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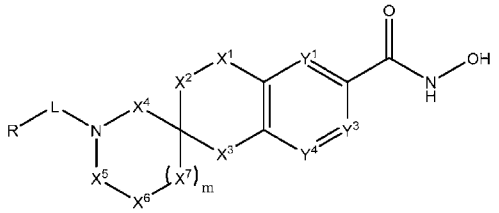
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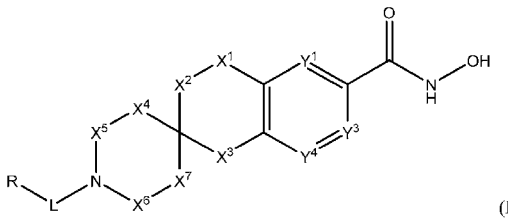
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(54) Title: 3-SPIRO-7-HYDROXAMIC ACID TETRALINS AS HDAC INHIBITORS



(I)



(II)

(57) Abstract: The present invention is directed to compounds of Formulae I and II which are inhibitors of histone deacetylases (HDACs) such as HDAC6, and their use in the treatment of diseases such as cell proliferative diseases (e.g., cancer), neurological (e.g., neurodegenerative disease or neurodevelopmental disease), inflammatory or autoimmune disease, infection, metabolic disease, hematologic disease, or cardiovascular disease.

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3-SPIRO-7-HYDROXAMIC ACID TETRALINS AS HDAC INHIBITORS

Cross-Reference to Related Applications

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 62/149,360, filed April 17, 2015, the contents of which are hereby incorporated by reference.

Field of the Invention

[0002] The present invention relates to inhibitors of zinc-dependent histone deacetylases (HDACs) useful in the treatment of diseases or disorders associated with HDACs including cell proliferation diseases (e.g., cancer), neurological and inflammatory diseases. Specifically, this invention is concerned with compounds and compositions inhibiting HDACs, methods of treating diseases associated with HDACs, and methods of synthesizing these compounds.

Background of the Invention

[0003] Many members of the HDAC family require zinc (Zn) to function properly. For instance, the isozyme histone deacetylase 6 (HDAC6) is a zinc-dependent histone deacetylase that possesses histone deacetylase activity. Other family members include HDACs 1-5 and 7-11. (De Ruijter et al, *Biochem. J.* 2003. 370; 737-749).

[0004] HDAC6 is known to deacetylate and associate with α-tubulin, cortactin, heat shock protein 90, ß-catenin, glucose-regulated protein 78kDa, myosin heavy chain 9, heat shock cognate protein 70, and dnaJ homolog subfamily A member 1 (reviewed in Li et al, *FEBS J.* 2013, 280: 775-93; Zhang et al, *Protein Cell.* 2015, 6(1): 42-54). Diseases in which HDAC6 inhibition could have a potential benefit include cancer (reviewed in Aldana-Masangkay et al, *J. Biomed. Biotechnol.* 2011, 875824), specifically: multiple myeloma (Hideshima et al, *Proc. Natl. Acad. Sci. USA* 2005, 102(24):8567-8572); lung cancer (Kamemura et al, *Biochem. Biophys. Res. Commun.* 2008, 374(1):84-89); ovarian cancer (Bazzaro et al, *Clin. Cancer Res.* 2008, 14(22):7340- 7347); breast cancer (Lee et al, *Cancer Res.* 2008, 68(18):7561-7569; Park et al, *Oncol. Rep.* 2011, 25: 1677-81; Rey et al, *Eur. J. Cell Biol.* 2011, 90: 128-35); prostate cancer (Seidel et al, *Biochem. Pharmacol.* 2015 (15)00714-5); pancreatic cancer (Nawrocki et al, *Cancer Res.* 2006, 66(7):3773- 3781); renal cancer (Cha et al, *Clin. Cancer Res.* 2009, 15(3): 840-850); hepatocellular cancer (Ding et al, *FEBS Lett.* 2013, 587:880-6; Kanno et al, *Oncol.*

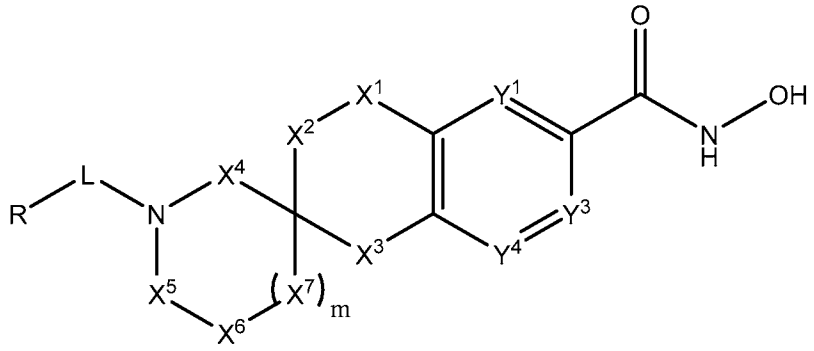
Rep. 2012, 28: 867-73); lymphomas (Ding et al, *Cancer Cell Int.* 2014, 14:139; Amengual et al, *Clin Cancer Res.* 2015, 21(20):4663-75); and leukemias such as acute myeloid leukemia (AML) (Fiskus et al, *Blood* 2008, 112(7):2896-2905) and acute lymphoblastic leukemia (ALL) (Rodriguez-Gonzalez et al, *Blood* 2008, 1 12(1 1): Abstract 1923)).

[0005] Inhibition of HDAC6 may also have a role in cardiovascular disease, including pressure overload, chronic ischemia, and infarction-reperfusion injury (Tannous et al, *Circulation* 2008, 1 17(24):3070-3078); bacterial infection, including those caused by uropathogenic Escherichia coli (Dhakal and Mulve, *J. Biol. Chem.* 2008, 284(1):446-454); neurological diseases caused by accumulation of intracellular protein aggregates such as Alzheimer's, Parkinson's and Huntington's disease (reviewed in Simoes-Pires et al, *Mol. Neurodegener.* 2013, 8: 7) or central nervous system trauma caused by tissue injury, oxidative-stress induced neuronal or axomal degeneration (Rivieccio et al, *Proc. Natl. Acad. Sci. USA* 2009, 106(46):19599-195604); and inflammation and autoimmune diseases through enhanced T cell-mediated immune tolerance at least in part through effects on regulatory T cells, including rheumatoid arthritis, psoriasis, spondylitis arthritis, psoriatic arthritis, multiple sclerosis, lupus, colitis and graft versus host disease (reviewed in Wang et al, *Nat. Rev. Drug Disc.* 2009 8(12):969-981; Vishwakarma et al, *Int. Immunopharmacol.* 2013, 16:72-8; Kalin et al, *J. Med. Chem.* 2012, 55:639-51); and fibrotic disease, including kidney fibrosis (Choi et al, *Vascul. Pharmacol.* 2015 72:130-140).

[0006] Four HDAC inhibitors are currently approved for the treatment of some cancers. These are suberanilohydroxamic acid (Vorinostat; Zolinza ®) for the treatment of cutaneous T cell lymphoma and multiple myeloma; Romidepsin (FK228; FR901228; Istodax ®) for the treatment of peripheral T cell lymphoma; Panobinostat (LBH-589; Farydak ®) for the treatment of multiple myeloma; and belinostat (PXD101; Beleodaq ®) for the treatment of peripheral T cell lymphoma. However, these drugs are of limited effectiveness and can give rise to unwanted side effects. Thus there is a need for HDAC inhibitors with an improved safety-efficacy profile.

Summary of the Invention

[0007] One aspect of the invention relates to compounds of Formula I:



(I)

and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, or isomers or thereof, wherein:

X^1, X^2, X^3, X^6, and X^7 are each independently $–CR^1R^2–$, $–NR^3–$, $–O–$, $–C(O)–$, $–SO_2–$, $–S(O)–$, or $–S–$;

X^4 and X^5 are each independently $–CR^1R^2–$, $–C(O)–$, $–SO_2–$, $–S(O)–$, or $–S–$;

Y^1, Y^3 and Y^4 are each independently N or CR^1;

L is a bond, $–(CR^1R^2)_n–$, $–C(O)NR^3–$, $–S(O)_2–$, $–S(O)_2NR^3–$, $–S(O)–$, $–S(O)NR^3–$, $–C(O)(CR^1R^2)_nO–$, or $–C(O)(CR^1R^2)_n–$;

R is independently –H, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, $–C_5$-C_{12}spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, or O, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, oxo, $–NO_2$, –CN, $–R^1$, $–R^2$, $–SR^3$, $–OR^3$, $–NHR^3$, $–NR^3R^4$, $–S(O)_2NR^3R^4$, $–S(O)_2R^1$, $–C(O)R^1$, $–CO_2R^1$, $–NR^3S(O)_2R^1$, $–S(O)R^1$, $–S(O)NR^3R^4$, $–NR^3S(O)R^1$, heterocycle, aryl, or heteroaryl;

