heterocycle. The monocyclic heterocycle is a 3, 4, 5, 6 or 7 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S where the ring is saturated or unsaturated, but not aromatic. The 3 or 4 membered ring contains 1 heteroatom selected from the group consisting of O, N and S. The 5 membered ring can contain zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The 6 or 7 membered ring contains zero, one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S. The monocyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle. Representative examples of monocyclic heterocycle include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. The bicyclic heterocycle is a monocyclic heterocycle fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycle, or a monocyclic heteroaryl. The bicyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle portion of the bicyclic ring system. Representative examples of bicyclic heterocyclyls include, but are not limited to, 2,3-dihydrobenzofuran-2-yl, 2,3-dihydrobenzofuran-3-yl, indolin-1-yl, indolin-2-yl, indolin-3-yl, 2,3-dihydrobenzothien-2-yl, decahydroquinolinyl, decahydroisoquinolinyl, octahydro-1H-indolyl, and octahydrobenzofuranyl. In certain embodiments, the bicyclic heterocyclyl is a 5 or 6 membered monocyclic heterocyclyl ring fused to phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl. The heterocyclyl may be optionally substituted with one or two oxo groups.

[0078] The term “oxo” as used herein means a =O group.

[0079] The term “saturated” as used herein means the referenced chemical structure does not

contain any multiple carbon-carbon bonds. For example, a saturated cycloalkyl group as defined herein includes cyclohexyl, cyclopropyl, and the like.

[0080] The term “substituted”, as used herein, means that a hydrogen radical of the designated moiety is replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible compound. The term “substitutable”, when used in reference to a designated atom, means that attached to the atom is a hydrogen radical, which can be replaced with the radical of a suitable substituent.

[0081] The phrase “one or more” substituents, as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and the substituents may be either the same or different. As used herein, the term “independently selected” means that the same or different values may be selected for multiple instances of a given variable in a single compound.

[0082] The term “thioxo” as used herein means a ═S group.

[0083] The term “unsaturated” as used herein means the referenced chemical structure contains at least one multiple carbon-carbon bond, but is not aromatic. For example, a unsaturated cycloalkyl group as defined herein includes cyclohexenyl, cyclopentenyl, cyclohexadienyl, and the like.

[0084] It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure. Both the R and the S stereochemical isomers, as well as all mixtures thereof, are included within the scope of the disclosure.

[0085] “Pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio or which have otherwise been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[0086] “Pharmaceutically acceptable salt” refers to both acid and base addition salts.

[0087] “Therapeutically effective amount” refers to that amount of a compound which, when administered to a subject, is sufficient to effect treatment for a disease or disorder described herein. The amount of a compound which constitutes a “therapeutically effective amount” will vary depending on the compound, the disorder and its severity, and the age of the subject to be treated.

[0088] “Treating” or “treatment” as used herein covers the treatment of a disease or disorder described herein, in a subject, preferably a human, and includes: [0089] i. inhibiting a disease or disorder, i.e., arresting its development; [0090] ii. relieving a disease or disorder, i.e., causing regression of the disorder; [0091] iii. slowing progression of the disorder; and/or [0092] iv. inhibiting, relieving, ameliorating, or slowing progression of one or more symptoms of the disease or disorder

[0093] “Subject” refers to a warm blooded animal such as a mammal, preferably a human, or a human child, which is afflicted with, or has the potential to be afflicted with one or more diseases and disorders described herein.

Methods of Preparation

[0094] Many general references providing chemical synthetic schemes and conditions useful for synthesizing the disclosed compounds are available (see, e.g., Smith and March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Fifth Edition, Wiley-Interscience, 2001; or Vogel, A Textbook of Practical Organic Chemistry, Including Qualitative Organic

Analysis, Fourth Edition, New York: Longman, 1978).
[0095] Compounds as described herein can be purified by any of the means, including chromatographic means, such as HPLC, preparative thin layer chromatography, flash column chromatography and ion exchange chromatography. Any suitable stationary phase can be used, including normal and reversed phases as well as ionic resins. Most typically the disclosed compounds are purified via silica gel and/or alumina chromatography. See, e.g., Introduction to Modern Liquid Chromatography, 2nd Edition, ed. L. R. Snyder and J. J. Kirkland, John Wiley and Sons, 1979; and Thin Layer Chromatography, ed E. Stahl, Springer-Verlag, New York, 1969.
[0096] During any of the processes for preparation of the subject compounds, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups as described in standard works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry," Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie," Houben-Weyl, 4.sup.th edition, Vol. 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosauren, Peptide, Proteine," Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and/or in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide and Derivate," Georg Thieme Verlag, Stuttgart 1974. The protecting groups may be removed at a convenient subsequent stage.
[0097] The compounds disclosed herein can be made using procedures familiar to the person of ordinary skill in the art and as described herein. For example, compounds of structural formula (I) can be prepared according to Schemes and Examples below, or analogous synthetic schemes. One of skill in the art can adapt the reaction sequences to fit the desired target molecule. Of course, in certain situations one of skill in the art will use different reagents to affect one or more of the individual steps or to use protected versions of certain of the substituents. Additionally, one skilled in the art would recognize that compounds of the disclosure can be synthesized using different routes altogether.
EXAMPLES
[0098] The compounds and the methods of the disclosure are illustrated further by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures and compounds described in them.
Target Preparation
[0099] The X-ray crystallographic structure of a cyclic peptide des4.3.1 (PDB 6WSJ) bound to HDAC6 was used as the starting point for the design of the small macrocycles that inhibit HDACs. In PyMOL, all waters, crystallization buffer components, and metals were deleted from the model. Additionally, all residues in des4.3.1, except the d-arginine at position 4 and the unnatural amino acid SHA at position 5, were deleted from the model. These modifications were saved to a new PDB file containing HDAC6 in chain A, and a dipeptide dARG-SHA in chain B. In a text editor, the sidechain atoms of the d-arginine and the C-alpha proton of the d-arginine were deleted from the model. The residue identity of the remaining atoms belonging to d-arginine were changed to either 'DPR', 'PRO', or 'ALA'. These modifications result in three separate PDB files, with HDAC6 in chain A, and either dPRO-SHA, PRO-SHA, or dALA-SHA in chain B. These three models serve as the input to the hash closure steps detailed below.
Macrocycle Design
[0100] The dipeptides in the above models are modified using a PyRosetta™ script with N-terminal acetyl amide and C-terminal methyl amide patches. The N-terminal phi torsion angle, and the C-terminal psi torsion angle of the modified dipeptides are perturbed to bring the terminal amides into a hydrogen-bonding geometry. The relative transform between the plane of the terminal amides is then calculated and hashed in the C-to-N direction. Closures are found by then

