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(54) **TREATMENT OF NEURODEGENERATIVE DISEASES AND CANCER OF THE BRAIN USING HISTONE DEACETYLASE INHIBITORS**

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(60) Provisional application No. 60/329,705, filed on Oct. 16, 2001.

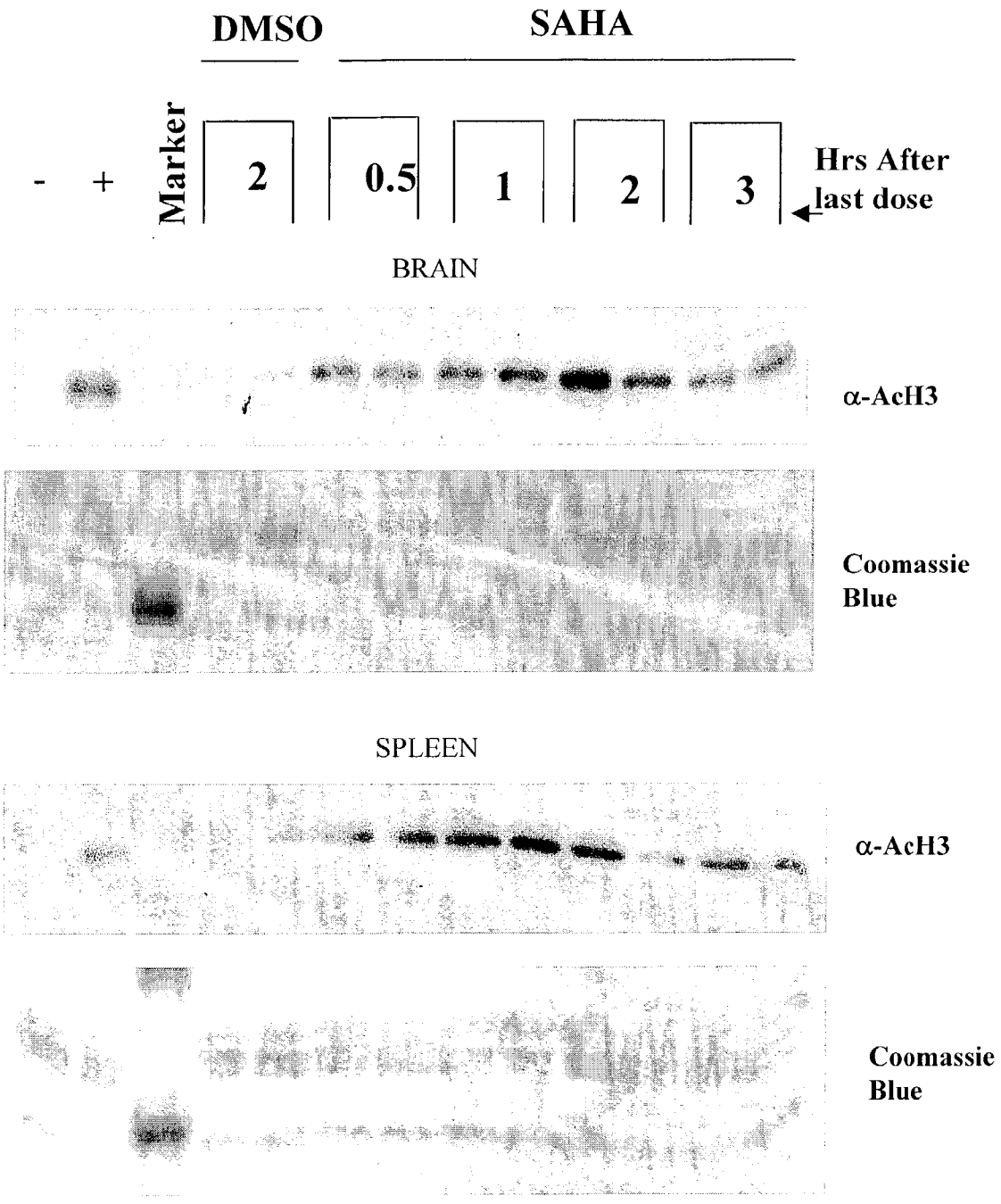
Publication Classification

(51) **Int. Cl.**[7] **A61K 31/19**

(52) **U.S. Cl.** **514/575**

(57) **ABSTRACT**

The present application is directed to a method of treating diseases of the central nervous system (CNS) comprising administering to a individual in need of treatment a therapeutically effective amount of an inhibitor of histone deacetylase. In particular embodiments, the CNS disease is a neurodegenerative disease. In further embodiments, the neurogenerative disease is an inherited neurodegenerative disease, such as those inherited neurodegenerative diseases which are polyglutamine expansion diseases. The individual can be a mammal such as a primate or human.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Hrs After last dose
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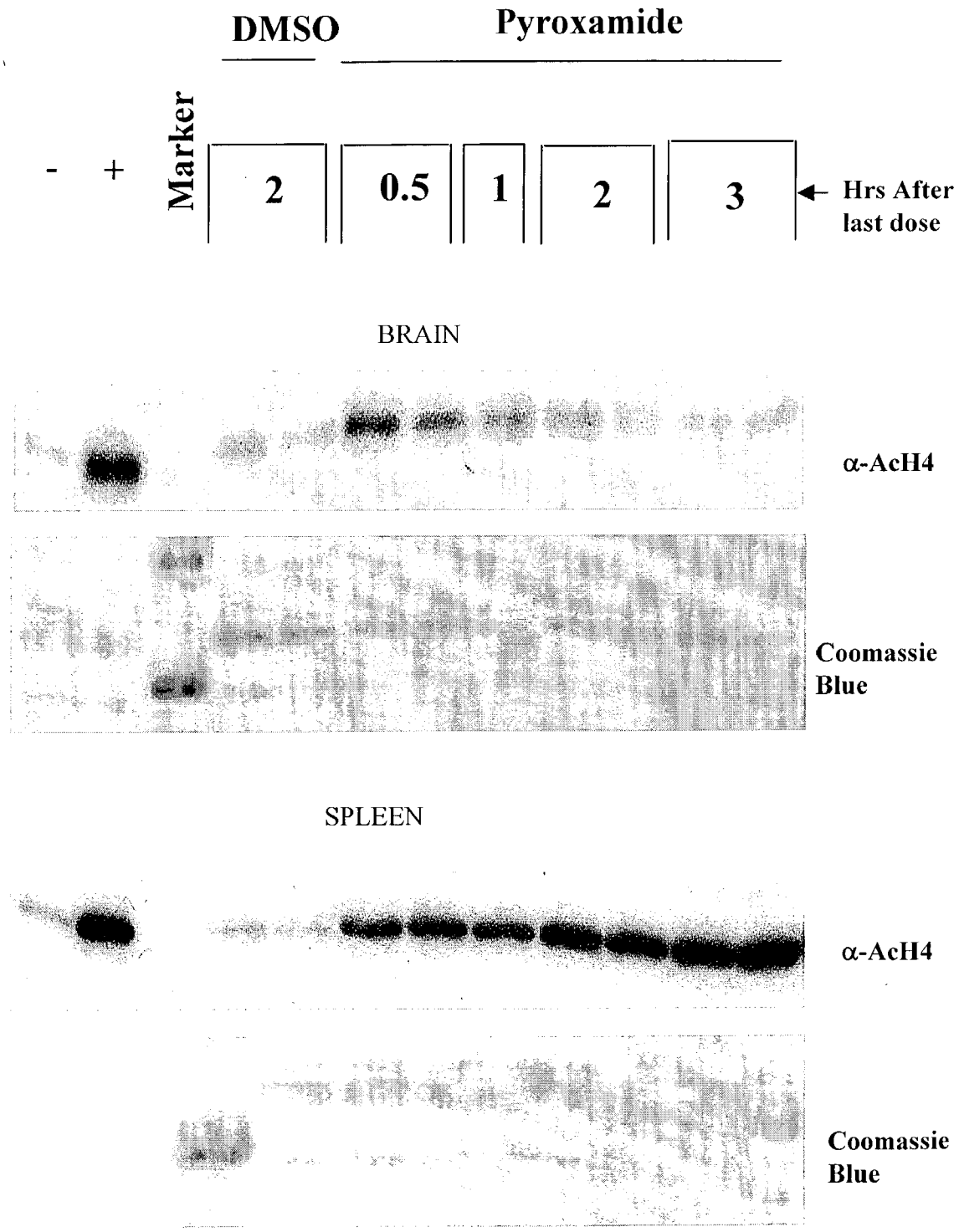
α-AcH3
Coomassie Blue
SPLEEN
α-AcH3
Coomassie Blue

FIG. 1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Hrs After last dose
BRAIN
α-AcH4
Coomassie Blue
SPLEEN
α-AcH4
Coomassie Blue

FIG. 2

TREATMENT OF NEURODEGENERATIVE DISEASES AND CANCER OF THE BRAIN USING HISTONE DEACETYLASE INHIBITORS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/329,705 filed on Oct. 16, 2001. The entire teachings of the above-referenced application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Compounds which inhibit histone deacetylase (HDACs) have been shown to cause growth arrest, differentiation and/or apoptosis of many different types of tumor cell in vitro and in vivo. HDACs catalyze the removal of the acetyl group from the lysine residues in the N-terminal tails of nucleosomal core histones resulting in a more compact chromatin structure, a configuration that is generally associated with repression of transcription. These HDAC inhibitors fall into four general classes: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); hydroxamic acids (e.g., SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides (Trapoxin A and Apicidin); 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such compounds can be found in U.S. Pat. No. 5,369,108, issued on Nov. 29, 1994, U.S. Pat. No. 5,700,811, issued on Dec. 23, 1997, and U.S. Pat. No. 5,773,474, issued on Jun. 30, 1998 to Breslow et al., U.S. Pat. No. 5,055,608, issued on Oct. 8, 1991, and U.S. Pat. No. 5,175,191, issued on Dec. 29, 1992 to Marks et al., as well as, Yoshida, M., et al., Bioassays 17, 423-430 (1995), Saito, A., et al., PNAS USA 96, 4592-4597, (1999), Furamai R. et al., PNAS USA 98 (1), 87-92 (2001), Komatsu, Y., et al., Cancer Res. 61(11), 4459-4466 (2001), Su, G. H., et al., Cancer Res. 60, 3137-3142 (2000), Lee, B. I. et al., Cancer Res. 61(3), 931-934, Suzuki, T., et al., J. Med. Chem. 42(15), 3001-3003 (1999) and published PCT Application WO 01/18171 published on Mar. 15, 2001 to Solan-Kettering Institute for Cancer Research and The Trustees of Columbia University the entire content of all of which are hereby incorporated by reference.