R^1 and R^2 are independently, at each occurrence, –H, $–R^3$, $–R^4$, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P and O, –OH, halogen, $–NO_2$, –CN, $–NHC_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)_2$, $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–N(C_1$-C_6alkyl$)S(O)_2R^5$, $–S(O)_2(C_1$-C_6alkyl), $–(C_1$-C_6alkyl$)S(O)_2R^5$, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)S(O)_2C_1$-C_6alkyl, or $(CHR^5)_nNR^3R^4$, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl,

cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, $–NO_2$, oxo, –CN, $–R^5$, $–OR^3$, $–NHR^3$, NR^3R^4, $–S(O)_2N(R^3)_2–$, $–S(O)_2R^5$, $–C(O)R^5$, $–CO_2R^5$, $–NR^3S(O)_2R^5$, $–S(O)R^5$, $–S(O)NR^3R^4$, $–NR^3S(O)R^5$, heterocycle, aryl, or heteroaryl;

or R^1 and R^2 can combine with the carbon atom to which they are both attached to form a cycloalkyl, heterocycle, spirocycle, spiroheterocycle, or spirocycloalkenyl;

or R^1 and R^2, when on adjacent or non-adjacent atoms, can combine to form a heterocycle, cycloalkyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P and O, or cycloalkenyl;

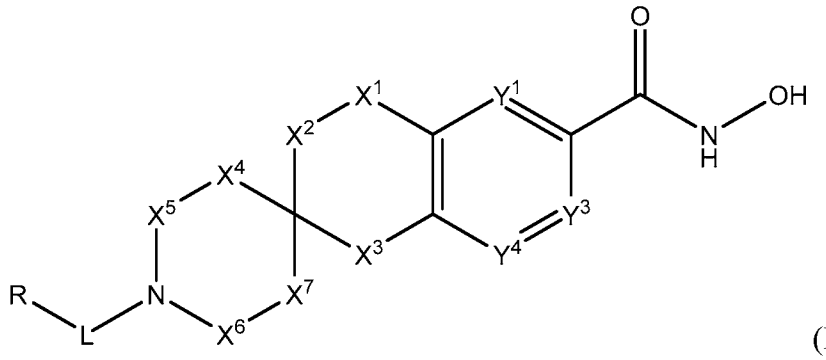
R^3 and R^4 are independently, at each occurrence, –H, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from N, S, P, and O, $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2(C_1$-C_6alkyl), $–(C_1$-C_6alkyl$)S(O)_2R^5$, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, or $–(CHR^5)_nN(C_1$-C_6alkyl$)_2$, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more substituents selected from –OH, halogen, $–NO_2$, oxo, –CN, $–R^5$, $–O(C_1$-$C_6)$alkyl, $–NH(C_1$-$C_6)$alkyl, $–N(C_1$-C_6alkly$)_2$, $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2NHC_1$-C_6alkyl, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)S(O)_2C_1$-C_6alkyl, $–S(O)R^5$, $–S(O)N(C_1$-C_6alkyl$)_2$, $–N(C_1$-C_6alkyl$)S(O)R^5$, heterocycle, aryl, or heteroaryl;

R^5 is independently, at each occurrence, –H, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from N, S, P and O, –OH, halogen, $–NO_2$, –CN, $–NHC_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)_2$, $–S(O)_2NH(C_1$-C_6alkyl), $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2C_1$-C_6alkyl, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)SO_2C_1$-C_6alkyl, $–S(O)(C_1$-C_6alkyl), $–S(O)N(C_1$-C_6alkyl$)_2$, $–N(C_1$-C_6alkyl$)S(O)(C_1$-C_6alkyl) or $–(CH_2)_nN(C_1$-C_6alkyl$)_2$;

n is an integer from 0 to 6; and

m is 0, 1, 2 or 3.

[0008] In another aspect, the invention relates to compounds of Formula II:



(II)

and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers or isomers thereof, wherein:

X^1 is independently $-CR^1R^2-$, $-NR^3-$, $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$;

X^2, X^3, X^4, and X^7 are each independently $-CR^1R^2-$, $-NR^3-$, $-O-$, $-C(O)-$, $-SO_2-$, $-S(O)-$, or $-S-$;

X^5 and X^6 are each independently $-CR^1R^2-$, $-C(O)-$, $-SO_2-$, $-S(O)-$, or $-S-$;

Y^1, Y^3 and Y^4 are each independently N or CR^1;

L is a bond, $-(CR^1R^2)_n-$, $-C(O)NR^3-$, $-S(O)_2-$, $-S(O)_2NR^3-$, $-S(O)-$, $-S(O)NR^3-$, $-C(O)(CR^1R^2)_nO-$, or $-C(O)(CR^1R^2)_n-$;

R is independently –H, $-C_1$-C_6alkyl, $-C_2$-C_6alkenyl, $-C_4$-C_8cycloalkenyl, $-C_2$-C_6alkynyl, $-C_3$-C_8cycloalkyl, $-C_5$-C_{12}spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, or O, wherein each –alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, oxo, $-NO_2$, –CN, $-R^1$, $-R^2$, $-SR^3$, $-OR^3$, $-NHR^3$, $-NR^3R^4$, $-S(O)_2NR^3R^4$, $-S(O)_2R^1$, $-C(O)R^1$, $-CO_2R^1$, $-NR^3S(O)_2R^1$, $-S(O)R^1$, $-S(O)NR^3R^4$, $-NR^3S(O)R^1$, heterocycle, aryl, or heteroaryl;

R^1 and R^2 are independently, and at each occurrence, –H, $-R^3$, $-R^4$, $-C_1$-C_6alkyl, $-C_2$-C_6alkenyl, $-C_4$-C_8cycloalkenyl, $-C_2$-C_6alkynyl, $-C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, or O, –OH, halogen, $-NO_2$, –CN, $-NHC_1$-C_6alkyl, $-N(C_1$-C_6alkyl$)_2$, $-S(O)_2N(C_1$-C_6alkyl$)_2$, $-N(C_1$-C_6alkyl$)S(O)_2R^5$, $-S(O)_2(C_1$-C_6alkyl), $-(C_1$-C_6alkyl$)S(O)_2R^5$, $-C(O)C_1$-C_6alkyl, $-CO_2C_1$-C_6alkyl, $-N(C_1$-C_6alkyl$)S(O)_2C_1$-C_6alkyl, or $(CHR^5)_nNR^3R^4$, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more

substituents selected from –OH, halogen, $–NO_2$, oxo, –CN, $–R^5$, $–OR^3$, $–NHR^3$, NR^3R^4, $–S(O)_2N(R^3)_2–$, $–S(O)_2R^5$, $–C(O)R^5$, $–CO_2R^5$, $–NR^3S(O)_2R^5$, $–S(O)R^5$, $–S(O)NR^3R^4$, $–NR^3S(O)R^5$, heterocycle, aryl, or heteroaryl;

or R^1 and R^2 can combine with the carbon atom to which they are both attached to form a cycloalkyl, heterocycle, spirocycle, spiroheterocycle, or spirocycloalkenyl;

or R^1 and R^2, when on adjacent or non-adjacent atoms, can combine to form a heterocycle, cycloalkyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P and O, or cycloalkenyl;

R^3 and R^4 are independently, at each occurrence, –H, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from N, S, P and O, $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2(C_1$-C_6alkyl), $–(C_1$-C_6alkyl$)S(O)_2R^5$, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, or $–(CHR^5)_nN(C_1$-C_6alkyl$)_2$, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more substituents selected from –OH, halogen, $–NO_2$, oxo, –CN, $–R^5$, $–O(C_1$-$C_6)$alkyl, $–NH(C_1$-$C_6)$alkyl, $–N(C_1$-C_6alkly$)_2$, $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2NHC_1$-C_6alkyl, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)S(O)_2C_1$-C_6alkyl, $–S(O)R^5$, $–S(O)N(C_1$-C_6alkyl$)_2$, $–N(C_1$-C_6alkyl$)S(O)R^5$, heterocycle, aryl, or heteroaryl;

each R^5 is independently –H, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from N, S, O and P, –OH, halogen, $–NO_2$, –CN, $–NHC_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)_2$, $–S(O)_2NH(C_1$-C_6alkyl), $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2C_1$-C_6alkyl, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)SO_2C_1$-C_6alkyl, $–S(O)(C_1$-C_6alkyl), $–S(O)N(C_1$-C_6alkyl$)_2$, $–N(C_1$-C_6alkyl$)S(O)(C_1$-C_6alkyl) or $–(CH_2)_nN(C_1$-C_6alkyl$)_2$; and

n is an integer from 0 to 6.

[0009] Another aspect of the invention relates to a method of treating a disease or disorder associated with HDAC6 modulation in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula I or Formula II.

[0010] Another aspect of the invention is directed to a method of inhibiting HDAC6. The method involves administering to a patient in need thereof an effective amount of a compound of Formula I or Formula II.

[0011] Another aspect of the invention is directed to pharmaceutical compositions comprising a compound of Formula I or Formula II and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier can further include an excipient, diluent, or surfactant. The pharmaceutical composition can be effective for treating a disease or disorder associated with HDAC6 modulation in a subject in need thereof. The pharmaceutical compositions can comprise the compounds of the present invention for use in treating diseases described herein. The compositions can contain at least one compound of the invention and a pharmaceutically acceptable carrier. The invention also provides the use of the compounds described herein in the manufacture of a medicament for the treatment of a disease associated with HDACs.

[0012] The present invention also provides methods for the treatment of human diseases or disorders including, without limitation, oncological, neurological, inflammatory, autoimmune, infectious, metabolic, hematologic, or cardiovascular diseases or disorders.

[0013] The present invention also provides compounds that are useful in inhibiting of zinc-dependent HDAC enzymes, and in particular HDAC6. These compounds can also be useful in the treatment of diseases including cancer,

[0014] The present invention further provides compounds that can inhibit HDAC6. In some embodiments, the efficacy-safety profile of the compounds of the current invention can be improved relative to other known HDAC (e.g. HDAC6) inhibitors. Additionally, the present technology also has the advantage of being able to be used for a number of different types of diseases, including cancer and non-cancer indications. Additional features and advantages of the present technology will be apparent to one of skill in the art upon reading the Detailed Description of the Invention, below.