searching for common binned transforms between a database of N-to-C hashtables and the C-to-N hashtable of the dipeptide bound to HDAC6.
[0101] Full atom representations of any conformer found to close the dipeptide in this search are constructed on the surface of HDAC6. Clashes between these conformers and HDAC6 are then evaluated in a voxel-based clash check. Conformers with less than 5 clashing voxels were then saved to disk as PDB files.
[0102] Each output PDB file of a macrocycle found in the hash closure step is parameterized as a ligand for use in the Rosetta™ software suite using mol2genparams.py. Each macrocycle is then evaluated using GALigandDock within the Rosetta™ software suite, using the below commands:
TABLE-US-00001 $ROSETTABIN/rosetta_scripts -mute all \ -gen_potential \ -beta_cart \ -no_autogen_cart_improper \ -parser:protocol dock_flex.xml \ -s DUMMY.pdb \ -in:file:extra_res_fa DUMMY.params LG1.params \ -parser:script_vars ligand=LG1 \ -nstruct 5 \ -overwrite \
[0103] Where “dock.xml” is as below:
TABLE-US-00002 <ROSETTASCRIPTS> <SCOREFXNS> <ScoreFunction name=“genpot_soft” weights=“beta_cart”> <Reweight scoretype=“fa_rep” weight=“0.2”/> </ScoreFunction> <ScoreFunction name=“genpot” weights=“beta_cart”> </ScoreFunction> </SCOREFXNS> <RESIDUE_SELECTORS> <Index name=“SelLig” resnums=“1” reverse=“true” /> <Not name=“not_lig” selector=“SelLig”/> <Neighborhood name=“Lig_neighbors” selector=“SelLig” distance=“10.0” /> <And name=“binding_surface” selectors=“Lig_neighbors,not_lig”/> <ResidueName name=“metal” residue_names=“ZN”/> </RESIDUE_SELECTORS> <MOVERS> <GALigandDock name=“dock” scorefxn=“genpot_soft” scorefxn_relax=“genpot” runmode=“dockflex” premin_ligand=“1” padding=“2.5” multiple_ligands=“%%ligid%%” estimate_dG=“1” /> </MOVERS> <PROTOCOLS> <Add mover=“dock”/> </PROTOCOLS> <OUTPUT scorefxn=“genpot”/> </ROSETTASCRIPTS>
[0104] The input file “DUMMY.pdb” was prepared from the X-ray crystallographic structure of a cyclic peptide des4.3.1 (PDB 6WSJ) bound to HDAC6. This model was modified to contain HDAC6 first, the Zn atom second, and the coordinates of a DUMMY ligand placed near the active site last. This ligand is replaced with the ligand in “LG1.params” at runtime.
[0105] The models of the designed macrocycle:HDAC6 complexes were sorted by the most favorable GALigandDock reported dG of binding and manually inspected. Approximately 200 models were inspected. Macrocycles were prioritized for synthesis if the lowest energy docked model closely aligned with their respective outputs form the hash closure (i.e. those macrocycles that “forward docked”), and made additional contacts with HDAC6 beyond those made by the starting dipeptides. Ultimately, 11 such macrocycles were chosen for chemical synthesis and testing.
Compound Synthesis
[0106] All macrocycles were prepared by WuXi apptec under a fee-for-service contract. Below is a detailed protocol for the synthesis of aaae-HDAC-1. A similar protocol was used to prepare the ten other macrocyclic HDAC inhibitors.
[0107] Dichloromethane was added to a vessel contiaing CTC resing (0.1 mmol, 0.65 mmol/g, 0.15 g) and Fmoc-1,4-cis-ACHA (0.38 mg, 0.1 mmol, 1.0 eq) and bubbled with nitrogen. Diisopropylethylamine (4 eq.) (DIEA) was added dropwise and mixed for 2 hours at which point methanol (0.15 mL) was added. This mixture was allowed to bubble for an additional 30 minutes. The reaction vessel was drained of solvent, and washed with dimethylformamide (DMF) five times. After washing, a solution of 20% piperidine in DMF was added to the reaction vessel and bubbled for 30 minutes, at which point the vessel was drained of solvent, and washed 5× with DMF. To the reaction vessel, a solution of Fmoc-protected amino acids was added, followed by a

solution of activating reagents. This reaction proceeded for 1 hour with mixing by nitrogen bubbling, at which point the reaction vessel is drained of solvent, and washed with 5× with DMF. This cycle of deprotect, wash, couple, wash is repeated until the full-length linear peptide is completed, and the N-terminal Fmoc-protecting group is removed. After completion of the linear peptide, the resin was washed with methanol thrice and dried under vacuum.

[0108] The reagents used in the coupling steps for synthesis of aaae-HDAC-1 are depicted in the below table

TABLE-US-00003 Coupling step # Amino acid Coupling reagents 1 Fmoc-1,4-cis-ACHA (1.0 eq) DIEA (4 eq) 2 (S)-2-((((9H-fluoren-9- HATU (1.42 eq) yl)methoxy)carbonyl)amino)-7- DIEA (3.00 eq) (tritylthio)heptanoic acid (1.50 eq) 3 Fmoc-D-Ala-OH (3.00 eq) HATU (2.85 eq) DIEA (6.00 eq) 4 (2S,4S)-1-(((9H-fluoren-9- HATU (1.42 eq) yl)methoxy)carbonyl)-4-(tert- DIEA (3.00 eq) butoxy)pyrrolidine-2-carboxylic acid (1.50 eq)

[0109] The linear side-chain protected peptide was cleaved from the resin by addition of a cleavage solution (1% trifluoroacetic acid in dichloromethane) to the resin at room temperature. The cleavage was carried out twice for 3 minutes each with continuous nitrogen bubbling. The Filtrate of the cleavage reaction was collected, pooled, and diluted with 100 mL of dichloromethane. To the dilute linear protected peptide, TBTU (64.2 mg, 2 eq), and HOBt (27 mg, 2 eq.) was added. The pH of this solution was adjusted to ca. pH 8.0 with DIEA. the mixture was stirred for 30 minutes at 25 degrees celsius. The reaction mixture was then washed with 1M HCl, and the organic layer was concentrated to dryness under reduced pressure. The resulting residue was treated with global-deprotection solution (92/5% trifluoroacetic acid, 2.5% 3-mercaptopropionic acid, 2.5% TIS, 2.5% water) and stirred for 30 minutes. The mixture was precipitated with cold isopropyl ether and centrifuged for 3 minutes at 3000 rpm. The resulting insoluble material was subsequently precipitated with additional isopropyl ether two additional times, each time discarding the solvent. The resulting solid material containing the crude cyclic peptide was dried under vacuum for 2 hours to remove any residual isopropyl ether.