[0003] Preferred hydroxamic acid based HDAC inhibitors are suberoylanilide hydroxamic acid (SAHA) and pyroxamide. SAHA has been shown to bind directly in the catalytic pocket of the histone deacetylase enzyme. SAHA induces cell cycle arrest, differentiation and/or apoptosis of transformed cells in culture and inhibits tumor growth in rodents. SAHA is effective at inducing these effects in both solid tumors and hematological cancers. It has been shown that SAHA is effective at inhibiting tumor growth in animals with no toxicity to the animal. The SAHA-induced inhibition of tumor growth is associated with an accumulation of acetylated histones in the tumor. SAHA is effective at inhibiting the development and continued growth of carcinogen-induced (N-methylnitrosourea) mammary tumors in rats. SAHA was administered to the rats in their diet over the 130 days of the study. Thus, SAHA is a nontoxic, orally active antitumor agent whose mechanism of action involves the inhibition of histone deacetylase activity.

SUMMARY OF THE INVENTION

[0004] It has been surprisingly discovered that certain HDAC inhibitors, for example, SAHA and pyroxamide can cross the blood brain barrier at sufficient amounts to significantly inhibit HDAC activity causing the accumulation of acetylated histones in the brain. This discovery therefore provides for the use of HDAC inhibitors in the treatment of disorders of the central nervous system including cancer of the brain and neurodegenerative diseases.

[0005] The present application is directed to a method of treating diseases of the central nervous system (CNS) comprising administering to a individual in need of treatment a therapeutically effective amount of an inhibitor of histone deacetylase. In particular embodiments, the CNS disease is a neurodegenerative disease. In further embodiments, the neurogenerative disease is an inherited neurodegenerative disease, such as those inherited neurodegenerative diseases which are polyglutamine expansion diseases.

[0006] The individual can be a mammal such as a primate or human.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] **FIG. 1** is a scan of a Western blot and Coomassie stained gel indicating levels of acetylated histone (αAcH3) at the indicated timepoints following treatment with vehicle (DMSO) or three doses of SAHA (100 mg/kg/hr).

[0008] **FIG. 2** is a scan of a Western blot and Coomassie stained gel indicating levels of acetylated histone (αAcH4) at the indicated timepoints following treatment with vehicle (DMSO) or three doses of Pyroxamide (100 mg/kg/hr).

DETAILED DESCRIPTION OF THE INVENTION

[0009] The present application is directed to a method of treating diseases of the central nervous system (CNS) comprising administering to a individual in need of treatment a therapeutically effective amount of an inhibitor of histone deacetylase. In particular embodiments, the CNS disease is a neurodegenerative disease. In further embodiments, the neurogenerative disease is an inherited neurodegenerative disease, such as those inherited neurodegenerative diseases which are polyglutamine expansion diseases. In a preferred embodiment, the neurodegenerative disease is Huntington's disease.

[0010] The individual can be a mammal such as a primate or human.

[0011] Therapeutically effective amount as that term is used herein refers to an amount which elicits the desired therapeutic effect. The therapeutic effect is dependent upon the disease being treated. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disease and/or inhibition (partial or complete) of progression of the disease. The amount needed to elicit the therapeutic response can be determined based on the age, health, size and sex of the patient. Optimal amounts can also be determined based on monitoring of the patient's response to treatment.

[0012] Generally, diseases of the central nervous system, are referred to as neurodegenerative, indicating that they are characterized by gradually evolving, relentlessly progressive neuronal death occurring for reasons that are still largely unknown. The identification of these diseases depends upon exclusion of such possible causative factors as

infections, metabolic derangements, and intoxications. A considerable proportion of the disorders classed as neurogenerative are genetic, with either dominant or recessive inheritance. Others, however, occur only sporadically as isolated instances in a given family. Classification of the degenerative diseases cannot be based upon any exact knowledge of cause or pathogenesis; their subdivision into individual syndromes rests on descriptive criteria based largely upon neuropathologic and clinical aspects. This group of diseases presents as several distinct clinical syndromes, the recognition of which can assist the clinician in arriving at a diagnosis.

[0013] However, research in the past decade has uncovered a new classification of inherited neurodegenerative diseases, the polyglutamine (polyQ) expansion diseases. In each, the underlying mutation is an expansion of a CAG trinucleotide repeat that encodes polyQ in the respective disease protein. All are progressive, ultimately fatal disorders that typically begin in adulthood and progress over 10 to 30 years. The clinical features and pattern of neuronal degeneration differ among the diseases, yet increasing evidence suggests that polyQ diseases share important pathogenic features. In particular, abnormal protein conformations(s) promoted by polyQ expansion seem to be central to pathogenesis. This class of PolyQ expansion neurodegenerative disease are Huntington's Disease (HD), Dentatorubralpallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (SBMA), and five spinocerebellar ataxias (SCA1, SCA2, SCA3/MJD(Machado-Joseph Disease), SCA6 and SCA7). These diseases are listed in the general listing of neurodegenrative disease below. Many of these diseases not yet connected with PolyQ expansion are thought to result from abnormal protein folding and aggregation (e.g., Alzheimer's disease).

[0014] Generally, neurodegenerative diseases can be grouped as follows:

[0015] I. Disorders characterized by progressive dementia in the absence of other prominent neurologic signs.

[0016] A. Alzheimer's disease

[0017] B. Senile dementia of the Alzheimer type

[0018] C. Pick's disease (lobar atrophy)

[0019] II. Syndromes combining progressive dementia with other prominent neurologic abnormalities

[0020] A. Mainly in adults

[0021] 1. Huntington's disease

[0022] 2. Multiple system atrophy combining dementia with ataxia and/or manifestations of Parkinson's disease

[0023] 3. Progressive supranuclear aplsy (Steel-Richardson-Olszewski)

[0024] 4. Diffuse Lewy body disease

[0025] 5. Corticodentatonigral degeneration

[0026] B. Mainly in children or young adults

[0027] 1. Hallervorden-Spatz disease

[0028] 2. Progressive familial myoclonic epilepsy

[0029] III. Syndromes of gradually developing abnormalities of posture and movement

[0030] A. Paralysis agitans (Parkinson's disease)

[0031] B. Striatonigral degeneration

[0032] C. Progressive supranuclear palsy

[0033] D. Torsion dystonia (torsion spasm; dystonia musculorum deformans)

[0034] E. Spasmodic torticollis and other dyskinesis

[0035] F. Familial tremor

[0036] G. Gilles de la Tourette syndrome

[0037] IV. Syndromes of progressive ataxia

[0038] A. Cerebellar degenerations

[0039] 1. Cerebellar cortical degeneration

[0040] 2. Olivopontocerebellar atrophy (OPCA)

[0041] B. Spinocerebellar degeneration (Friedreich's atazia and related disorders)

[0042] V. Syndrome of central autonomic nervous system failure (Shy-Drager syndrome)

[0043] VI. Syndromes of muscular weakness and wasting without sensory changes (motor neuron disease

[0044] A. Amyotrophic lateral sclerosis

[0045] B. Spinal muscular atrophy

[0046] 1. Infantile spinal muscular atrophy (Werdnig-Hoffman)

[0047] 2. Juvenile spinal muscular atrophy (Wohlfart-Kugelberg-Welander)

[0048] 3. Other forms of familial spinal muscular atrophy

[0049] C. Primary lateral sclerosis

[0050] D. Hereditary spastic paraplegia

[0051] VII. Syndromes combining muscular weakness and wasting with sensory changes (progressive neural muscular atrophy; chronic familial polyneuropathies)

[0052] A. Peroneal muscular atrophy (Charcot-Marie-Tooth)

[0053] B. Hypertrophic interstitial polyneuropathy (Dejerine-Sottas)

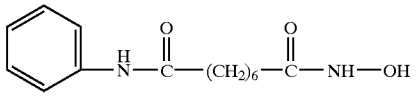
[0054] C. Miscellaneous forms of chronic progressive neuropathy

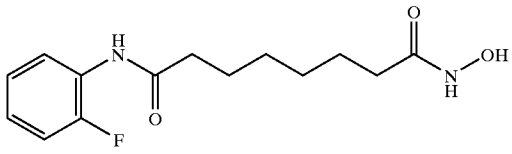
[0055] VIII. Syndromes of progressive visual loss

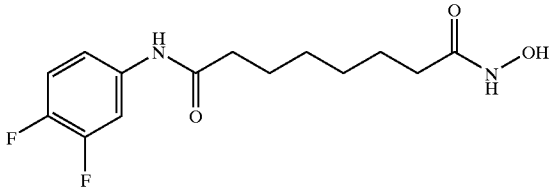
[0056] A. Pigmentary degeneration of the retina (retinitis pigmentosa)

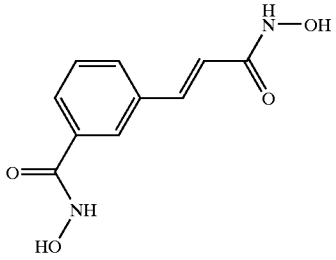
[0057] B. Hereditary optic atrophy (Leber's disease)

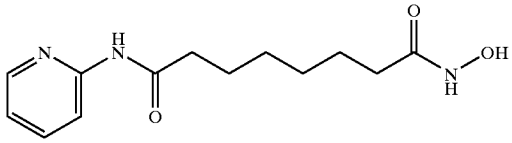
[0058] HDAC inhibitors suitable for use in the invention include, but are not limited to the following specific structures:

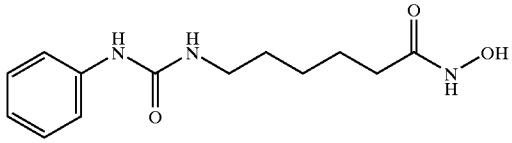


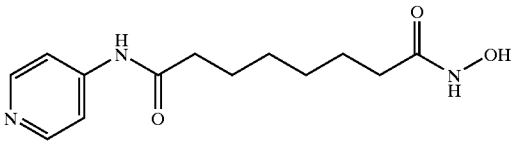


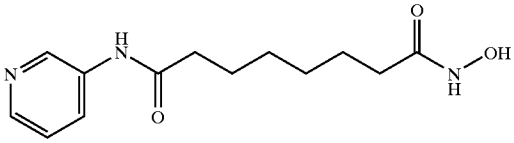


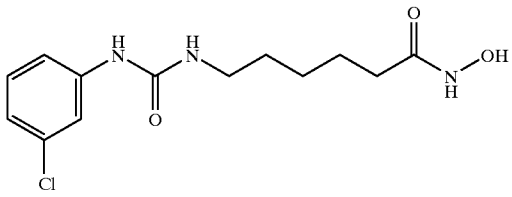












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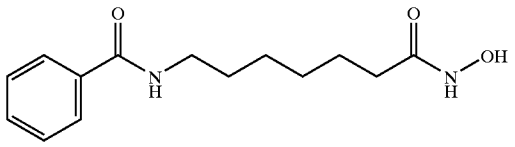

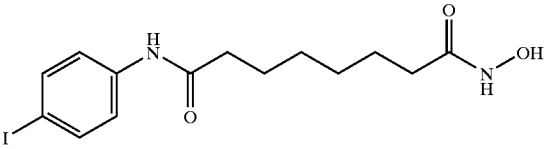

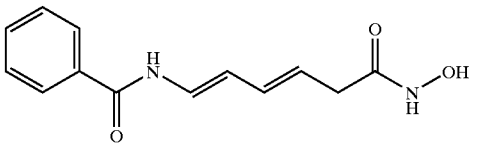

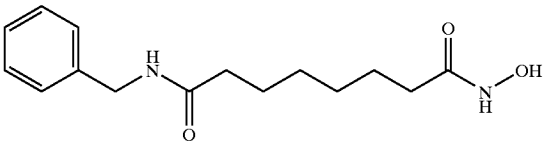

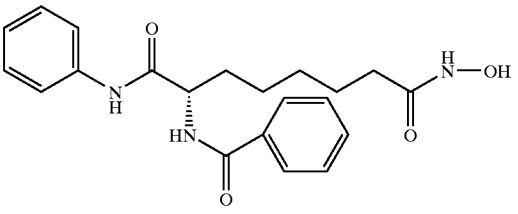

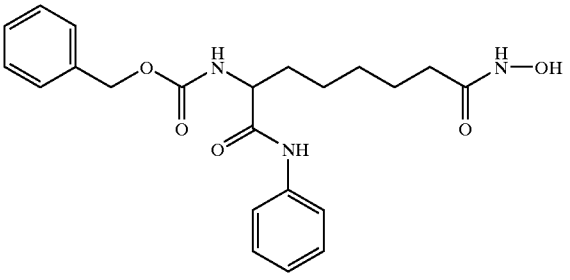

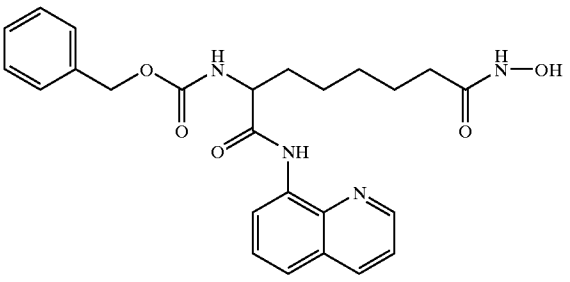

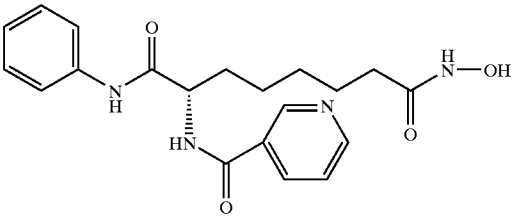

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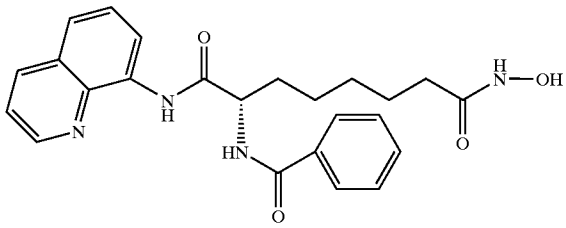

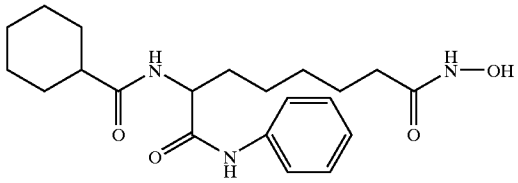

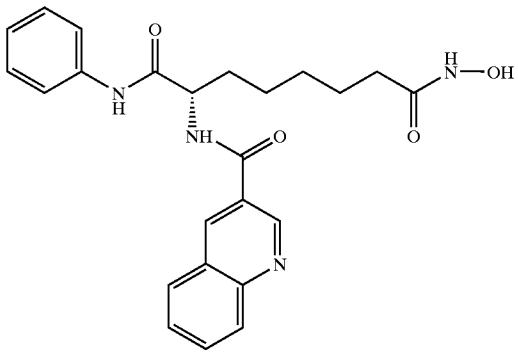

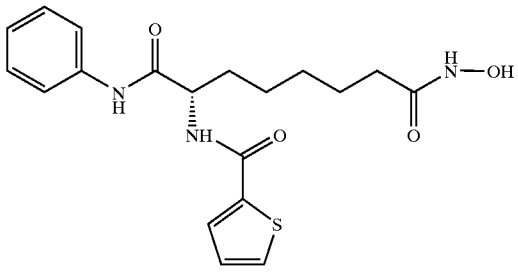

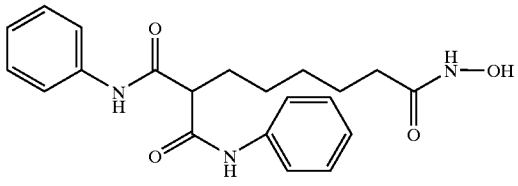

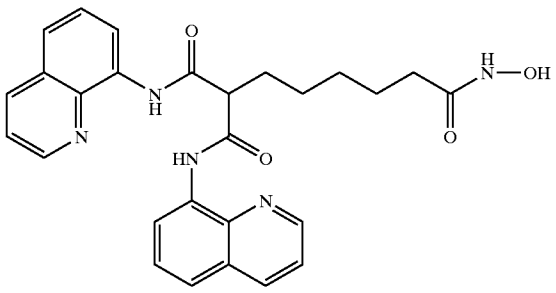

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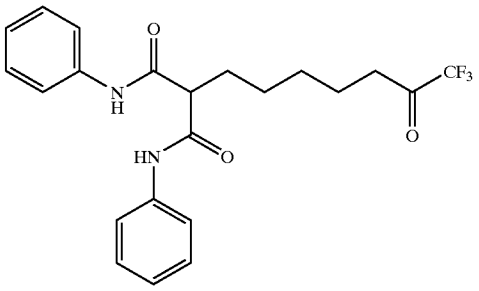