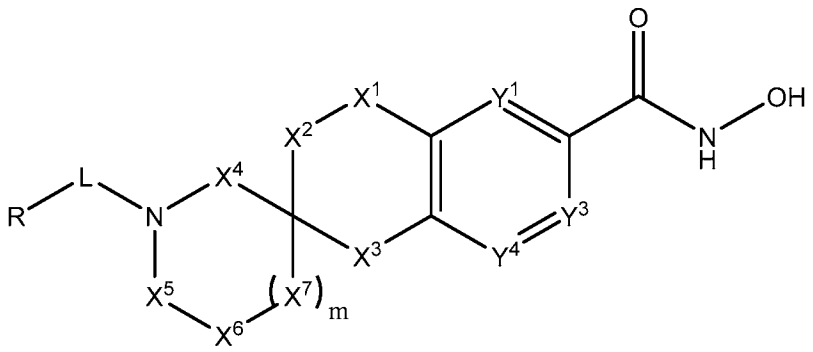
Brief Description of the Drawings

[0015] Figure 1 shows an X-ray crystal structure of methyl (R)-1'-[(4-methanesulfonylphenyl)methyl]-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate.

Detailed Description of the Invention

[0016] HDAC6 is a zinc-dependent histone deacetylase that has two catalytic domains. HDAC6 can interact with and deacetylate non-histone proteins, including HSP90 and α-tubulin. Acetylation of HSP90 is associated with loss of function of HSP90. HDAC6 is also implicated in the degradation of misfolded proteins as part of the aggresome. Accordingly, inhibition of HDAC6 can have downstream effects that can play a role in the development of certain diseases such as cancer. The present invention provides inhibitors of HDAC6 and methods for using the same to treat disease.

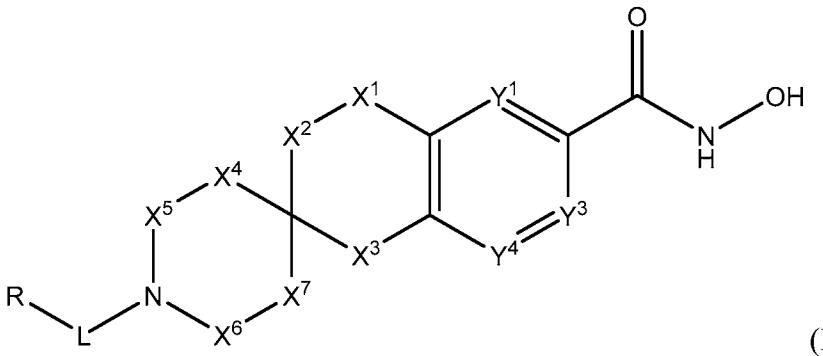
[0017] In a first aspect of the invention, compounds of the Formula I are described:



(I)

and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof, wherein m, R, L, X^1, X^2, X^3, X^4, X^5, X^6, X^7, Y^1, Y^3, and Y^4 are described as above.

[0018] In a second aspect of the invention, compounds of the Formula II are described:



(II)

and pharmaceutically acceptable salts, prodrugs, solvates, hydrates, tautomers, and isomers thereof, wherein R, L, X^1, X^2, X^3, X^4, X^5, X^6, X^7, Y^1, Y^3, and Y^4 are described as above.

[0019] The details of the invention are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Definitions

[0020] The articles "a" and "an" are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0021] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

[0022] The term "optionally substituted" is understood to mean that a given chemical moiety (e.g. an alkyl group) can (but is not required to) be bonded other substituents (e.g. heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (i.e. a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus the term "optionally substituted" means that a given chemical moiety has the potential to contain other functional groups, but does not necessarily have any further functional groups.

[0023] The term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 2 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl). The aryl group may be optionally substituted by one or more substituents, e.g., 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, −H, −halogen, −O-C_1-C_6alkyl, −C_1-C_6alkyl, −OC_2-C_6alkenyl, −OC_2-C_6alkynyl, −C_2-C_6alkenyl, −C_2-C_6alkynyl, −OH,

$-OP(O)(OH)_2$, $-OC(O)C_1$-C_6alkyl, $-C(O)C_1$-C_6alkyl, $-OC(O)OC_1$-C_6alkyl, $-NH_2$, $-NH(C_1$-C_6alkyl), $-N(C_1$-C_6alkyl$)_2$, $-S(O)_2$-C_1-C_6alkyl, $-S(O)NHC_1$-C_6alkyl, and $-S(O)N(C_1$-C_6alkyl$)_2$. The substituents can themselves be optionally substituted. Furthermore when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these aryl groups include indanyl, indenyl, tetrahydronaphthalenyl, and tetrahydrobenzoannulenyl.

[0024] Unless otherwise specifically defined, "heteroaryl" means a monovalent monocyclic aromatic radical of 5 to 24 ring atoms or a polycyclic aromatic radical, containing one or more ring heteroatoms selected from N, S, P, and O, the remaining ring atoms being C. Heteroaryl as herein defined also means a bicyclic heteroaromatic group wherein the heteroatom is selected from N, S, P, and O. The aromatic radical is optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyrazolyl, pyrimidinyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyranyl, isothiazolyl, thiazolyl, thiadiazole, indazole, benzimidazolyl, thieno[3,2-b]thiophene, triazolyl, triazinyl, imidazo[1,2-b]pyrazolyl, furo[2,3-c]pyridinyl, imidazo[1,2-a]pyridinyl, indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, thieno[2,3-b]pyridinyl, benzothiazolyl, indolyl, indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, benzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, dihydrobenzoxanyl, quinolinyl, isoquinolinyl, 1,6-naphthyridinyl, benzo[de]isoquinolinyl, pyrido[4,3-b][1,6]naphthyridinyl, thieno[2,3-b]pyrazinyl, quinazolinyl, tetrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, isoindolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, imidazo[5,4-b]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, tetrahydro pyrrolo[1,2-a]pyrimidinyl, 3,4-dihydro-2H-1λ^2-pyrrolo[2,1-b]pyrimidine, dibenzo[b,d] thiophene, pyridin-2-one, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1H-pyrido[3,4-b][1,4] thiazinyl, benzooxazolyl, benzoisoxazolyl, furo[2,3-b]pyridinyl, benzothiophenyl, 1,5-naphthyridinyl, furo[3,2-b]pyridine, [1,2,4]triazolo[1,5-a]pyridinyl, benzo [1,2,3]triazolyl, imidazo[1,2-a]pyrimidinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, 3,4-dihydro-2H-pyrazolo [1,5-b][1,2]oxazinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, thiazolo[5,4-d]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, thieno[2,3-b]pyrrolyl, 3H-indolyl,

and derivatives thereof. Furthermore when containing two fused rings the heteroaryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these heteroaryl groups include indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, 3,4-dihydro-1H--isoquinolinyl, 2,3-dihydrobenzofuran, indolinyl, indolyl, and dihydrobenzoxanyl.

[0025] "Alkyl" refers to a straight or branched chain saturated hydrocarbon. C_1-C_6alkyl groups contain 1 to 6 carbon atoms. Examples of a C_1-C_6alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, sec-butyl and tert-butyl, isopentyl and neopentyl.

[0026] The term "alkenyl" means an aliphatic hydrocarbon group containing a carbon—carbon double bond and which may be straight or branched having about 2 to about 6 carbon atoms in the chain. Certain alkenyl groups have 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl, or propyl are attached to a linear alkenyl chain. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, and i-butenyl. A C_2-C_6 alkenyl group is an alkenyl group containing between 2 and 6 carbon atoms.

[0027] The term "alkynyl" means an aliphatic hydrocarbon group containing a carbon—carbon triple bond and which may be straight or branched having about 2 to about 6 carbon atoms in the chain. Certain alkynyl groups have 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl, or propyl are attached to a linear alkynyl chain. Exemplary alkynyl groups include ethynyl, propynyl, n-butynyl, 2-butynyl, 3-methylbutynyl, and n-pentynyl. A C_2-C_6 alkynyl group is an alkynyl group containing between 2 and 6 carbon atoms.

[0028] The term "cycloalkyl" means monocyclic or polycyclic saturated carbon rings containing 3-18 carbon atoms. Examples of cycloalkyl groups include, without limitations, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, norboranyl, norborenyl, bicyclo[2.2.2]octanyl, or bicyclo[2.2.2]octenyl. A C_3-C_8 cycloalkyl is a cycloalkyl group containing between 3 and 8 carbon atoms. A cycloalkyl group can be fused (e.g., decalin) or bridged (e.g., norbornane).

[0029] The term "cycloalkenyl" means monocyclic, non-aromatic unsaturated carbon rings containing 4-18 carbon atoms. Examples of cycloalkenyl groups include, without limitation, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and norborenyl. A C_4-C_8 cycloalkenyl is a cycloalkenyl group containing between 4 and 8 carbon atoms.

[0030] The terms "heterocyclyl" or "heterocycloalkyl" or "heterocycle" refer to monocyclic or polycyclic 3 to 24-membered rings containing carbon and heteroatoms taken from oxygen, phosphorous nitrogen, or sulfur and wherein there is not delocalized π electrons (aromaticity) shared among the ring carbon or heteroatoms. Heterocyclyl rings include, but are not limited to, oxetanyl, azetadinyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl. A heteroycyclyl or heterocycloalkyl ring can also be fused or bridged, e.g., can be a bicyclic ring.