[0110] The peptide was then purified from this material by reverse-phase preparative HPLC (A: 0.075% TFA in water, B: ACN) to give aaae-HDAC-1 (9.8 mg, 97.8% purity, 19.8% yield) as white solid.

Results

[0111] At least four macrocycles (depicted in FIG. **1**) show selectivies towards HDAC6 ranging from 100× to greater than 1000× vs other HDACs. The potency and selectivities towards HDAC6 these four compounds display are on par, and in some cases better than, several small molecules currently in clinical trials as putative HDAC6-selective inhibitors for the treatment of various cancers. The structures of additional compounds of the disclosure are depicted in Table 1. Their activities against HDAC6 and its related enzymes are provided in Tables 2 and 3.

TABLE-US-00004 TABLE 1 Potency of designed HDAC6-selective macrocyclic inhibitors compared to HDAC6- selective inhibitors currently in clinical trials. Each row is a different HDAC, each column, a different inhibitor. Values are IC50s (nM). aaae- aaae- aaap- aaeb- KA2507.sup.2 Ricolinostat.sup.2 Citarinostat.sup.2 HDAC-1 HDAC-2 HDAC-3 HDAC-5 HDAC1 9895 332 153 1150 815 843 506 HDAC2 >10000 632 620 2900 1760 1650 1730 HDAC3 >10000 199 268 549 354 308 189 HDAC4 9613 >10000 9972 >10000 >10000 >10000 >10000 HDAC5 1997 4310 3396 >10000 >10000 7740 >10000 HDAC6 2.5 22 2.8 3.7 1.6 1.3 2.6 HDAC7 2333 5290 4031 >10000 >10000 >10000 >10000 HDAC8 621 776 155 1520 3400 697 1420 HDAC9 5648 >10000 >10000 >10000 >10000 >10000 >10000 HDAC11 >10000 3433 2676 >10000 >10000 >10000 >10000

##STR00007## ##STR00008## ##STR00009##

TABLE-US-00005 TABLE 2 Potency of designed macrocyclic inhibitors of HDACs. Each row is a different HDAC, each column, a different inhibitor. Values are IC.sub.50s (nM). macrocycle aaae- aaae- aaap- aahb- aaeb- HDAC-1 HDAC-2 HDAC-3 HDAC-4 HDAC-5 HDAC HDAC6 3.66 1.62

1.26 789.10 2.61 IC.sub.50 HDAC 1 1,150.00 815.10 842.60 4,599.00 505.80 (nM) HDAC 2 2,903.00 1,761.00 1,645.00 8,525.00 1,730.00 HDAC 3 548.50 354.40 308.00 2,864.00 189.30 HDAC 4 N.D. N.D. N.D. N.D. N.D. HDAC 5 N.D. N.D. 7,744.00 N.D. N.D. HDAC 7 N.D. N.D. N.D. N.D. N.D. HDAC 8 1,518.00 3,401.00 697.30 2,072.00 1,415.00 HDAC 9 N.D. N.D. 14,650.00 N.D. N.D. HDAC 11 N.D. N.D. 16,830.00 N.D. N.D.

TABLE-US-00006 TABLE 3 Potency of designed macrocyclic inhibitors of HDACs. Each row is a different HDAC, each column, a different inhibitor. Values are IC.sub.50s (nM). macrocycle aapb- aark- aapb- aahb- aahb- aapb- HDAC-6 HDAC-7 HDAC-8 HDAC-9 HDAC-10 HDAC-11 HDAC HDAC6 40.69 7.94 5.48 39.52 70.16 10.53 IC.sub.50 HDAC 1 88.93 952.20 76.23 1,263.00 1,424.00 68.19 (nM) HDAC 2 224.70 2,446.00 205.90 2,559.00 3,082.00 128.00 HDAC 3 10.22 408.80 18.25 919.90 803.70 58.66 HDAC 4 N.D. N.D. N.D. N.D. N.D. N.D. HDAC 5 N.D. N.D. 12,330.00 N.D. N.D. 6,449.00 HDAC 7 N.D. N.D. 24,760.00 N.D. N.D. 15,870.00 HDAC 8 853.90 976.40 502.70 2,720.00 2,324.00 454.80 HDAC 9 N.D. N.D. N.D. N.D. N.D. N.D. HDAC 11 N.D. N.D. N.D. N.D. N.D. N.D.

[0112] Additional compounds of the disclosure are provided in Table 4.