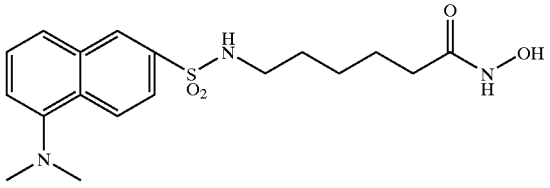

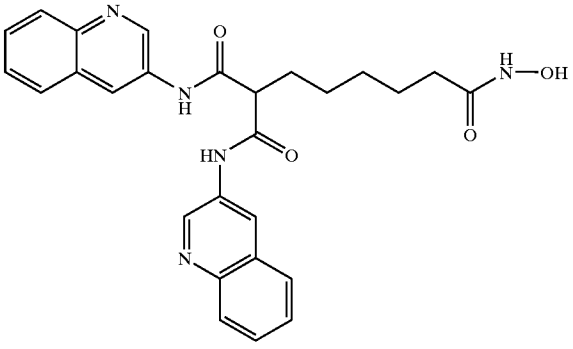

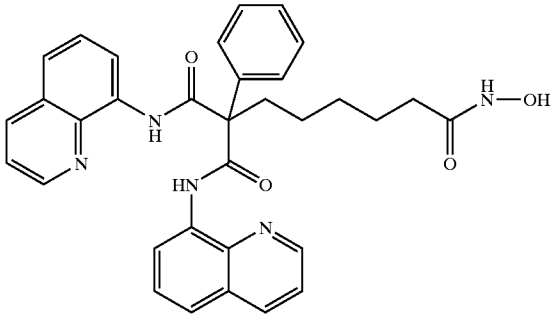

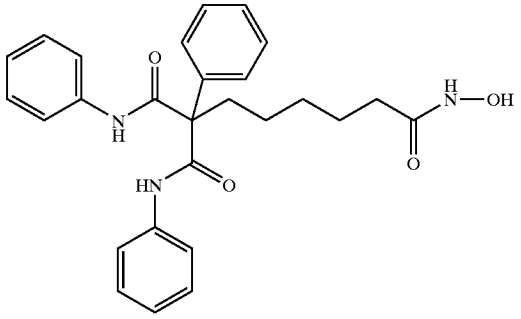

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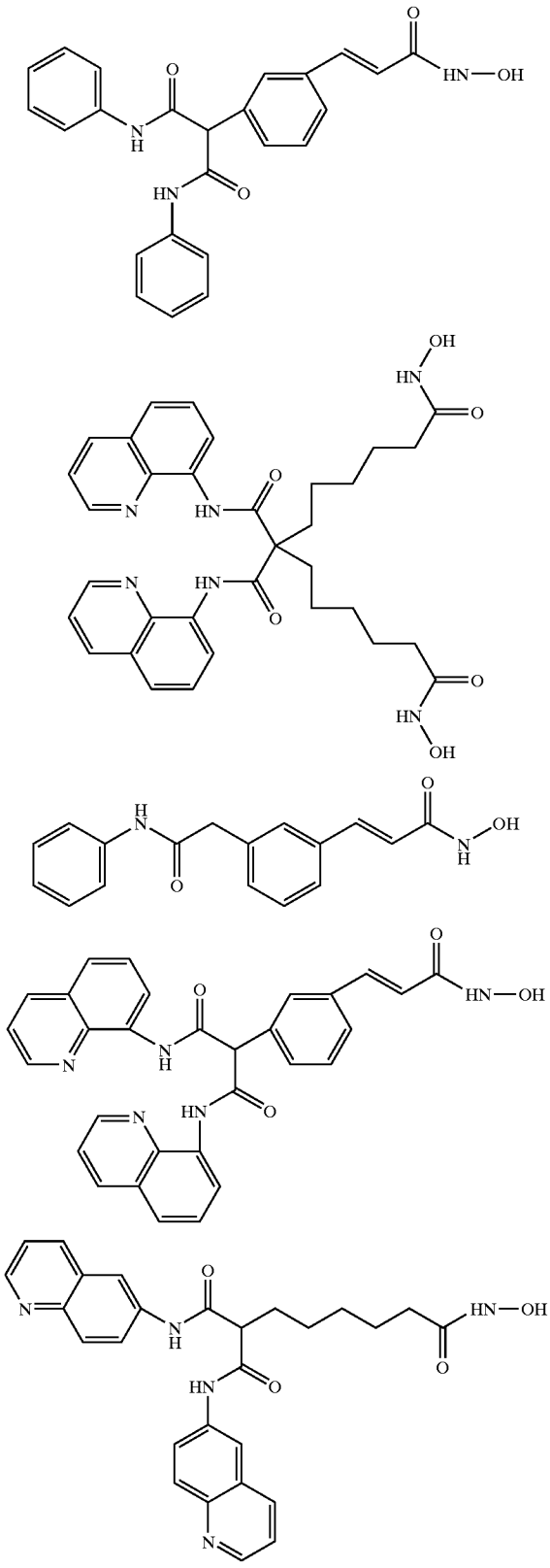


[0059] Further, HDAC inhibitors which can be useful can include the four general classes described above: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); hydroxamic acids (e.g., SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides (Trapoxin A and Apicidin; 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such compounds can be found in U.S. Pat. No. 5,369,108, issued on Nov. 29, 1994, U.S. Pat. No. 5,700,811, issued on Dec. 23, 1997, and U.S. Pat. No. 5,773,474, issued on Jun. 30, 1998 to Breslow et al., U.S. Pat. No. 5,055,608, issued on Oct. 8, 1991, and U.S. Pat. No. 5,175,191, issued on Dec. 29, 1992 to Marks et al., as well as, Yoshida, M., et al., Bioassays 17, 423-430 (1995), Saito, A., et al., PNAS USA 96, 4592-4597, (1999), Furamai R. et al., PNAS USA 98 (1), 87-92 (2001), Komatsu, Y., et al., Cancer Res. 61(11), 4459-4466 (2001), Su, G. H., et al., Cancer Res. 60, 3137-3142 (2000), Lee, B. I. et al., Cancer Res. 61(3), 931-934, Suzuki, T., et al., J. Med. Chem. 42(15), 3001-3003 (1999) and published PCT Application WO 01/18171 published on Mar. 15, 2001 to Sloan-Kettering Institute for Cancer Research and The Trustees of Columbia University the entire content of all of which are hereby incorporated by reference.

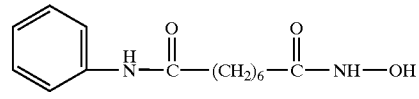
EXPERIMENTAL METHODS

[0060] Mice (2 mice per condition) were injected by intraperitoneal injection (IP) with either SAHA (100 mg/kg), pyroxamide (200 mg/kg), or vehicle (dimethylsulfoxide). Each mouse was administered three injections at the indicated dose at 1 hour intervals. After the final IP injection tissues (brain, spleen or liver) were isolated at the times indicated. Histones were isolated from tissues essentially as described by Yoshida et al., (1990) J. Biol. Chem. 265:17174-17179. Equal amounts of histones (1 μg) were electrophoresed on 15% SDS-polyacrylamide gels and transferred to Hybond-P filters (Amersham). Filters were blocked with 3% milk and probed with a rabbit purified polyclonal anti-acetylated histone H4 antibody (αAc-H4) and anti-acetylated histone H3 antibody (αAc-H3) (Upstate Biotechnology, Inc.). Levels of acetylated histone were visualized using a horseradish peroxidase-conjugated goat anti-rabbit antibody (1:5000) and the SuperSignal chemiluminescent substrate (Pierce). As a loading control for the histone proteins, parallel gels were run and stained with Coomassie Blue (CB). The results are shown in **FIGS. 1 and 2**.

What is claimed is:

1. A method of inhibiting histone deacetylase in the brain of a mammal comprising administering to the mammal a histone deacetylase inhibiting amount of a histone deacetylase inhibitor compound.

2. The method of claim 1, wherein the histone deacetylase inhibitor compound is selected from:



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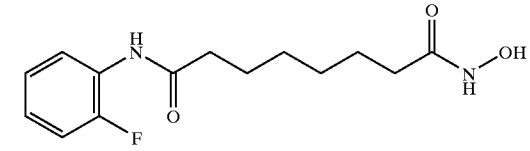

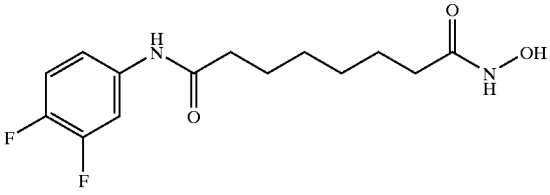

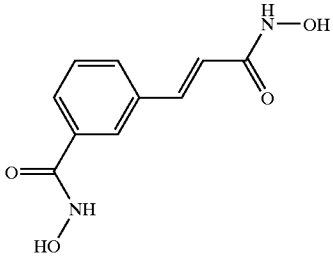

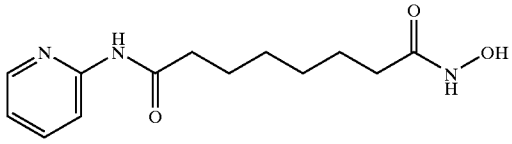

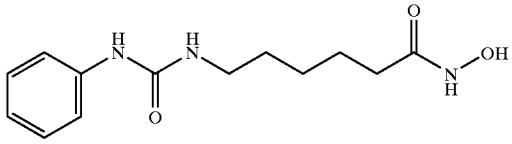

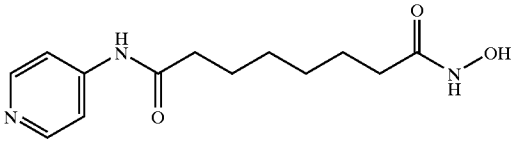

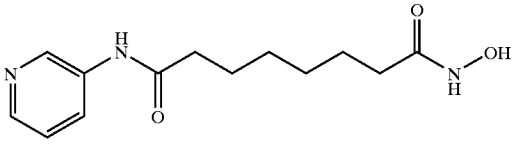

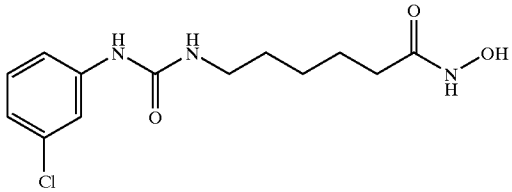

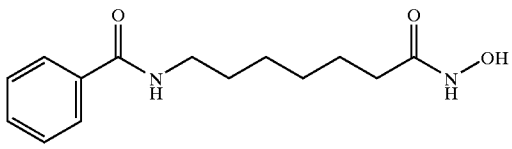

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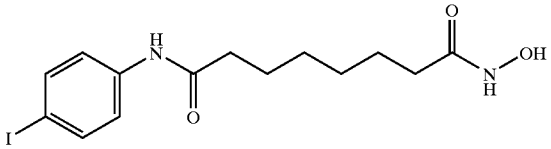