[0031] As used herein, the term "halo" or "halogen" means a fluoro, chloro, bromo, or iodo group.

[0032] The term "carbonyl" refers to a functional group composing a carbon atom double-bonded to an oxygen atom. It can be abbreviated herein as "oxo", as C(O), or as C=O.

[0033] "Spirocycle" or "spirocyclic" means carbogenic bicyclic ring systems with both rings connected through a single atom. The ring can be different in size and nature, or identical in size and nature. Examples include spiropentane, spirohexane, spiroheptane, spirooctane, spirononane, or spirodecane. One or both of the rings in a spirocycle can be fused to another carbocyclic, heterocyclic, aromatic, or heteroaromatic ring. One or more of the carbon atoms in the spirocycle can be substituted with a heteroatom (e.g., O, N, S, or P). A C_5-C_{12} spirocycle is a spirocycle containing between 5 and 12 carbon atoms. One or more of the carbon atoms can be substituted with a heteroatom.

[0034] The term "spirocyclic heterocycle" or "spiroheterocycle" is understood to mean a spirocycle wherein at least one of the rings is a heterocycle (e.g., at least one of the rings is furanyl, morpholinyl, or piperadinyl). A spirocyclic heterocycle can contain between 5 and 12 atoms, at least one of which is a heteroatom selected from N, O, S and P.

[0035] The disclosure also includes pharmaceutical compositions comprising an effective amount of a disclosed compound and a pharmaceutically acceptable carrier. Representative "pharmaceutically acceptable salts" include, e.g., water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, sethionate, lactate, lactobionate, laurate, magnesium, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0036] The term "stereoisomers" refers to the set of compounds which have the same number and type of atoms and share the same bond connectivity between those atoms, but differ in three dimensional structure. The term "stereoisomer" refers to any member of this set of compounds.

[0037] The term "diastereomers" refers to the set of stereoisomers which cannot be made superimposable by rotation around single bonds. For example, cis- and trans- double bonds, endo- and exo- substitution on bicyclic ring systems, and compounds containing multiple stereogenic centers with different relative configurations are considered to be diastereomers. The term "diastereomer" refers to any member of this set of compounds. In some examples presented, the synthetic route may produce a single diastereomer or a mixture of diastereomers. In some cases these diastereomers were separated and in other cases a wavy bond is used to indicate the structural element where configuration is variable.

[0038] The term "enantiomers" refers to a pair of stereoisomers which are non-superimposable mirror images of one another. The term "enantiomer" refers to a single member of this pair of stereoisomers. The term "racemic" refers to a 1:1 mixture of a pair of enantiomers.

[0039] The term "tautomers" refers to a set of compounds that have the same number and type of atoms, but differ in bond connectivity and are in equilibrium with one another. A "tautomer" is a single member of this set of compounds. Typically a single tautomer is drawn but it is understood that this single structure is meant to represent all possible tautomers that might exist. Examples include enol-ketone tautomerism. When a ketone is drawn it is understood that both the enol and ketone forms are part of the invention.

[0040] An "effective amount" when used in connection with a compound is an amount effective for treating or preventing a disease in a subject as described herein.

[0041] The term "carrier", as used in this disclosure, encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject.

[0042] The term "treating" with regard to a subject, refers to improving at least one symptom of the subject's disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

[0043] The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0044] The term "administer", "administering", or "administration" as used in this disclosure refers to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

[0045] The term "prodrug," as used in this disclosure, means a compound which is convertible in vivo by metabolic means (e.g., by hydrolysis) to a disclosed compound. Furthermore, as used herein a prodrug is a drug which is inactive in the body, but is transformed in the body typically either during absorption or after absorption from the gastrointestinal tract

into the active compound. The conversion of the prodrug into the active compound in the body may be done chemically or biologically (i.e., using an enzyme).

[0046] The term "solvate" refers to a complex of variable stoichiometry formed by a solute and solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, MeOH, EtOH, and AcOH. Solvates wherein water is the solvent molecule are typically referred to as hydrates. Hydrates include compositions containing stoichiometric amounts of water, as well as compositions containing variable amounts of water.

[0047] The term "isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers). With regard to stereoisomers, the compounds of Formula I or Formula II may have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers.

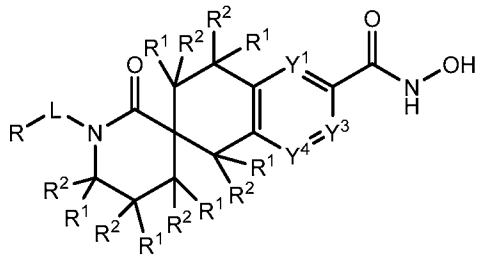
[0048] A "patient" or "subject" is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

[0049] In one embodiments of the compounds of Formula I or Formula II, X^4 is $-C(O)-$.

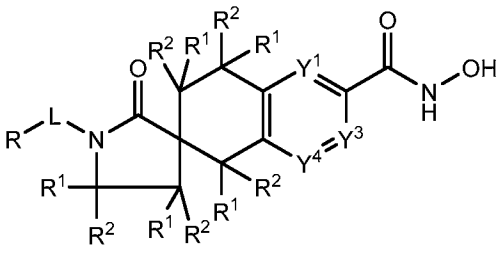
[0050] In one or more embodiments of the compounds of Formula I, m is 0 or 1.

[0051] In one or more embodiments of the compounds of Formula I and Formula II, Y^1, Y^3 and Y^4 are each CR^1.

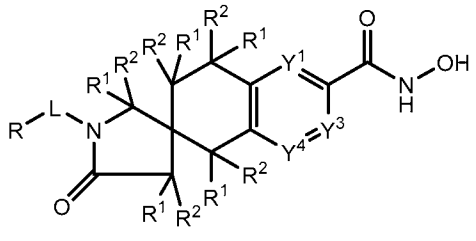
[0052] In one embodiment of the compound of Formula I, the compound is of the Formula I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-j, I-k, or I-m:



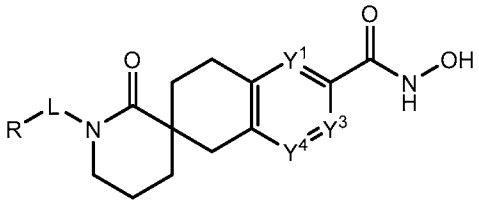
(I-a);



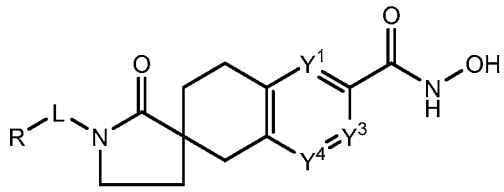
(I-b);



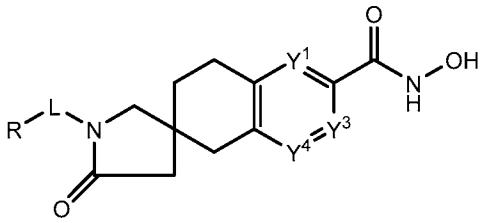
(I-c);



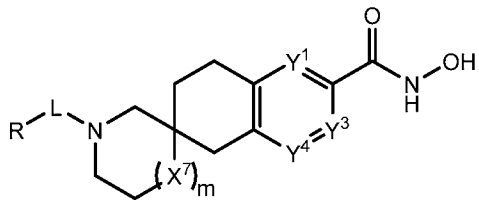
(I-d);



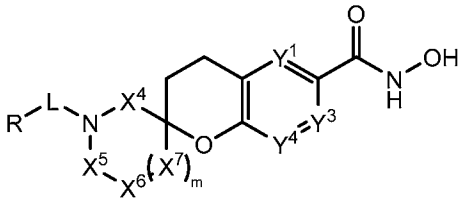
(I-e);



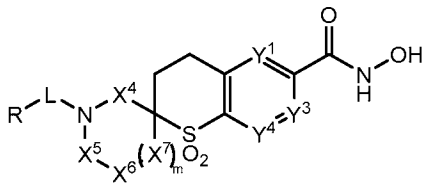
(I-f);



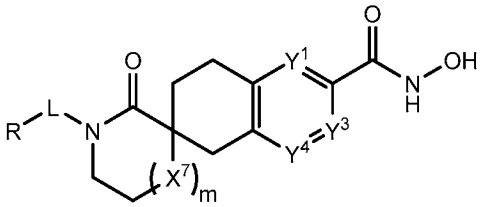
(I-g);



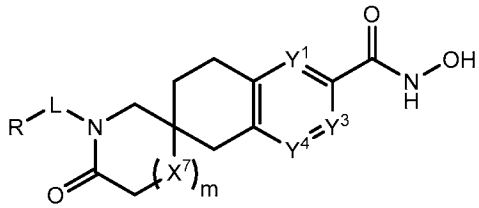
(I-h);



(I-j);

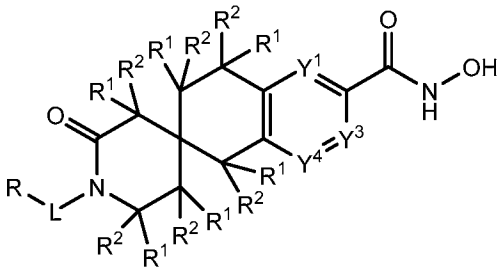


(I-k);

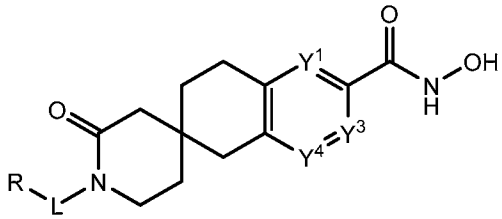


(I-m).