TABLE-US-00007 TABLE 4 The compounds of the disclosure. Chemical structure/name [00010]  embedded image (4.sup.2S,2R,8R,11S,Z)-11-(5-mercaptopentyl)-2,8- dimethyl-11H-7,10,13-triaza-1(1,4)-triazola- 4(1,2)-pyrrolidinacyclotetradecaphane-3,6,9,12- tetraone [00011]  embedded image (5S,8R,13R)-5-(5-mercaptopentyl)-8-methyl- 4,7,10,15-tetraoxo-3,6,9,14-tetraaza-1(1,3)- benzenacyclohexadecaphane-13-carboxamide [00012]  embedded image (1S,4S,7R,14R)-4-(5-mercaptopentyl)-7- methyl-11-phenyl-2,5,8,11-tetraazabicyclo[12.2.2]octadecane-3,6,9,12- tetraone [00013]  embedded image aaae-HDAC-1 (3R,6S,9R,12R,17S,18aS)-17-hydroxy-6-(5- mercaptopentyl)-3-methyltetradecahydro-9,12-ethanopyrrolo[1,2- a][1,4,7,10]tetraazacyclohexadecine-1,4,7,14- tetraone [00014]  embedded image (4S,7S,10R)-7-(5-mercaptopentyl)-10-methyl-4-((perfluorophenyl)methyl)-4,5,7,8,10,11- hexahydro-1H- benzo[l][1,4,7,10]tetraazacyclopentadecine- 3,6,9,12(2H,13H)-tetraone [00015]  embedded image (10S,13R)-10-(5-mercaptopentyl)-13-methyl- 3,8,11,14-tetraaza-1(1,2),6(1,3)-dibenzenacyclopentadecaphane-4,9,12,15- tetraone [00016]  embedded image aapb-HDAC-11 (1.sup.2S,8S,11R)-8-(5-mercaptopentyl)-11-methyl- 6,9,12-triaza-1(1,2)-pyrrolidina-4(1,3)-benzenacyclotetradecaphane-2,7,10,13- tetraone [00017]  embedded image (3S,6S,9R)-6-(5-mercaptopentyl)-9-methyl-3- ((perfluorophenyl)methyl)-1,4,7,10- tetraazacyclopentadecane-2,5,8,11-tetraone [00018]  embedded image aaae-HDAC-2 (1R,4S,7R,10S,14R)-10-(hydroxymethyl)-4-(5- mercaptopentyl)-7-methyl-2,5,8,11- tetraazabicyclo[12.2.2]octadecane-3,6,9,12- tetraone [00019]  embedded image aark-HDAC-7 (1.sup.2R,8.sup.3R,7R,11S)-11-(5-mercaptopentyl)-7- methyl-5,9,12-triaza-1(1,2),8(1,3)-dipyrrolidina- 3(1,3)-benzenacyclotridecaphane-82,2,6,10,13- pentaone [00020]  embedded image (5S,8R,12R,15S,Z)-5-(5-mercaptopentyl)-8,15- dimethyl-4,7,10,14-tetraoxo-11H-3,6,9,13-tetraaza-1(4,1)-triazolacyclopentadecaphane- 12-carboxamide [00021]  embedded image (1.sup.2R,12S,Z)-12-(5-mercaptopentyl)-8.sup.1H- 5,10,13-triaza-8(1,4)-triazola-1(1,2)-pyrrolidina- 3(1,3)-benzenacyclotetradecaphane-2,6,11,14- tetraone [00022]  embedded image aahb-HDAC-9 (7R,17S,19aR)-17-(5-mercaptopentyl)-7- methyl-2,3,7,8,14,15,17,18-octahydro-1H- benzo[m]pyrrolo[2,1- f][1,4,7,11]tetraazacyclopentadecine- 5,9,16,19(6H,19aH)-tetraone [00023]  embedded image (3aR,6S,9R)-6-(5-mercaptopentyl)-9-phenyl- 1,2,3,3a,5,6,9,10,13,18-decahydrobenzo[m]pyrrolo[1,2- a][1,4,7,11]tetraazacyclohexadecine- 4,7,11,19(8H,12H)-tetraone [00024]  embedded image (1.sup.2R,3.sup.2S, 10S)-10-(5-mercaptopentyl)-8,11- diaza-3(2,1)-piperidina-1(1,2)-pyrrolidina- 6(1,3)-benzenacyclododecaphane-2,4,9,12- tetraone [00025]  embedded image (3S,11R,17aR)-3-(5-mercaptopentyl)-11- phenyldodecahydro-1H-pyrrolo[2,1-f][1,4,7,11]tetraazacyclopentadecine- 1,4,9,13(10H)-tetraone [00026]  embedded image aahb-HDAC-10 (7R,17S,19aR)-7-isobutyl-17-(5- mercaptopentyl)-2,3,7,8,14,15,17,18- octahydro-1H-