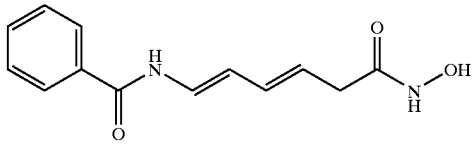

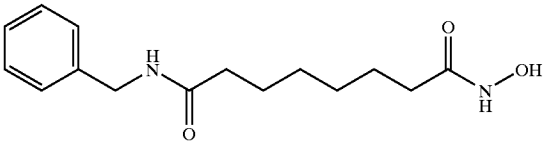

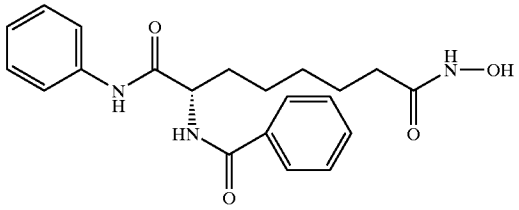

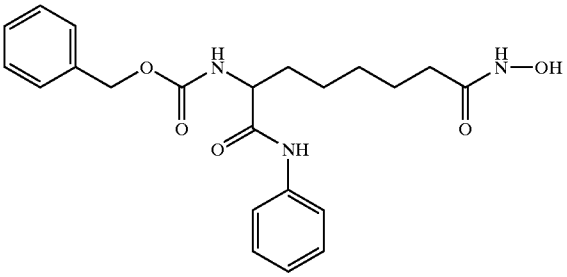

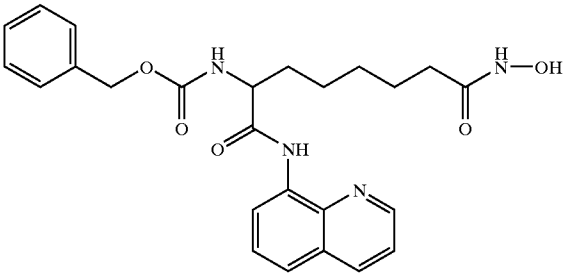

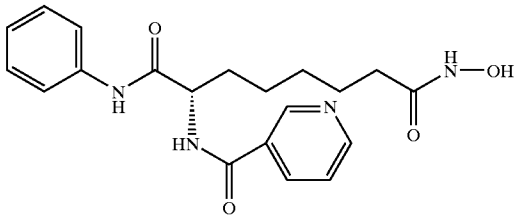

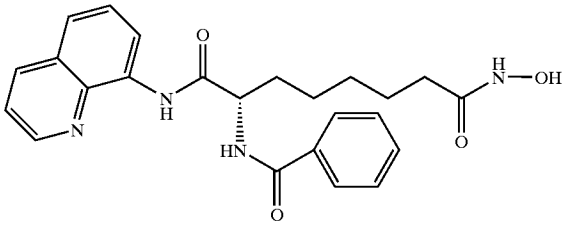

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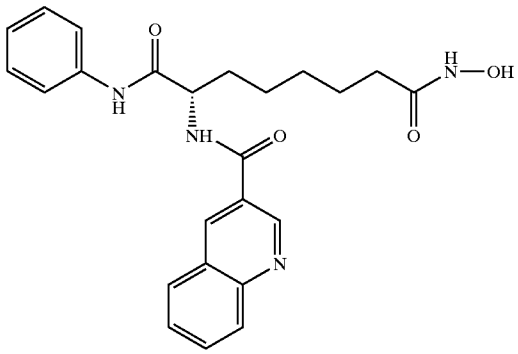

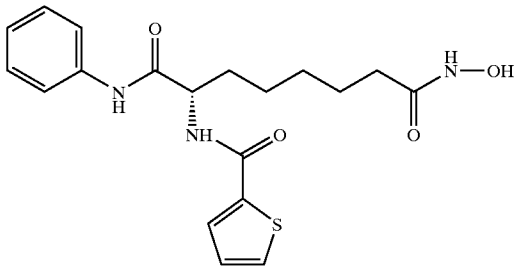

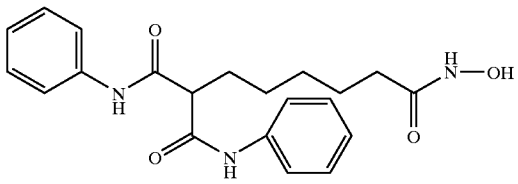

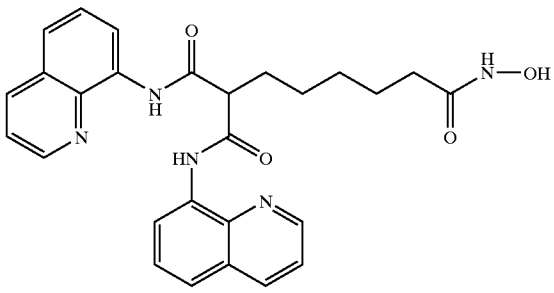

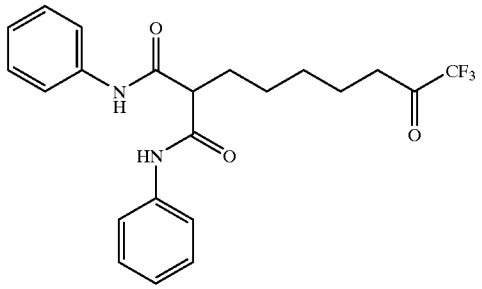

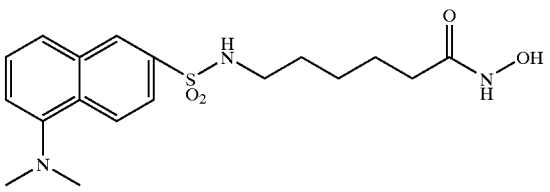

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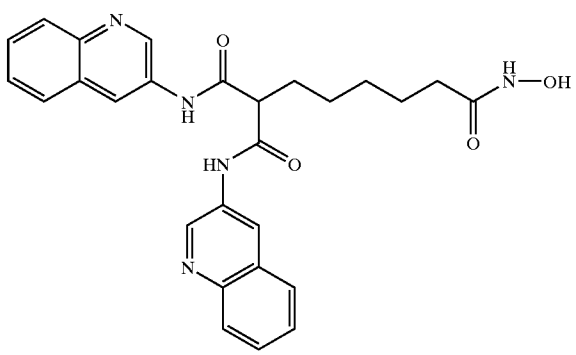

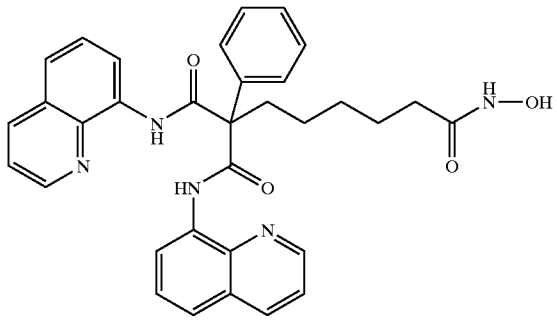

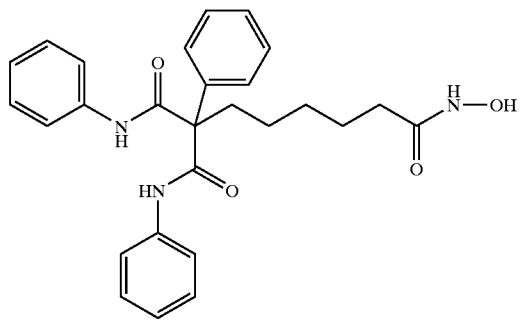

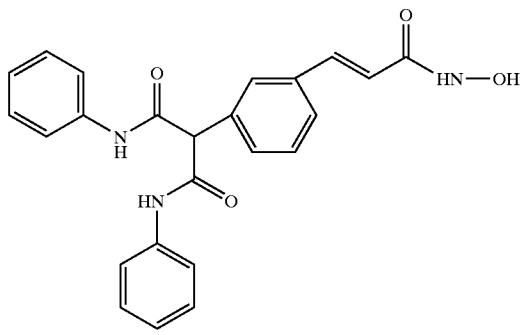

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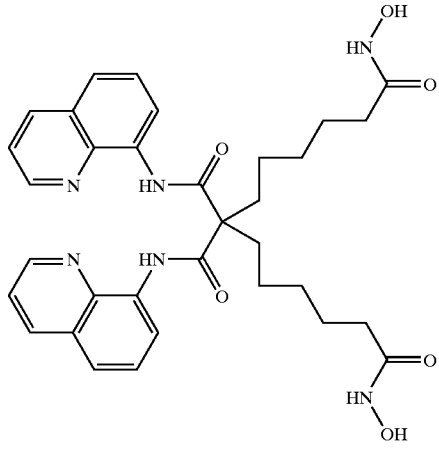
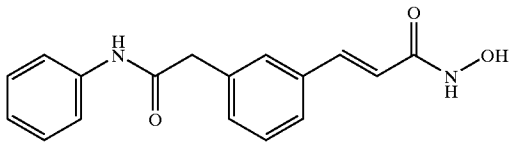
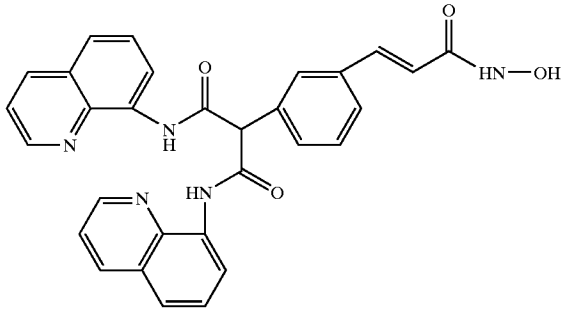
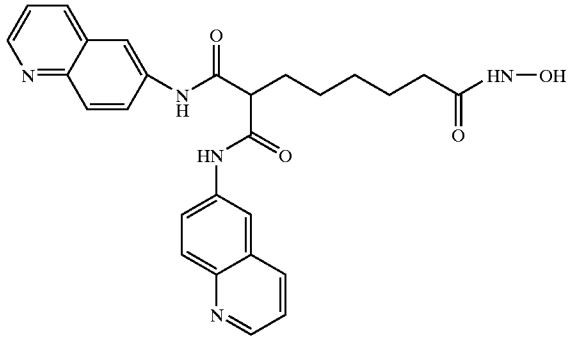


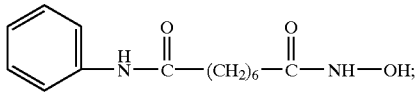






or a pharmaceutically acceptable salt thereof.

3. The method of claim 2, wherein the histone deacetylase inhibitor compound is selected from:



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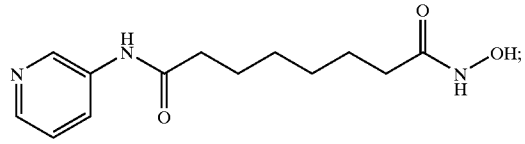
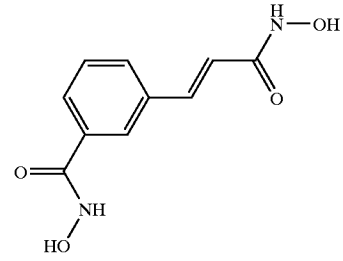




or a pharmaceutically acceptable salt thereof.

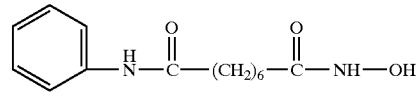
4. A method of treating a disease of the central nervous system in an individual in need thereof comprising administering to the individual a therapeutically effective amount of a histone deacetylase inhibitor compound.