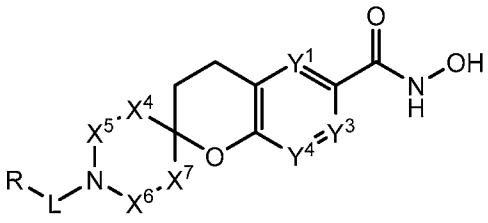
[0053] In one embodiment of the compound of Formula II, the compound is of the Formula II-a, II-b, II-c, II-d or II-e:



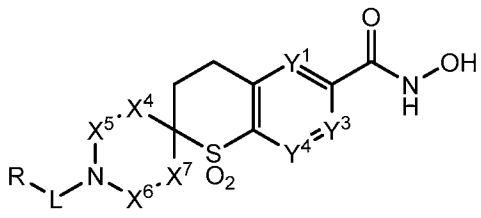
(II-a);



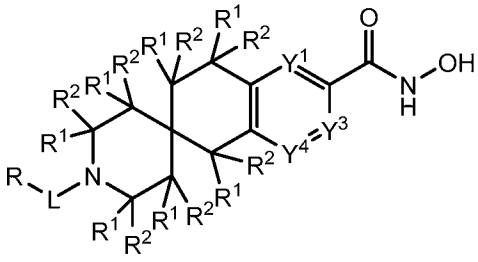
(II-b);



(II-c);



(II-d);



(II-e).

[0054] In an illustrative embodiment, a compound of Formula I can be selected from:

1'-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-1);

N-hydroxy-1'-(4-methoxyphenethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-2);

N-hydroxy-1'-(4-methoxybenzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-3);

N-hydroxy-1'-(4-methoxyphenethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-4);

1'-(1H-benzo[d]imidazol-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-5);

1'-(3,4-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-6);

1'-(cyclohexylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-7);

N-hydroxy-1'-(4-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-8);

1'-(3-(dimethylamino)propyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-9);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-10);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-11);

(R)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-12);

(S)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-13);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-14);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-15);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-16);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-17);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-18);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-19);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-20);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-21);

(R)-N-hydroxy-1'-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-22);

(S)-N-hydroxy-1'-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-23);

(R)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-24);

(S)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-25);

(R)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-26);

(R)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-27);

(S)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-28);

(S)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-29);

(R)-1'-((2-chlorothiazol-5-yl)methyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-30);

(R)-N-hydroxy-1'-((2-hydroxythiazol-5-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-31);

(R)-N-hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-32);

(R)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-33);

(R)-N-hydroxy-1'-isopentyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-34);

(R)-1'-(but-2-yn-1-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-35);

(R)-N-hydroxy-1'-(2-methoxyethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-36);

(R)-1'-cinnamyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-37);

(R)-N-hydroxy-1'-(2-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-38);

(R)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-39);

(R)-1'-(2-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-40);

(R)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-41);

(R)-1'-(benzo[c][1,2,5]oxadiazol-5-ylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-42);

(R)-N-hydroxy-1'-(2-morpholino-2-oxoethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-43);

(R)-N-hydroxy-1'-(2-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-44);

(R)-N-hydroxy-1'-((1-isopropyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-45);

(R)-N-hydroxy-1'-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-46);

(R)-N-hydroxy-1'-(2-methylallyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-47);

(R)-1'-(2,5-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-48);

(R)-1'-(2,6-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-49);

(R)-1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-50);

(R)-N-hydroxy-1'-(3-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-51);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-2-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-52);

(R)-1'-(3-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-53);

(R)-1'-(3-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-54);

(R)-1'-(4-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-55);

(R)-N-hydroxy-1'-(4-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-56);

(R)-1'-(2-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-57);

(R)-N-hydroxy-1'-(naphthalen-2-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-58);

(R)-1'-(2-(difluoromethoxy)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-59);

(S)-N-hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-60);

(S)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-61);

(S)-N-hydroxy-1'-isopentyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-62);

(S)-1'-(but-2-yn-1-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-63);

(S)-N-hydroxy-1'-(2-methoxyethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-64);

(S)-1'-cinnamyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-65);

(S)-N-hydroxy-1'-(2-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-66);

(S)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-67);

(S)-1'-(2-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-68);

(S)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-69);

(S)-1'-(benzo[c][1,2,5]oxadiazol-5-ylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-70);

(S)-N-hydroxy-1'-(2-morpholino-2-oxoethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-71);

(S)-N-hydroxy-1'-(2-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-72);

(S)-N-hydroxy-1'-((1-isopropyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-73);

(S)-1'-(2,5-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-74);

(S)-1'-(2,6-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-75);

(S)-1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-76);

(S)-N-hydroxy-1'-(3-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-77);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-2-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-78);

(S)-1'-(3-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-79);

(S)-N-hydroxy-2'-oxo-1'-(4-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-80);

(S)-1'-(3-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-81);

(S)-1'-(4-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-82);

(S)-N-hydroxy-1'-(4-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-83);

(S)-1'-(2-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-84);

(S)-1'-(4-(tert-butyl)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-85);

(S)-N-hydroxy-1'-(naphthalen-2-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-86);

(S)-1'-(2-(difluoromethoxy)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-87);

(R)-N-hydroxy-1'-(4-(methylsulfonyl)benzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-88);

(R)-N-hydroxy-1'-(naphthalen-1-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-89);

(R)-1'-(3-fluoro-4-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-90);

(R)-1'-(benzo[d][1,3]dioxol-5-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-91);

(R)-N-hydroxy-1'-(3-(methylthio)phenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-92);

(R)-1'-(4-(dimethylamino)phenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-93);

(R)-N-hydroxy-1'-(6-isopropylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-94);

(R)-N-hydroxy-2'-oxo-1'-(quinolin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-95);

(R)-1'-(2,3-dihydrobenzofuran-7-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-96);

(R)-1'-(6-(tert-butylamino)pyrimidin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-97);

(R)-1'-(1,3-dimethyl-1H-pyrazol-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-98);

(R)-N-hydroxy-1'-(imidazo[1,2-a]pyridin-6-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-99);

(S)-1'-(2,4-dimethylphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-100);

(S)-N-hydroxy-1'-(6-isopropylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-101);

(S)-N-hydroxy-2'-oxo-1'-(quinolin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-102);

(S)-N-hydroxy-1'-(imidazo[1,2-a]pyridin-6-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-103);

(R)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-104);

(S)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-105);

(R)-N-hydroxy-2'-oxo-1'-(4-((trifluoromethyl)sulfonyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-106);

(S)-N-hydroxy-2'-oxo-1'-(4-((trifluoromethyl)sulfonyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-107);

(R)-N-hydroxy-1'-(3-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-108);

(R)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-109);

(R)-1'-(5-fluoropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-110);

(R)-N-hydroxy-1'-(2-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-111);

(R)-1'-(3-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-112);

(R)-1'-(3-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-113);

(R)-N-hydroxy-1'-(6-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-114);

(S)-N-hydroxy-1'-(2-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-115);

(S)-1'-(3-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-116);

(S)-1'-(3-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-117);

(S)-N-hydroxy-1'-(6-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-118);

(R)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-119);

(R)-1'-(4-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-120);

(R)-1'-(2-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-121);

(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-122);

(R)-1'-(2,3-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-123);

(R)-N-hydroxy-1'-(4-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-124);

(R)-1'-(2-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-125);

(S)-1'-(2-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-126);

(S)-1'-(2-fluoro-4-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-127);

(R)-1'-(4-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-128);

(S)-1'-(4-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-129);

(S)-1'-(5-chloropyridin-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-130);

(R)-N-hydroxy-1'-(2-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-131);

(S)-N-hydroxy-1'-(2-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-132);

(R)-N-hydroxy-1'-(6-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-133);

(S)-N-hydroxy-1'-(6-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-134);

(R)-N-hydroxy-1'-(5-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-135);

(R)-N-hydroxy-1'-(4-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-136);

(S)-N-hydroxy-1'-(4-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-137);

(R)-1'-(5-chloropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-138);

(S)-1'-(5-chloropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-139);

(R)-1'-(3-chloropyridin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-140);

(S)-1'-(3-chloropyridin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-141);

(S)-N-hydroxy-1'-(4-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-142);

(R)-N-hydroxy-1'-(5-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-143);

(S)-N-hydroxy-1'-(5-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-144);

(R)-N-hydroxy-1'-(2-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-145);

(S)-N-hydroxy-1'-(2-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-146);

(S)-1'-(2-fluoro-5-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-147);

(S)-1'-(3-fluoro-5-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-148);

(R)-N-hydroxy-1'-(2-methoxypyridin-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-149);

(S)-N-hydroxy-1'-(2-methoxypyridin-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-150);

(R)-1'-(6-(dimethylamino)pyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-151);

(S)-1'-(6-(dimethylamino)pyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-152);

(S)-1'-(5-fluoropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-153);

(S)-1'-(4-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-154);

(S)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-155);

(S)-1'-(2,3-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-156);

(S)-1'-(2-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-157);

(S)-N-hydroxy-1'-(3-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-158);

(R)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-159);

(S)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-160);