benzo[m]pyrrolo[2,1- f][1,4,7,11]tetraazacyclopentadecine- 5,9,16,19(6H,19aH)-tetraone [00027]
(1.sup.2R,3S,11S)-3-ethyl-11-(5-mercaptopentyl)-4- methyl-4,9,12-triaza-1(1,2)-pyrrolidina-7(1,3)- benzenacyclotridecaphane-2,5,10,13-tetraone [00028]
(1.sup.2R,12S)-12-(5-mercaptopentyl)-6,10,13- triaza-1(1,2)-pyrrolidina-4(1,2),9(1,3)-dibenzenacyclotetradecaphane-2,7,11,14- tetraone [00029]
(1.sup.2R,4.sup.4Z,9.sup.4Z,3R,8R,13S)-13-(5- mercaptopentyl)-3,8-dimethyl-41H,91H- 6,11,14-triaza-4,9(1,4)-ditriazola-1(1,2)- pyrrolidinacyclopentadecaphane-2,7,12,15- tetraone [00030]
(8.sup.2R,5S,11R,Z)-5-(5-mercaptopentyl)-4,7,9,13- tetraoxo-1.sup.1H-3,6,12-triaza-1(4,1)-triazola- 8(2,1)-pyrrolidinacyclotetradecaphane-11- carboxamide [00031]
aaap-HDAC-3 (1.sup.2R,3.sup.1S,10S)-10-(5-mercaptopentyl)-3.sup.1,3.sup.2,3.sup.3,3.sup.4-tetrahydro-8,11-diaza-3(1,2)- isoquinolina-1(1,2)-pyrrolidina-6(1,3)- benzenacyclododecaphane-2,4,9,12-tetraone [00032]
(3aR,6S,9S)-6-(5-mercaptopentyl)-9- ((perfluorophenyl)methyl)-3,3a,5,6,8,9,12,17- octahydro-1H-benzo[l]pyrrolo[1,2- a][1,4,7,10]tetraazacyclopentadecine- 4,7,10,18(2H,11H)-tetraone [00033]
(1.sup.2R,3S,11S)-11-(5-mercaptopentyl)-3,4- dimethyl-4,9,12-triaza-1(1,2)-pyrrolidina-7(1,3)- benzenacyclotridecaphane-2,5,10,13-tetraone [00034]
(1.sup.2R,3.sup.3S,10S)-10-(5-mercaptopentyl)- 3.sup.1,3.sup.2,3.sup.3,3.sup.4-tetrahydro-8,11-diaza-3(3,2)- isoquinolina-1(1,2)-pyrrolidina-6(1,3)- benzenacyclododecaphane-2,4,9,12-tetraone [00035]
(1.sup.2R,4S,12R)-4-(5-mercaptopentyl)-2,5,10,14- tetraoxo-3,6,11-triaza-1(2,1)-pyrrolidina-8(1,3)- benzenacyclotetradecaphane-12-carboxamide [00036]
(1.sup.2R,7R,12S,Z)-12-(5-mercaptopentyl)-7- methyl-8.sup.1H-5,10,13-triaza-8(1,4)-triazola- 1(1,2)-pyrrolidina-3(1,3)- benzenacyclotetradecaphane-2,6,11,14- tetraone [00037]
(1.sup.2R,11S)-4-isopropyl-11-(5-mercaptopentyl)- 4,9,12-triaza-1(1,2)-pyrrolidina-7(1,3)- benzenacyclotridecaphane-2,5,10,13-tetraone [00038]
(3S,7S,10R,13R,19aS)-13-isobutyl-3-(5- mercaptopentyl)tetradecahydro-1H-7,10-ethanopyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine- 1,4,11,15(12H)-tetraone [00039]
(1.sup.2R,4S,12R)-4-(5-mercaptopentyl)-2,5,10,14- tetraoxo-3,6,11-triaza-1(2,1)-pyrrolidina-8(1,3)- benzenacyclotetradecaphane-12-carboxamide [00040]
(3S,11S,17aS)-3-(5-mercaptopentyl)-11- phenyldodecahydro-1H-pyrrolo[2,1- f][1,4,7,11]tetraazacyclopentadecine- 1,4,9,13(10H)-tetraone [00041]
aapb-HDAC-8 (1.sub.2R,3.sup.1S,3.sup.2R,11S)-11-(5-mercaptopentyl)- 4,9,12-triaza-1(1,2)-pyrrolidina-7(1,3)-benzena- 3(1,2)-cyclohexanacyclotridecaphane- 2,5,10,13-tetraone [00042]
(8.sup.2S,5S,11S,14S,Z)-11-isobutyl-5-(5- mercaptopentyl)-14-methyl-1.sup.1H-3,6,12-triaza- 1(4,1)-triazola-8(2,1)- pyrrolidinacyclotetradecaphane-4,7,9,13- tetraone [00043]
(8.sup.2S,5S,11S,14R,Z)-11-isobutyl-5-(5- mercaptopentyl)-14-methyl-11H-3,6,12-triaza- 1(4,1)-triazola-8(2,1)- pyrrolidinacyclotetradecaphane-4,7,9,13- tetraone [00044]
(8.sup.2S,5S,13S,Z)-5-(5-mercaptopentyl)-4,7,9,15- tetraoxo-1.sup.1H-11-thia-3,6, 14-triaza-1(4,1)- triazola-8(2,1)-pyrrolidinacyclohexadecaphane- 13-carboxamide [00045]
(3S,6R,9R,13S,18aS)-3-(5-mercaptopentyl)-13- propyltetradecahydro-6,9-ethanopyrrolo[1,2- d][1,4,7,10]tetraazacyclohexadecine-1,4,11,14- tetraone [00046]
(1.sup.2S,7R,12S,Z)-12-(5-mercaptopentyl)-7- methyl-8.sup.1H-5,10,13-triaza-8(1,4)-triazola- 1(1,2)-pyrrolidina-3(1,3)- benzenacyclotetradecaphane-2,6,11,14- tetraone [00047]
(3aS,6S)-6-(5-mercaptopentyl)- 3,3a,5,6,9,10,11,12,14,19-decahydro-1H-benzo[j]pyrrolo[2,1- f][1,4,7, 12]tetraazacycloheptadecine- 4,7,13,20(2H,8H)-tetraone [00048]
(1.sup.2S,3.sup.1R,3.sup.4R,12S)-12-(5-mercaptopentyl)- 5,10,13-triaza-1(1,2)-pyrrolidina-8(1,3)- benzena-3(1,4)- cyclohexanacyclotetradecaphane-2,6,11,14- tetraone [00049]
(1.sup.2S,3.sup.1S,3.sup.2S,11S,Z)-11-(5-mercaptopentyl)-3.sup.1-methyl-7.sup.1H-4,9,12-triaza-7(1,4)-triazola-1(1,2)- pyrrolidina-3(1,2)-cyclohexanacyclotridecaphane-2,5,10,13- tetraone [00050]
(1.sup.2S,3.sup.1R,3.sup.2S,6R,11S,Z)-11-(5-mercaptopentyl)- 6-methyl-7.sup.1H-4,9,12-triaza-