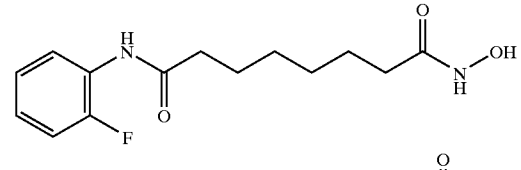
5. The method of claim 4, wherein the disease is a polyglutamine expansion disease.

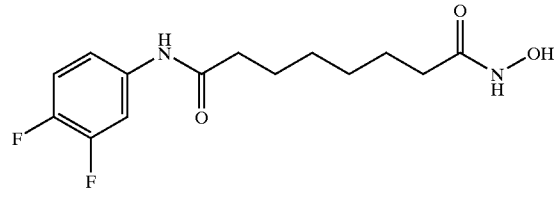
6. The method of claim 5, wherein the polyglutamine expansion disease is Huntington's disease.

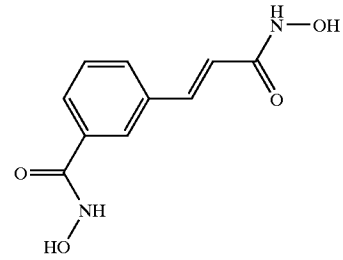
7. The method of claim 4, wherein the individual is a human.

8. The method of claim 4, wherein the inhibitor of histone deacetylase is selected from:









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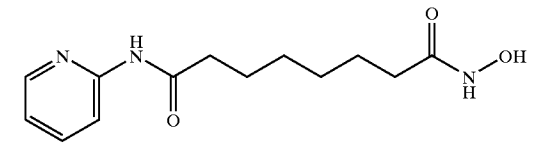

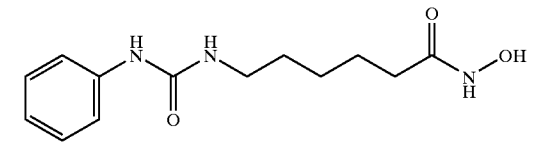

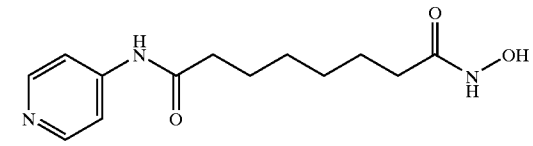

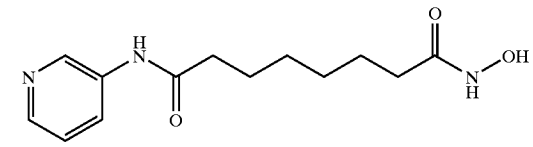

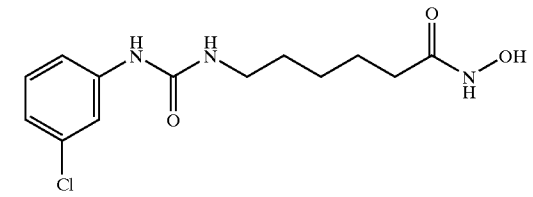

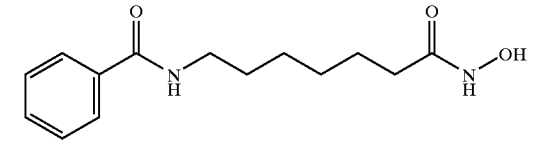

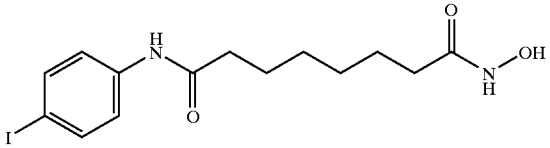

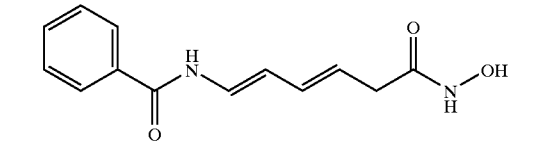

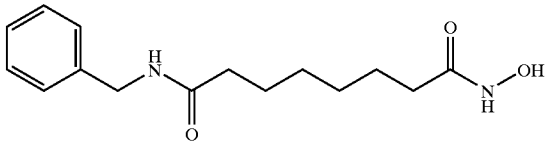

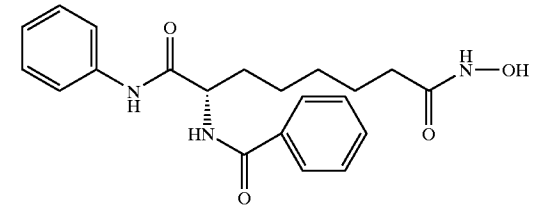

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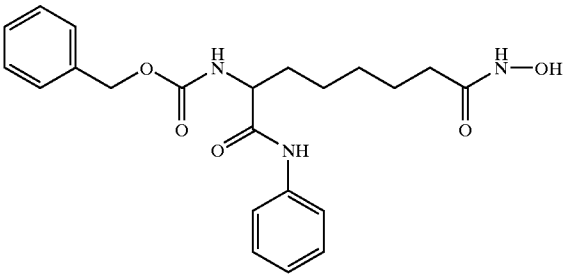

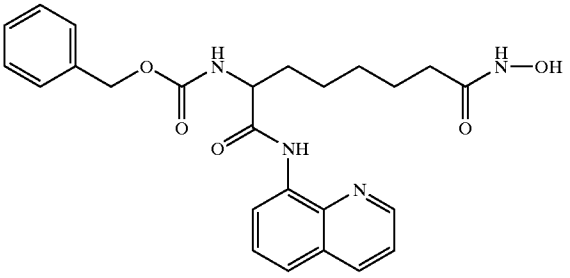

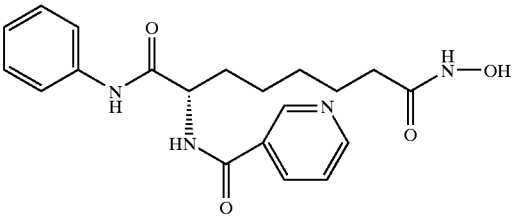

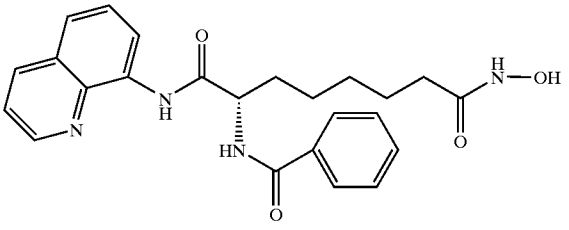

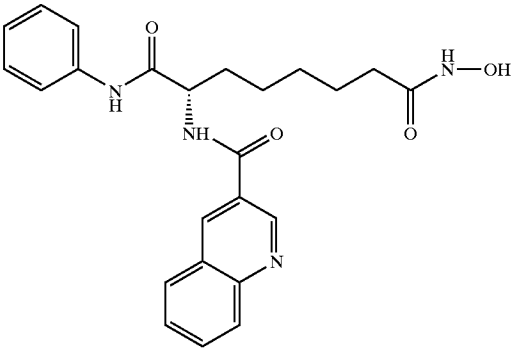

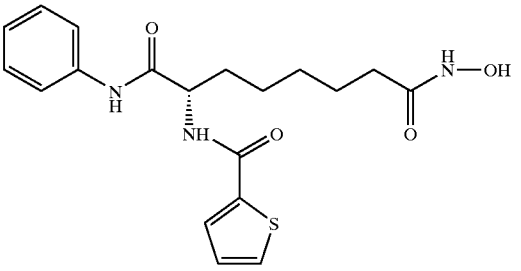

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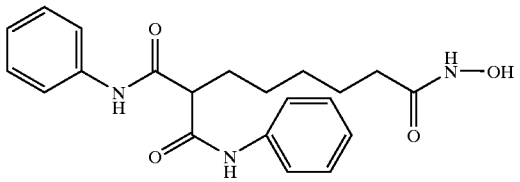

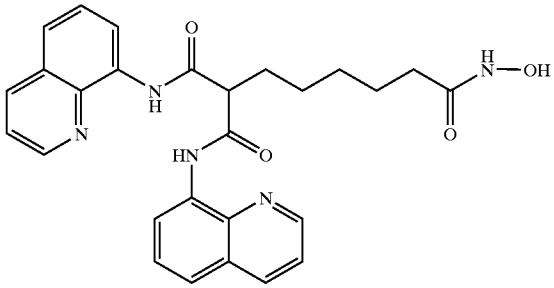

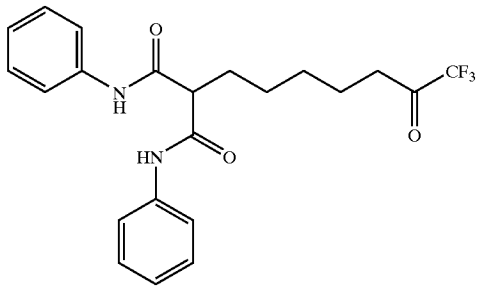

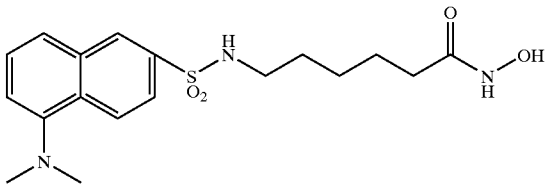

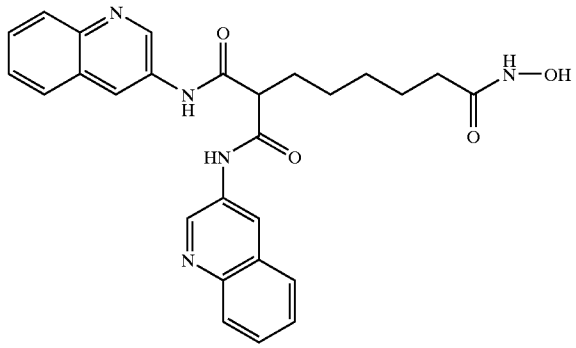

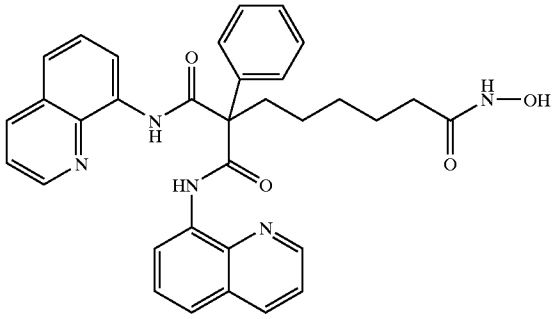

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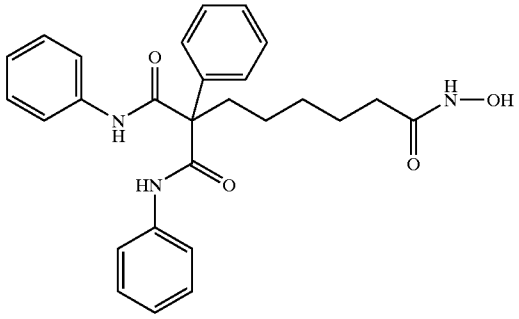