(R)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-161);

(S)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-162);

(R)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-163);

(S)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-164);

(R)-N-hydroxy-2'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-165);

(S)-N-hydroxy-2'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-166);

(R)-1'-(2,5-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-167);

(R)-N-hydroxy-1'-(1-methyl-1H-pyrazol-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-168);

(S)-1'-(2,5-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-169);

(S)-N-hydroxy-1'-(1-methyl-1H-pyrazol-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-170);

(R)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-171);

(S)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-172);

(S)-1'-(4-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-173);

(S)-1'-(2-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-174);

(R)-1'-(2-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-175);

1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-176);

N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-177);

N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-178);

(R)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-179);

(S)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-180);

(R)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-181);

(S)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-182);

(S)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-183);

(S)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-184);

(R)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide(I-185);

(S)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide(I-186);

(R)-N-hydroxy-1'-(3-methoxypropyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide(I-187);

(S)-N-hydroxy-1'-(3-methoxypropyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide(I-188);

(R)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-189);

(S)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-190);

(R)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-191);

(S)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-192);

(R)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-193);

(R)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-194);

(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-195);

(R)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-196);

(R)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-197);

(S)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-198);

(R)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-199);

(S)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-200);

(R)-N-hydroxy-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-201);

(S)-N-hydroxy-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-202);

(R)-N-hydroxy-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-203);

(S)-N-hydroxy-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-204);

(R)-1'-(cyclobutylmethyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-205);

(R)-1'-ethyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-206);

(R)-N-hydroxy-1'-isobutyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-207);

(R)-N-hydroxy-1'-isopropyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-208);

(R)-1'-cyclopropyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-209);

(S)-1'-(cyclobutylmethyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-210);

(S)-1'-ethyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-211);

(S)-N-hydroxy-1'-isobutyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-212);

(S)-N-hydroxy-1'-isopropyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-213);

(S)-1'-cyclopropyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-214);

(R)-N-hydroxy-1'-(oxetan-3-ylmethyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-215);

(R)-1'-benzyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-216);

(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-217);

(S)-1'-benzyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-218);

(R)-N-hydroxy-1'-(3-methoxypropyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-219);

(R)-N-hydroxy-5'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-220);

(R)-N-hydroxy-5'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-221);

(S)-N-hydroxy-1'-(3-methoxypropyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-222);

(S)-N-hydroxy-5'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-223);

(S)-N-hydroxy-5'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-224);

(R)-N-hydroxy-1'-(2-methylbenzyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-225);

(R)-N-hydroxy-5'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-226);

(R)-1'-(4-fluorophenyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide(I-227);

(R)-N-hydroxy-5'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-228);

(R)-N-hydroxy-5'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-229);

N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-230);

N-hydroxy-2'-oxo-1'-phenylspiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-231);

1'-benzyl-N-hydroxy-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-232);

N-hydroxy-2'-oxo-1'-(pyridin-3-yl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-233);

N-hydroxy-2'-oxo-1'-((tetrahydro-2H-pyran-4-yl)methyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-234);

N-hydroxy-1'-isopropyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-235);

N-hydroxy-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-236);

N-hydroxy-1'-methyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-237);

N-hydroxy-2-oxo-1-phenylspiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-238);

1-benzyl-N-hydroxy-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-239);

N-hydroxy-2-oxo-1-(pyridin-3-yl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide(I-240);

N-hydroxy-2-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-241);

N-hydroxy-2-oxo-1-(pyridin-4-ylmethyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-242);

N-hydroxy-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-243); and

N-hydroxy-1-methyl-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-244).

[0055] In one or more embodiments, the compound of Formula II can be selected from:

N-hydroxy-1'-(4-methoxybenzyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-1);

1'-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-2);

1'-(cyclohexanecarbonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-3);

N-hydroxy-1'-(4-methoxybenzoyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-4);

N-hydroxy-1'-((4-methoxyphenyl)sulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-5);

1'-(cyclohexylsulfonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-6);

N6-hydroxy-N1'-phenylspiro[chromane-2,4'-piperidine]-1',6-dicarboxamide (II-7);

1'-cyclohexyl-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-8); and

N-hydroxy-1'-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carbonyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-9).

[0056] In one or more embodiments, the compound of Formula I can be selected from:

N-hydroxy-1'-methyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-245);

N-hydroxy-1-methyl-3',4'-dihydro-1'H-spiro[azepane-3,2'-naphthalene]-6'-carboxamide (I-246);

N-hydroxy-1-methyl-3',4'-dihydro-1'H-spiro[azocane-3,2'-naphthalene]-6'-carboxamide (I-247);

N-hydroxy-1-methyl-2-oxo-3',4'-dihydro-1'H-spiro[azepane-3,2'-naphthalene]-6'-carboxamide (I-248);

N-hydroxy-1-methyl-2-oxo-3',4'-dihydro-1'H-spiro[azocane-3,2'-naphthalene]-6'-carboxamide (I-249);

N-hydroxy-1'-methyl-6'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-250);

N-hydroxy-1-methyl-7-oxo-3',4'-dihydro-1'H-spiro[azepane-3,2'-naphthalene]-6'-carboxamide (I-251);

N-hydroxy-1-methyl-8-oxo-3',4'-dihydro-1'H-spiro[azocane-3,2'-naphthalene]-6'-carboxamide (I-252);

N-hydroxy-1'-methyl-2'-oxospiro[chromane-2,3'-piperidine]-6-carboxamide (I-253);

N-hydroxy-1-methyl-2-oxospiro[azepane-3,2'-chromane]-6'-carboxamide (I-254);

N-hydroxy-1-methyl-2-oxospiro[azocane-3,2'-chromane]-6'-carboxamide (I-255);

N-hydroxy-1-methyl-2-oxospiro[piperidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-256);

N-hydroxy-1-methyl-2-oxospiro[azepane-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-257); and

N-hydroxy-1-methyl-2-oxospiro[azocane-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-258).

[0057] In one embodiment of the compounds of Formulae I and II, Y^1, Y^3, and Y^4 are each CR^1. In other embodiments, Y^1 is N and Y^3 and Y^4 are each CR^1. In other embodiments, Y^3 is N and Y^1 and Y^4 are each CR^1. In other embodiments, Y^4 is N and Y^1 and Y^3 are each CR^1.

[0058] In some embodiments of the compounds of Formulae I and II, Y^1, Y^3, and Y^4 are each CR^1 and X^1, X^2, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^1 is $-C(O)-$, and X^2, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^2 is $-C(O)-$, and X^1, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^3 is $-C(O)-$, and X^1, X^2, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^4 is $-C(O)-$, and X^1, X^2, X^3, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^5 is $-C(O)-$, and X^1, X^2, X^3, X^4, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^6 is $-C(O)-$, and X^1, X^2, X^3, X^4, X^5, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^7 is $-C(O)-$, and X^1, X^2, X^3, X^5, X^5, and X^6 are each independently $-CR^1R^2-$.

[0059] In other embodiments of the compounds of Formulae I and II, X^1 is $-NR^3-$, and X^2, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^2 is $-NR^3-$, and X^1, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^3 is $-NR^3-$, and X^1, X^2, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^4 is $-NR^3-$, and X^1, X^2, X^3, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^5 is $-NR^3-$, and X^1, X^2, X^3, X^4, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^6 is $-NR^3-$, and X^1, X^2, X^3, X^4, X^5, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^7 is $-NR^3-$, and X^1, X^2, X^3, X^4, X^5, and X^6 are each independently $-CR^1R^2-$.

[0060] In other embodiments of the compounds of Formula I, X^1 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^2, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^2 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^1, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^3 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^1, X^2, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^4 is $-S-$, $-SO_2-$ or $-S(O)-$, and X^1, X^2, X^3, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^5 is $-S-$,

$-SO_2-$ or $-S(O)-$, and X^1, X^2, X^3, X^4, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^6 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^1, X^2, X^3, X^4, X^5, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^7 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^1, X^2, X^3, X^4, X^5, and X^6 are each independently $-CR^1R^2-$.

[0061] In other embodiments of the compounds of Formula II, X^1 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^2, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^2 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^1, X^3, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^3 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^1, X^2, X^4, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^4 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^1, X^2, X^3, X^5, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^5 is $-S-$, $-SO_2-$ or $-S(O)-$, and X^1, X^2, X^3, X^4, X^6, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^6 is $-S-$, $-SO_2-$ or $-S(O)-$, and X^1, X^2, X^3, X^4, X^5, and X^7 are each independently $-CR^1R^2-$. In some embodiments, X^7 is $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$, and X^1, X^2, X^3, X^4, X^5, and X^6 are each independently $-CR^1R^2-$.

[0062] In other embodiments of the compounds of Formulae I and II, L is a bond. In other embodiments, L is $-(CR^1R^2)_n-$. In other embodiments, L is $-S(O)_2-$. In other embodiments, L is $-S(O)_2NR^3-$, $-S(O)-$, or $-S(O)NR^3-$. In other embodiments, L is $-C(O)(CR^1R^2)_nO-$. In other embodiments, L is $-C(O)(CR^1R^2)_n-$ and n is 0. In other embodiments, L is $-C(O)NR^3-$.