7(1,4)-triazola- 1(1,2)-pyrrolidina-3(1,2)- cyclohexanacyclotridecaphane-2,5,10,13- tetraone [00051]embedded image (3S,12R,19aS)-3-(5-mercaptopentyl)-1,4,10,15-tetraoxooctadecahydro-1H-pyrrolo[2,1- f][1,4,7,12]tetraazacycloheptadecine-12- carboxamide [00052]embedded image (1.sup.2S,11S)-4-ethyl-11-(5-mercaptopentyl)- 4,9,12-triaza-1(1,2)-pyrrolidina-7(1,3)- benzenacyclotridecaphane-2,5,10,13-tetraone [00053]embedded image (3S,6R,9R,13S,19aS)-3-(5-mercaptopentyl)-13- phenyltetradecahydro-1H-6,9- ethanopyrrolo[2,1-f][1,4,7,11]tetraazacycloheptadecine- 1,4,11,15(12H)-tetraone [00054]embedded image (3S,7R,10R,13S,19aS)-13-isobutyl-3-(5- mercaptopentyl)tetradecahydro-1H-7,10-ethanopyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine- 1,4,11,15(12H)-tetraone [00055] embedded image (7R,17S,19aS)-17-(5-mercaptopentyl)-7- phenyl-2,3,7,8,10,15,17,18-octahydro-1H- benzo[n]pyrrolo[2,1- f][1,4,7,11]tetraazacyclopentadecine- 5,9,16,19(6H,19aH)-tetraone [00056]embedded image (3aS,6S)-6-(5-mercaptopentyl)- 3,3a,5,6,9,10,11,12,14,19-decahydro-1H- benzo[j]pyrrolo[2,1- f][1,4,7,12]tetraazacycloheptadecine- 4,7,13,20(2H,8H)-tetraone [00057]embedded image (3S,6S,9R,13R,19aS)-13-isobutyl-3-(5-mercaptopentyl)tetradecahydro-1H-6,9- ethanopyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine-1,4,11,15(12H)-tetraone [00058]embedded image aahb-HDAC-4 (7R,18S,20aS)-7-isobutyl-18-(5- mercaptopentyl)-1,2,3,7,8,15,16,18,19,20a- decahydrobenzo[n]pyrrolo[2,1- f][1,4,7,11]tetraazacyclohexadecine- 5,9,17,20(6H,10H)-tetraone [00059]embedded image (3S,6R,9R,13S,19aS)-3-(5-mercaptopentyl)-13- phenyltetradecahydro-1H-6,9- ethanopyrrolo[2,1-f][1,4,7,11]tetraazacycloheptadecine- 1,4,11,15(12H)-tetraone [00060]embedded image (3S,6R,9R,13S,19aS)-3-(5-mercaptopentyl)- 1,4,11,15-tetraoxooctadecahydro-1H-6,9-ethanopyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine-13- carboxamide [00061] embedded image (3S,6R,9R,18aS)-3-(5-mercaptopentyl)-12- phenyltetradecahydro-6,9-ethanopyrrolo[1,2- d][1,4,7,10]tetraazacyclohexadecine-1,4,11,14- tetraone [00062] embedded image (3aS,6S,9S,12R,15aR,19aS)-6-(5- mercaptopentyl)hexadecahydro-1H-9,12-ethanobenzo[i]pyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine- 4,7,14,20(2H,15H)-tetraone [00063]embedded image (3aS,6S,10R,13R,15aS,19aR)-6-(5- mercaptopentyl)hexadecahydro-1H-10,13- ethanobenzo[i]pyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine- 4,7,14,20(2H,15H)-tetraone [00064]embedded image (7R,17S,19aS)-17-(5-mercaptopentyl)-7- phenyl-2,3,7,8,10,15,17,18-octahydro-1H- benzo[n]pyrrolo[2, 1- f][1,4,7,11]tetraazacyclopentadecine-5,9,16,19(6H,19aH)-tetraone [00065]embedded image (3S,7S,10R,13R,19aS)-13-isobutyl-3-(5-mercaptopentyl)tetradecahydro-1H-7,10- ethanopyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine-1,4,11,15(12H)-tetraone [00066]embedded image (1.sup.2S,12S)-12-(5-mercaptopentyl)-5,10,13- triaza-1(1,2)-pyrrolidina-3,8(1,3)- dibenzenacyclotetradecaphane-2,6,11,14- tetraone [00067]embedded image (3S,6R,9R,13S,19aS)-3-(5-mercaptopentyl)-1,4,11,15-tetraoxooctadecahydro-1H-6,9- ethanopyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine-13- carboxamide [00068]embedded image (3S,7S,10R,13R,19aS)-13-isobutyl-3-(5-mercaptopentyl)tetradecahydro-1H-7,10- ethanopyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine-1,4,11,15(12H)-tetraone [00069]embedded image (1.sup.2S,3.sup.4S,4S,11S,Z)-11-(5-mercaptopentyl)-4- methyl-3.sup.4,3.sup.5-dihydro-5,9,12-triaza-3(4,2)- oxazola-1(1,2)-pyrrolidina-8(1,3)- benzenacyclotridecaphane-2,6,10,13-tetraone [00070]embedded image (3S,6S,9R,13R,19aS)-13-isobutyl-3-(5- mercaptopentyl)tetradecahydro-1H-6,9- ethanopyrrolo[2,1-f][1,4,7,11]tetraazacycloheptadecine- 1,4,11,15(12H)-tetraone [00071]embedded image aapb-HDAC-6 (1.sup.2S,4S,12R)-12-isobutyl-4-(5-mercaptopentyl)- 3,6,11-triaza-1(2,1)-pyrrolidina-8(1,3)- benzenacyclotetradecaphane-2,5,10,14- tetraone [00072]embedded image (1.sup.2S,4.sup.4Z,9.sup.4Z,3S,13S)-13-(5-mercaptopentyl)-3- methyl-4.sup.1H,9.sup.1H-6,11,14-triaza-4,9(1,4)- ditriazola-1(1,2)- pyrrolidinacyclopentadecaphane-2,7,12,15- tetraone [00073] embedded image (8.sup.2S,5S,11S,Z)-11-isobutyl-5-(5- mercaptopentyl)-1.sup.1H-3,6,12-triaza-1(4,1)- triazola-8(2,1)-pyrrolidinacyclotetradecaphane- 4,7,9,13-tetraone [00074] embedded image (3S,6R,9R,18aS)-12-ethyl-3-(5- mercaptopentyl)tetradecahydro-6,9-

ethanopyrrolo[1,2- d][1,4,7,10]tetraazacyclohexadecine-1,4,11,14- tetraone [00075] embedded image (3S,12R,19aS)-3-(5-mercaptopentyl)-1,4,10,15- tetraoxooctadecahydro-1H-pyrrolo[2,1- f][1,4,7,12]tetraazacycloheptadecine-12- carboxamide [00076] embedded image (3aS,6S,10R,13R,15aS,19aR)-6-(5- mercaptopentyl)hexadecahydro-1H-10,13-ethanobenzo[i]pyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine- 4,7,14,20(2H,15H)-tetraone [00077] embedded image (3aS,6S,9S,12R,15aR,19aS)-6-(5- mercaptopentyl)hexadecahydro-1H-9,12- ethanobenzo[i]pyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine- 4,7,14,20(2H,15H)-tetraone [00078] embedded image (1.sup.2S,4S,12S,Z)-12-(5-mercaptopentyl)-4- methyl-5,10,13-triaza-3(4,2)-thiazola-1(1,2)- pyrrolidina-8(1,4)- benzenacyclotetradecaphane-2,6,11,14- tetraone [00079] embedded image (3S,7R,10R,13S,19aS)-3-(5-mercaptopentyl)- 13-phenyltetradecahydro-1H-7,10- ethanopyrrolo[2,1- f][1,4,7,11]tetraazacycloheptadecine- 1,4,11,15(12H)-tetraone [00080] embedded image (8.sup.2S,5S,11S,Z)-11-benzyl-5-(5- mercaptopentyl)-1.sup.1H-3,6,12-triaza-1(4,1)- triazola-8(2,1)-pyrrolidinacyclotetradecaphane- 4,7,9,13-tetraone [00081] embedded image aaeb-HDAC-5 (1R,4S,7R,11S,15R)-11-benzyl-4-(5- mercaptopentyl)-7-methyl-2,5,8,12- tetraazabicyclo[13.2.2]nonadecane-3,6,9,13- tetraone

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[0115] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be incorporated within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated herein by reference for all purposes.