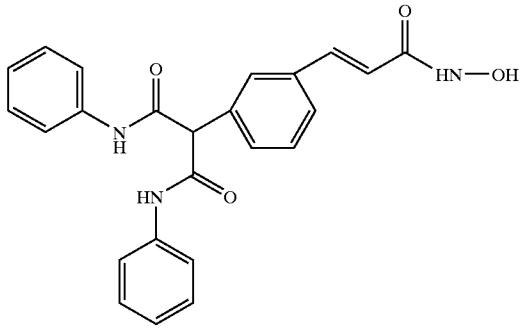

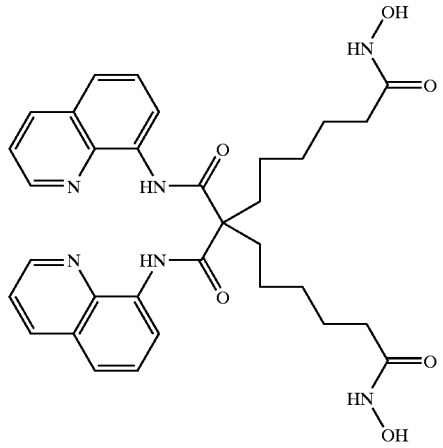

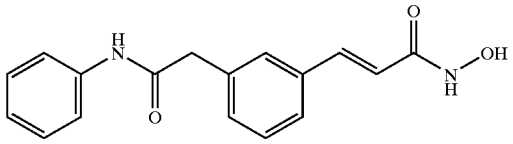

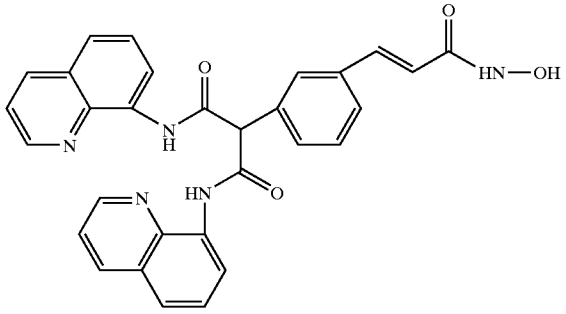

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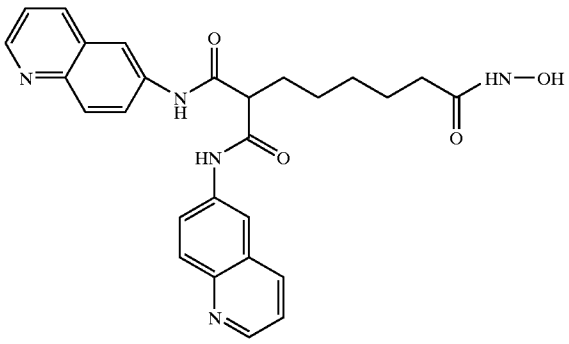
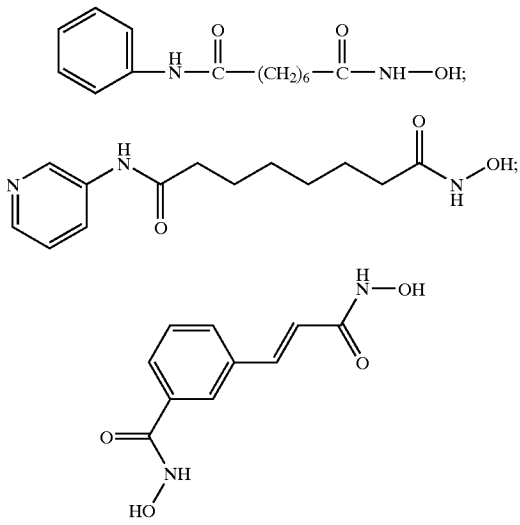


or a pharmaceutically acceptable salt thereof.

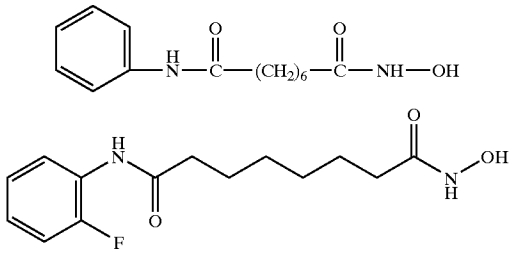
9. The method of claim 8, wherein the histone deacetylase inhibitor compound is selected from:



or a pharmaceutically acceptable salt thereof.

10. A method of treating a brain cancer in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a histone deacetylase inhibitor compound.

11. The method of claim 10, wherein the histone deacetylase inhibitor is selected from:



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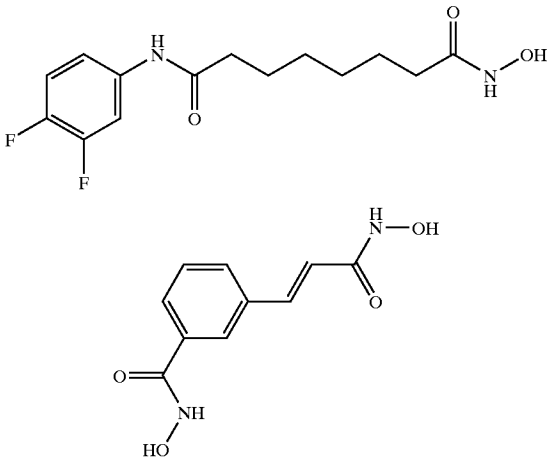

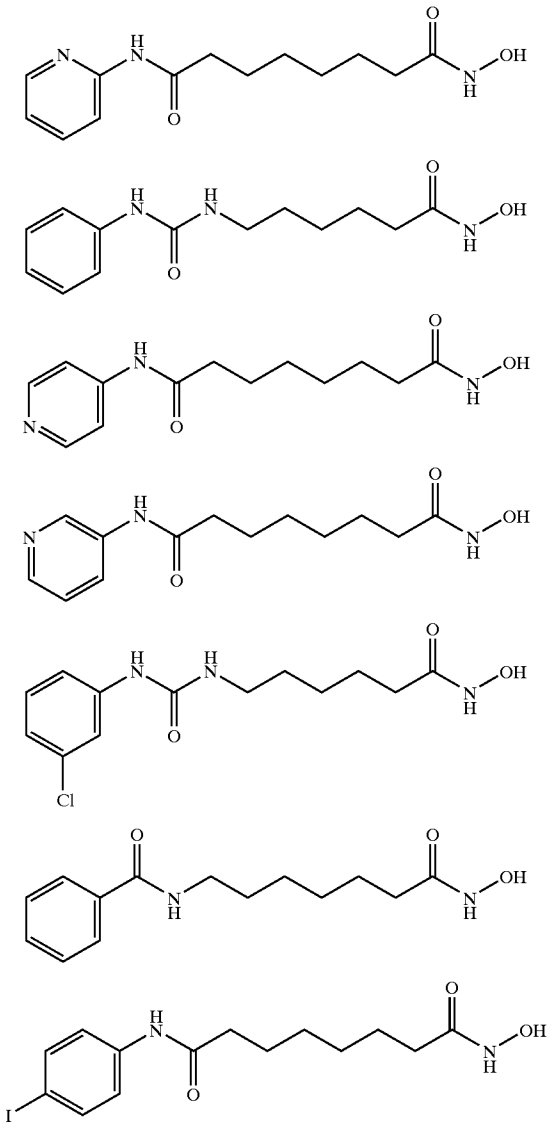

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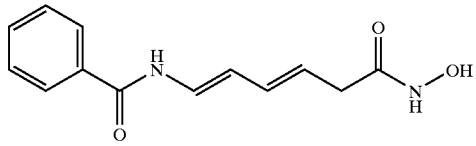