[0063] In other embodiments of the compounds of Formulae I and II, R is $-C_1$-C_6alkyl optionally substituted with one or more –OH, halogen, oxo, $-NO_2$, –CN, $-R^1$, $-R^2$, $-SR^3$, $-OR^3$, $-NHR^3$, $-NR^3R^4$, $-S(O)_2NR^3R^4$, $-S(O)_2R^1$, $-C(O)R^1$, $-CO_2R^1$, $-NR^3S(O)_2R^1$, $-S(O)R^1$, $-S(O)NR^3R^4$, $-NR^3S(O)R^1$, heterocycle, aryl, or heteroaryl. In other embodiments, R is $-C_2$-C_6alkenyl or $-C_2$-C_6alkynyl optionally substituted with one or more –OH, halogen, oxo, $-NO_2$, –CN, $-R^1$, $-R^2$, $-SR^3$, $-OR^3$, $-NHR^3$, $-NR^3R^4$, $-S(O)_2NR^3R^4$, $-S(O)_2R^1$, $-C(O)R^1$, $-CO_2R^1$, $-NR^3S(O)_2R^1$, $-S(O)R^1$, $-S(O)NR^3R^4$, $-NR^3S(O)R^1$, heterocycle, aryl, or heteroaryl. In other embodiments, R is aryl or heteroaryl optionally substituted with one or more –OH, halogen, oxo, $-NO_2$, –CN, $-R^1$, $-R^2$, $-SR^3$, $-OR^3$, $-NHR^3$, $-NR^3R^4$, $-S(O)_2NR^3R^4$, $-S(O)_2R^1$, $-C(O)R^1$, $-CO_2R^1$, $-NR^3S(O)_2R^1$, $-S(O)R^1$, $-S(O)NR^3R^4$, $-NR^3S(O)R^1$, heterocycle, aryl, or heteroaryl. In other embodiments, R is $-C_4$-C_8cycloalkenyl, $-C_3$-C_8cycloalkyl, $-C_5$-C_{12}spirocycle, heterocyclyl, or spiroheterocyclyl, optionally substituted with one or more –OH, halogen, oxo, $-NO_2$, –CN, –

R^1, $-R^2$, $-SR^3$, $-OR^3$, $-NHR^3$, $-NR^3R^4$, $-S(O)_2NR^3R^4$, $-S(O)_2R^1$, $-C(O)R^1$, $-CO_2R^1$, $-NR^3S(O)_2R^1$, $-S(O)R^1$, $-S(O)NR^3R^4$, $-NR^3S(O)R^1$, heterocycle, aryl, or heteroaryl.

[0064] In other embodiments of the compounds of Formula I, m is 0, 1, 2, or 3. In another embodiment m is 0. In yet another embodiment, m is 1. In yet another embodiment, m is 2. In yet another embodiment, m is 3.

[0065] In some embodiments of the invention, the compounds of Formula I or Formula II are enantiomers. In some embodiments the compounds are the (*S*)-enantiomer. In other embodiments the compounds are the (*R*)-enantiomer. In yet other embodiments, the compounds of Formula I or Formula II may be (+) or (-) enantiomers. As used herein, a chemical structure that is labelled as "R/S" indicates that the structure represents one enantiomer, the stereochemistry of which is not defined.

[0066] It should be understood that all isomeric forms are included within the present invention, including mixtures thereof. If the compound contains a double bond, the substituent may be in the E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans- configuration. All tautomeric forms are also intended to be included.

Methods of Synthesizing the Disclosed Compounds

[0067] The compounds of the present invention may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the schemes given below.

[0068] The compounds of Formula I or Formula II may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes and examples. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of Formula I or Formula II.

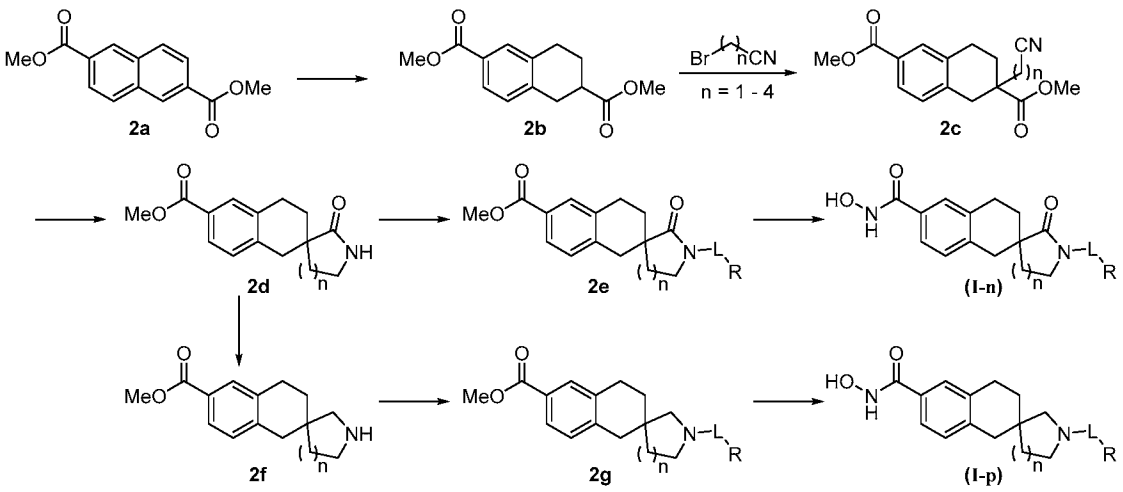
Those skilled in the art will recognize if a stereocenter exists in the compounds of Formula I or Formula II. Accordingly, the present invention includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

Preparation of Compounds

[0069] The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

[0070] The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the Formula I (e.g., Formula I-m, I-n, I-p, I-q, I-r and II-g) can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. These methods include but are not limited to those methods described below.

Scheme 1. General synthesis of compounds of Formula (I-n) and (I-p).

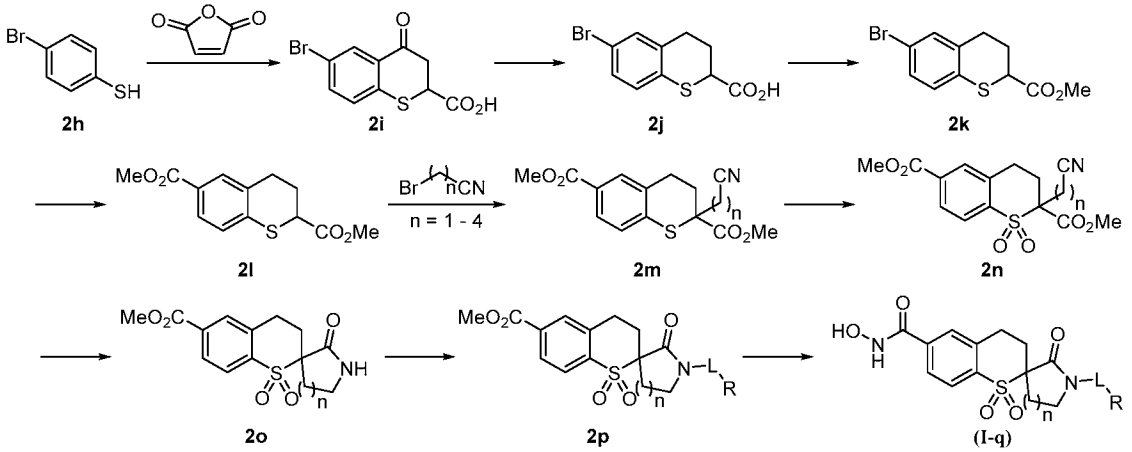


wherein L and R are defined as in Formula (I).

[0071] The general way of preparing target molecules of Formula (I-n) by using intermediates **2a**, **2b**, **2c**, **2d**, and **2e** is outlined in General Scheme 1. Hydrogenation of 2,6-dimethyl naphthalene-2,6-dicarboxylate (**2a**) in the presence of palladium on carbon under standard conditions affords **2b**. Deprotonation of **2b** with a base, followed by alkylation with a halo-nitrile provides intermediates **2c**. Spiro-lactams **2d** can be obtained by treatment of **2c** with platinum (IV) oxide (PtO_2) in the presence of hydrogen (H_2) gas and ammonia (NH_3). Addition of the R-L moiety can be achieved via standard methods of alkylation or arylation. For example, alkylation of **2d** with an alkyl halide in the presence of a base, e.g. sodium hydride, can provide compounds of intermediates **2e**. Alternatively, arylation of **2d** with an aryl bromide or aryl iodide in the presence of a metal catalyst, e.g. copper (I) iodide (CuI), and a base, e.g. cesium carbonate (Cs_2CO_3), can also provide compounds of intermediates **2e**. Treatment of **2e** with hydroxylamine and a base, e.g, sodium hydroxide, provides compounds of Formula (I-n).

[0072] The general way of preparing target molecules of Formula (I-p) by using intermediates **2a**, **2b**, **2c**, **2d**, **2f**, and **2g** is also outlined in General Scheme 1. Spiro-amines **2f** can be obtained by treatment of **2d** with borane-tetrahydrofuran complex under standard reduction conditions. Addition of the R-L moiety can be achieved via standard methods of alkylation, arylation, acylation, urea formation, or sulfonation. Treatment of **2g** with hydroxylamine and a base, e.g, sodium hydroxide, provides compounds of Formula (I-p).