Claims

1. A compound of the formula (I): ##STR00082## or a pharmaceutically acceptable salt thereof, wherein L is C.sub.1-C.sub.6 alkylene; R is —SH, —OH, —NH.sub.2, —CONH—OH, —CO.sub.2H, or —SO.sub.2NH.sub.2; R.sub.1 is hydrogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, hydroxy(C.sub.1-C.sub.6 alkyl), amino(C.sub.1-C.sub.6 alkyl), or benzyl; R.sub.2 is hydrogen or C.sub.1-C.sub.6 alkyl; or R.sub.1 and R.sub.2 together with the atoms to which they are attached, form a pyrrolidine ring optionally substituted with one or two R.sub.3; each R.sub.3 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy; X is C, CH, or CH.sub.2, and Y is C, CH, or CH.sub.2, where X and Y, together with the atoms to which they are attached, form a 10- to 20-member macrocycle, the macrocycle optionally substituted with one or more R.sub.4, and/or optionally fused with a phenyl, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic cycloalkyl, or bicyclic cycloalkyl moiety, each moiety optionally substituted with one or two R.sub.5, wherein each R.sub.4 is independently selected from the group consisting of halogen, —NO.sub.2, —CN, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, C.sub.1-C.sub.6 haloalkoxy, hydroxy(C.sub.1-C.sub.6 alkyl), hydroxy(C.sub.1-C.sub.6 alkoxy), alkoxy(C.sub.1-C.sub.6 alkyl), alkoxy(C.sub.1-C.sub.6 alkoxy), amino(C.sub.1-C.sub.6 alkyl), —CO.sub.2H, —CO.sub.2(C.sub.1-C.sub.6 alkyl), —CO(C.sub.1-C.sub.6 alkyl), carboxy(C.sub.1-C.sub.6 alkyl), —CONH.sub.2, —CONH(C.sub.1-C.sub.6 alkyl), —CON(C.sub.1-C.sub.6 alkyl).sub.2, —(C.sub.1-C.sub.6 alkyl)-CONH.sub.2,1H-imidazol-4-yl-methyl, or phenyl(C.sub.0-C.sub.1 alkyl)

optionally substituted with one or more of halogens or —OH, or two R.sub.4 groups, together with the carbon to which they are attached, form a ═O, each R.sub.5 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy.

2. The compound of claim 1, wherein L is C.sub.4-C.sub.6 alkylene.

3. The compound of claim 1, wherein L is pentylene.

4. The compound of any one of claims 1 to 3, wherein R is —SH, —CONH—OH, —CO.sub.2H, or —SO.sub.2NH.sub.2.

5. The compound of any one of claims 1 to 3, wherein R is —SH.

6. The compound of claim 1, which has the structure: ##STR00083##

7. The compound of any one of claims 1 to 6, wherein R.sub.1 is hydrogen or C.sub.1-C.sub.6 alkyl.

8. The compound of any one of claims 1 to 6, wherein R.sub.1 is hydrogen or methyl.

9. The compound of any one of claims 1 to 6, wherein R.sub.1 is hydrogen or C.sub.1-C.sub.6 alkyl.

10. The compound any one of claims 1 to 6, wherein R.sub.1 is hydrogen or methyl.

11. The compound of any one of claims 1 to 6, wherein R.sub.1 is methyl, and R.sub.2 is hydrogen, e.g., of formula: ##STR00084##

12. The compound of any one of claims 1 to 6, wherein R.sub.1 and R.sub.2 together with the atoms to which they are attached, form a pyrrolidine ring optionally substituted with one or two R.sub.3, e.g., of formula: ##STR00085##

13. The compound of claim 12, wherein each R.sub.3 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —OH, or C.sub.1-C.sub.6 alkoxy.

14. The compound of claim 12, wherein each R.sub.3 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, or —OH.

15. The compound of any one of claims 1 to 6, wherein R.sub.1 and R.sub.2 together with the atoms to which they are attached, form a pyrrolidine ring, e.g., of formula: ##STR00086##

16. The compound of any one of claims 1 to 15, wherein X and Y, together with the atoms to which they are attached, form a 12- to 20-member macrocycle, the macrocycle optionally substituted with one or more R.sub.4 and/or optionally fused with a phenyl, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic cycloalkyl, or bicyclic cycloalkyl moiety, each moiety optionally substituted with one or two R.sub.5.

17. The compound of any one of claims 1 to 15, wherein X and Y, together with the atoms to which they are attached, form a 14- to 18-member macrocycle, the macrocycle optionally substituted with one or more R.sub.4 and/or optionally fused with a phenyl, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic cycloalkyl, or bicyclic cycloalkyl moiety, each moiety optionally substituted with one or two R.sub.5.

18. The compound of any one of claims 1 to 15, wherein X and Y, together with the atoms to which they are attached, form a 16- to 18-member macrocycle, the macrocycle optionally substituted with one or more R.sub.4 and/or optionally fused with a phenyl, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic cycloalkyl, or bicyclic cycloalkyl moiety, each moiety optionally substituted with one or two R.sub.5.

19. The compound of any one of claims 1 to 15, wherein X and Y, together with the atoms to which they are attached, form a 16- or 17-member macrocycle, the macrocycle optionally substituted with one or more R.sub.4 and/or optionally fused with a phenyl, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic cycloalkyl, or bicyclic cycloalkyl moiety, each moiety optionally substituted with one or two R.sub.5.