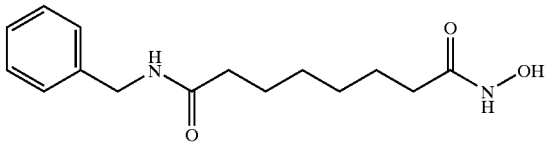

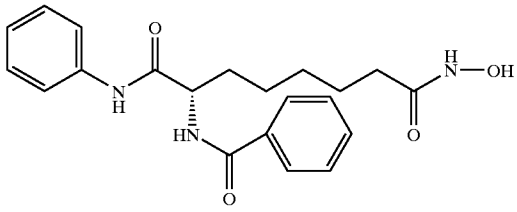

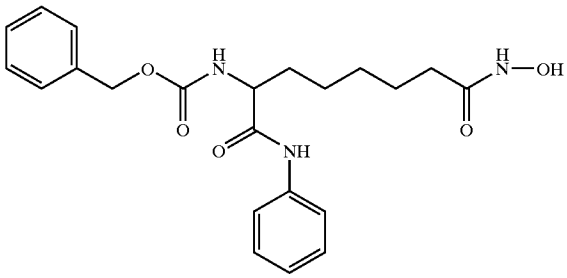

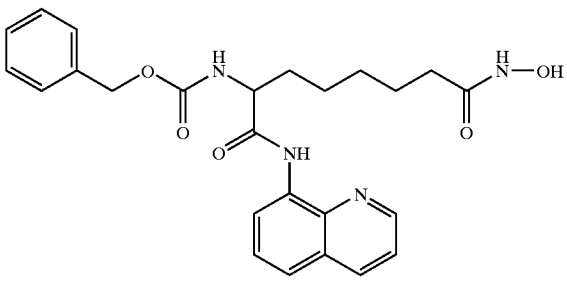

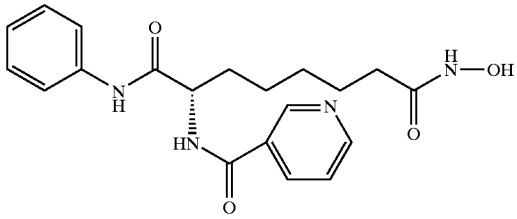

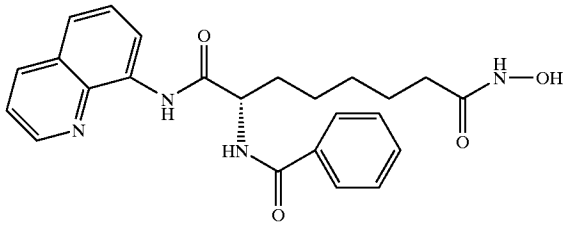

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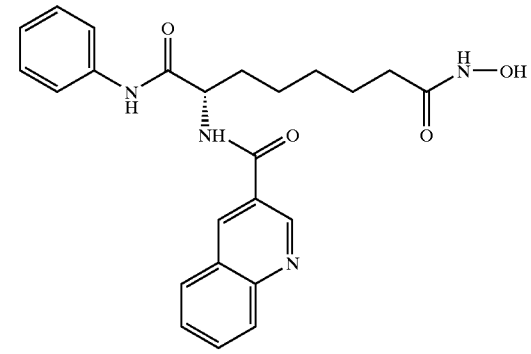

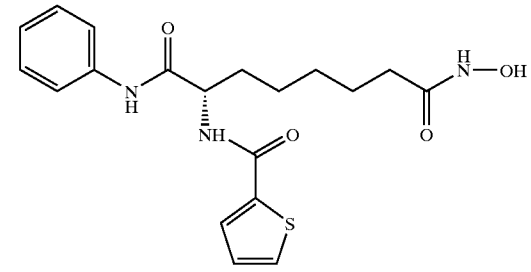

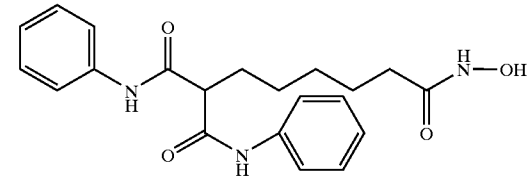

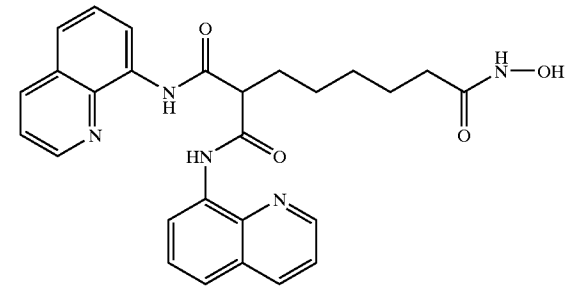

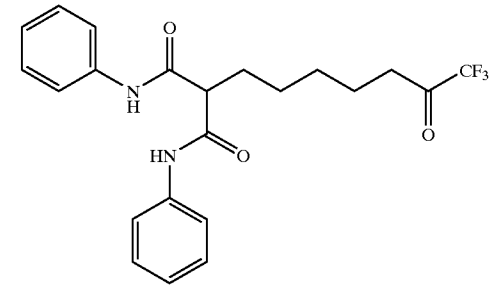

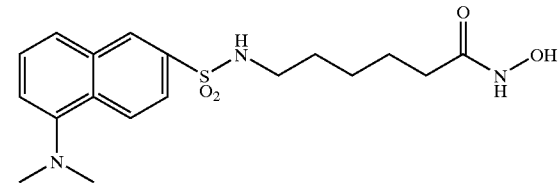

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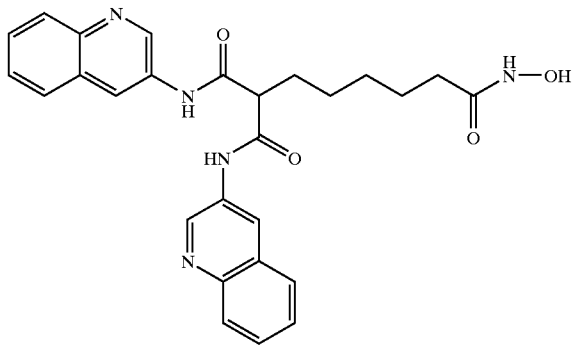

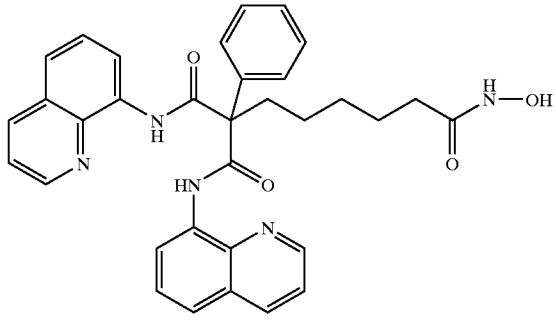

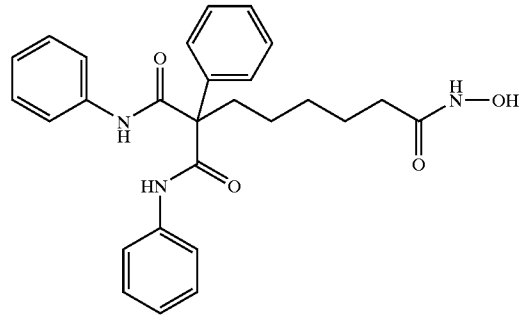

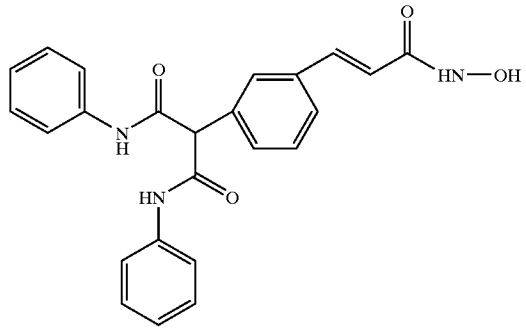

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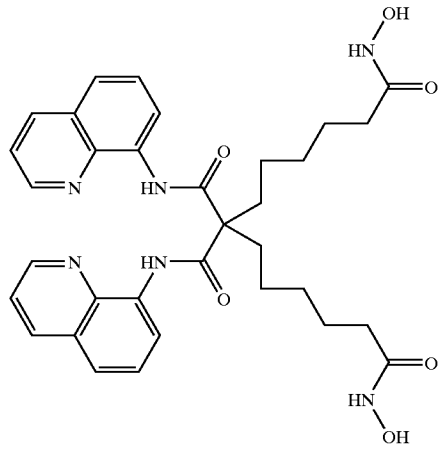
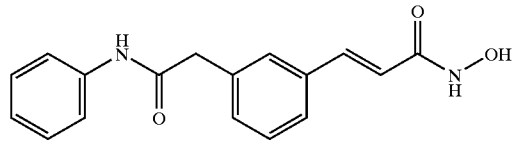
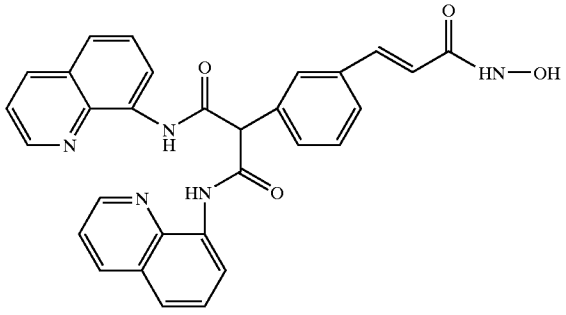
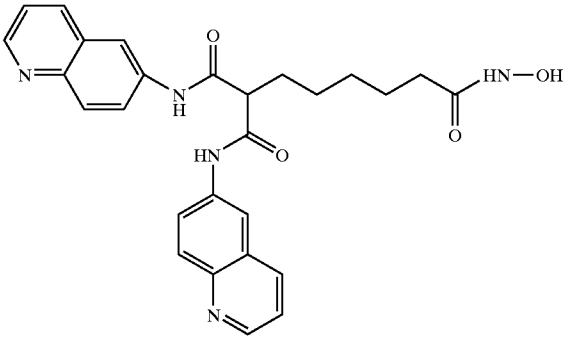


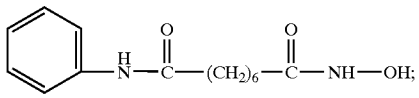


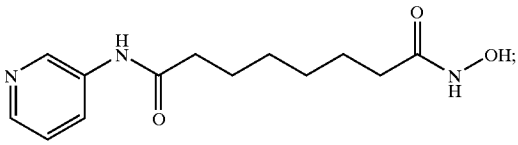




or a pharmaceutically acceptable salt thereof.

12. The method of claim 11, wherein the histone deacetylase inhibitor is selected from:





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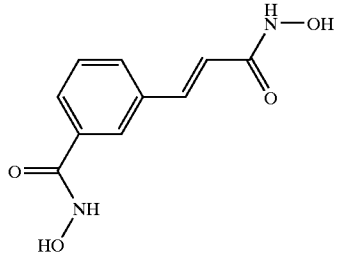

or a pharmaceutically acceptable salt thereof.

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