20. The compound of any one of claims 1 to 15, wherein X and Y, together with the atoms to which

they are attached, form a 16-member macrocycle, the macrocycle optionally substituted with one or more R.sub.4 and/or optionally fused with a phenyl, monocyclic heteroaryl, monocyclic heterocyclyl, monocyclic cycloalkyl, or bicyclic cycloalkyl moiety, each moiety optionally substituted with one or two R.sub.5.

21. The compound of any one of claims 1 to 15, wherein the ##STR00087## portion of the macrocycle has the following structure, where * notes the X-position and ** notes the Y-position: ##STR00088## ##STR00089## each further optionally substituted with one or more of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy.

22. The compound of any one of claims 1 to 15, wherein the ##STR00090## portion of the macrocycle has the following structure, where * notes the X-position and ** notes the Y-position: ##STR00091## ##STR00092##

23. The compound of claim 11, wherein the ##STR00093## portion of the macrocycle has the following structure, where * notes the X-position and ** notes the Y-position: ##STR00094## each further optionally substituted with one or more of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy.

24. The compound of claim 15, wherein the ##STR00095## portion of the macrocycle has the following structure, where * notes the X-position and ** notes the Y-position: ##STR00096## each further optionally substituted with one or more of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, —NH.sub.2, —NH(C.sub.1-C.sub.6 alkyl), —N(C.sub.1-C.sub.6 alkyl).sub.2, —OH, C.sub.1-C.sub.6 alkoxy, or C.sub.1-C.sub.6 haloalkoxy.

25. The compound of any one of claims 1 to 15, which has the structure: ##STR00097##

26. The compound of claim 25, wherein each R.sub.4 is independently selected from the group consisting of halogen, C.sub.1-C.sub.6 alkyl, C.sub.1-C.sub.6 haloalkyl, hydroxy(C.sub.1-C.sub.6 alkyl), amino(C.sub.1-C.sub.6 alkyl), carboxy(C.sub.1-C.sub.6 alkyl), —(C.sub.1-C.sub.6 alkyl)-CONH.sub.2,1H-imidazol-4-yl-methyl, or benzyl optionally substituted with one or more of halogens or —OH.

27. The compound of claim 1, which is any one listed in Table 4, or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1, which is: aaae-HDAC-1, aaae-HDAC-2, aaap-HDAC-3, or aaeb-HDAC-5, or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising a compound according to any one of claims 1-28 and a pharmaceutically acceptable carrier, solvent, adjuvant or diluent.

30. A method of treating a disease that is ameliorated by the inhibition of histone deacetylase 6 (HDAC6), the method comprising administering to a subject in need of such treatment one or more compounds according to any one of claims 1-28 or a pharmaceutical composition according to claim 29.

31. The method of claim 30, wherein the disease is a neurodegenerative disorder.

32. The method of claim 31, wherein the neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, Huntington's disease, Lewy body disease, Charcot-Marie-Tooth disease, Rett Syndrome, progressive supranuclear palsy, amyotrophic lateral sclerosis, and frontotemporal dementia.

33. The method of claim 31, wherein the neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, or Huntington's disease.

34. The method of claim 30, wherein the disease is cancer.

35. The method of claim 34, wherein the cancer is lymphoproliferative cancer.

36. The method of claim 35, wherein the lymphoproliferative cancer is multiple myeloma, Hodgkin's lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, anaplastic cell lymphoma, chronic lymphocytic leukemia, peripheral T cell lymphoma, cutaneous T cell

lymphoma.
37. The method of claim 34, wherein the cancer is ovarian cancer, breast cancer, bladder cancer, pancreatic cancer, esophageal cancer, colorectal cancer, stomach cancer, lung cancer, or liver cancer.
38. The method of claim 30, wherein the disease is heart disease.
39. The method of claim 38, wherein the heart disease is diastolic dysfunction, coronary heart disease, cardiomyopathy, endocarditis, congenital cardiovascular defects, congestive heart failure, dilated cardiomyopathy, hypertropic cardiomyopathy, valvular heart disease, myocardial infarction, congestive heart failure, diastolic/systolic heart failure, atrial arrhythmia, ventricular arrhythmia, cardiac valve disease, or ischemia.
40. The method of claim 30, wherein the disease is sepsis-induced inflammation.
41. The method of claim 30, wherein the disease is a kidney disease.
42. A method of inhibiting HDAC6, the method comprising administering one or more compounds according to any one of claims 1-28 or a pharmaceutical composition according to claim 29.
43. Use of one or more compounds according to any one of claims 1-28 or a pharmaceutical composition according to claim 29 for treating a disease that is ameliorated by the inhibition of HDACS.
44. The use of claim 43, wherein the disease is a neurodegenerative disorder.
45. The use of claim 44, wherein the neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, Huntington's disease, Lewy body disease, Charcot-Marie-Tooth disease, Rett Syndrome, progressive supranuclear palsy, amyotrophic lateral sclerosis, and frontotemporal dementia.
46. The use of claim 44, wherein the neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, or Huntington's disease.
47. The use of claim 43, wherein the disease is cancer.
48. The use of claim 47, wherein the cancer is lymphoproliferative cancer.
49. The use of claim 47, wherein the lymphoproliferative cancer is multiple myeloma, Hodgkin's lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, anaplastic cell lymphoma, chronic lymphocytic leukemia, peripheral T cell lymphoma, cutaneous T cell lymphoma.
50. The use of claim 47, wherein the cancer is ovarian cancer, breast cancer, bladder cancer, pancreatic cancer, esophageal cancer, colorectal cancer, stomach cancer, lung cancer, or liver cancer.
51. The use of claim 43, wherein the disease is heart disease.
52. The use of claim 51, wherein the heart disease is diastolic dysfunction, coronary heart disease, cardiomyopathy, endocarditis, congenital cardiovascular defects, congestive heart failure, dilated cardiomyopathy, hypertropic cardiomyopathy, valvular heart disease, myocardial infarction, congestive heart failure, diastolic/systolic heart failure, atrial arrhythmia, ventricular arrhythmia, cardiac valve disease, or ischemia.
53. The use of claim 43, wherein the disease is sepsis-induced inflammation.
54. The use of claim 43, wherein the disease is a kidney disease.
55. Use of one or more compounds according to any one of claims 1-28 or a pharmaceutical composition according to claim 29 for inhibiting HDAC6.