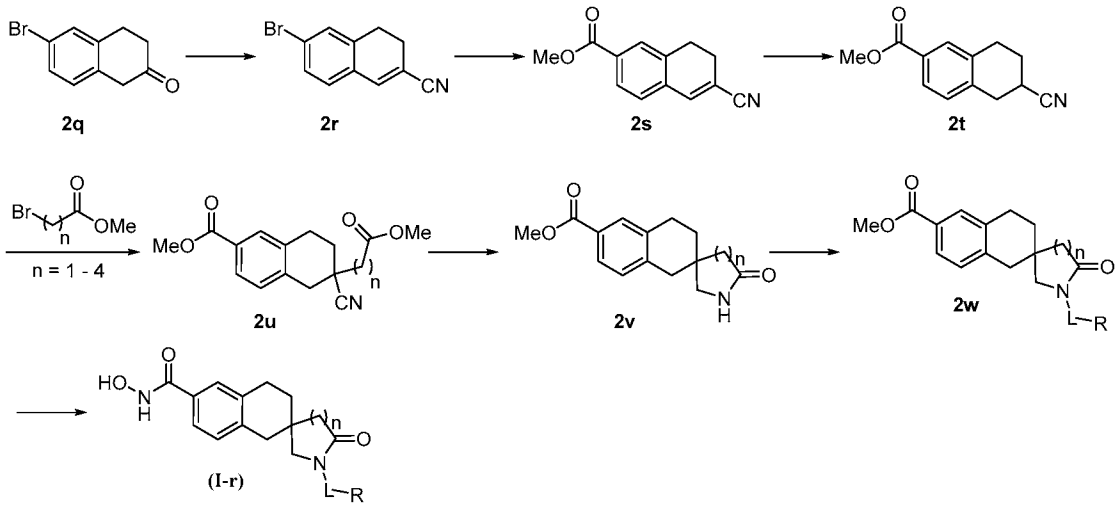
Scheme 2. General synthesis of sulfone compounds of the Formula (I-q).



wherein L and R are defined as in Formula (I).

[0073] The general way of preparing target molecules of Formula (I-q) by using intermediates **2h**, **2i**, **2j**, **2k**, **2l**, **2m**, **2n**, **2o**, and **2p** is outlined in General Scheme 2. Treatment of 4-bromobenzenethiol (**2h**) with 2,5-dihydrofuran-2,5-dione and a base, e.g. triethylamine, followed by aluminum chloride, affords **2i**. Treatment of **2i** with triethylsilane in the presence of an acid, e.g. trifluoroacetic acid, provides **2j**. Standard esterification methods afford methyl ester **2k**. Carbonylation of **2k** with carbon monoxide gas in the presence of a metal catalyst, e.g. [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2$), a base, e.g. triethylamine, and methanol, affords **2l**. Deprotonation of **2l** with a base, followed by alkylation with a halo-nitrile provides intermediates **2m**, which can be readily oxidized to the sulfones **2n** with m-chloroperoxybenzoic acid. Spiro-lactams **2o** can be obtained by treatment of **2n** with PtO_2 in the presence of H_2 gas and NH_3. Addition of the R-L moiety can be achieved via standard methods of alkylation or arylation. For example, alkylation of **2o** with an alkyl halide in the presence of a base, e.g. sodium hydride, can provide compounds of intermediates **2p**. Alternatively, arylation of **2o** with an aryl bromide or aryl iodide in the presence of a metal catalyst, e.g. palladium (II) acetate ($Pd(OAc)_2$), a ligand, e.g. 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos), and a base, e.g. Cs_2CO_3, can also provide compounds of intermediates **2p**. Treatment of **2p** with hydroxylamine and a base, e.g, sodium hydroxide, provides compounds of Formula (I-q).

Scheme 3. General synthesis of amide compounds of the Formula (I-r).

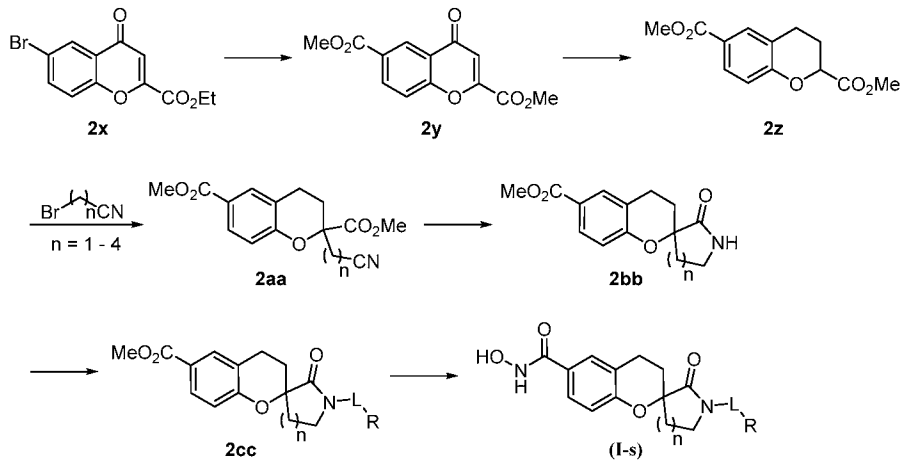


wherein L and R are defined as in Formula (I).

[0074] The general way of preparing target molecules of Formula (I-r) by using intermediates **2q**, **2r**, **2s**, **2t**, **2u**, **2v**, and **2w** is outlined in General Scheme 3. Nitrile addition to

6-bromo-3,4-dihydronaphthalen-2(1H)-one (**2q**), for example with trimethylsilyl cyanide in the presence of zinc diiodide, followed by dehydration, for example with phosphorus (V) oxychloride, provides **2r**. Carbonylation of **2r** with carbon monoxide gas in the presence of a metal catalyst, e.g. $Pd(dppf)Cl_2$, a base, e.g. triethylamine, and methanol, affords methyl ester **2s**. Treatment of **2s** with magnesium provides affords **2t**, which can be deprotonated with a base, and alkylated with a halo-ester to provide intermediates **2u**. Spiro-lactams **2v** can be obtained by treatment of **2u** with PtO_2 in the presence of H_2 gas and NH_3. Addition of the R-L moiety can be achieved via standard methods of alkylation or arylation. For example, alkylation of **2v** with an alkyl halide in the presence of a base, e.g. sodium hydride, can provide compounds of intermediates **2w**. Alternatively, coupling of **2v** with an aryl boronic acid in the presence of a metal catalyst, e.g. copper (II) acetate ($Cu(OAc)_2$), and a base, e.g. triethylamine, can also provide compounds of intermediates **2w**. Treatment of **2w** with hydroxylamine and a base, e.g, sodium hydroxide, provides compounds of Formula (I-r).

Scheme 4. General synthesis of ether compounds of the Formula (I-s).

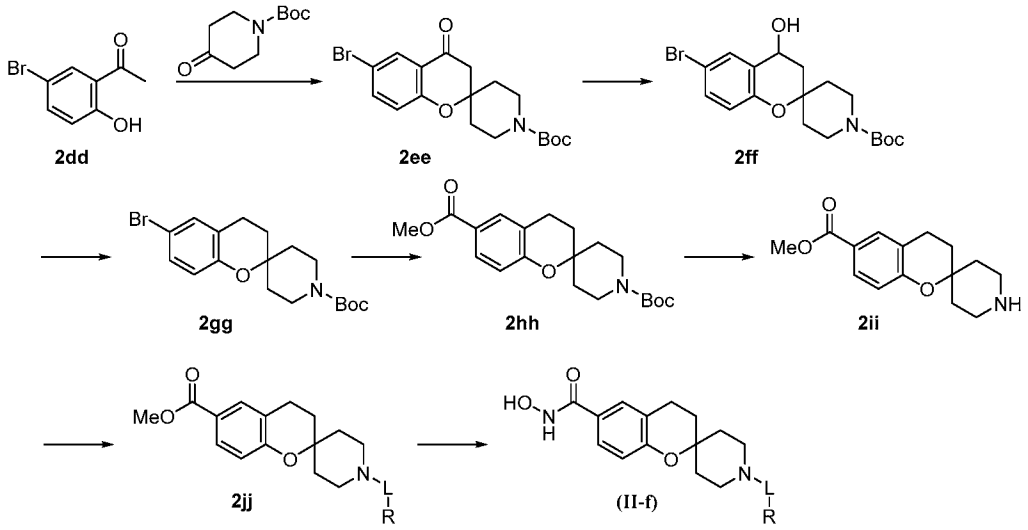


wherein L and R are defined as in Formula (I).

[0075] The general way of preparing target molecules of Formula (I-s) by using intermediates **2x**, **2y**, **2z**, **2aa**, **2bb**, and **2cc** is outlined in General Scheme 4. Carbonylation of ethyl 6-bromo-4-oxo-4H-chromene-2-carboxylate (**2x**) can be achieved by treatment with carbon monoxide gas in the presence of a metal catalyst, e.g. $Pd(dppf)Cl_2$, a base, e.g. triethylamine, and methanol, to afford methyl ester **2y**. Reduction of the chromenone, for example by treatment with H_2 gas in the presence of palladium on carbon and acetic acid, provides chromane **2z**.

Deprotonation of **2z** with a base, followed by alkylation with a halo-nitrile provides intermediates **2aa**. Spiro-lactams **2bb** can be obtained by treatment of **2aa** with PtO_2 in the presence of H_2 gas and NH_3. Addition of the R-L moiety can be achieved via standard methods of alkylation or arylation. For example, alkylation of **2bb** with an alkyl halide in the presence of a base, e.g. sodium hydride, can provide compounds of intermediates **2cc**. Alternatively, coupling of **2bb** with an aryl bromide or aryl iodide in the presence of a metal catalyst, e.g. $Pd(OAc)_2$, a ligand, e.g. XantPhos, and a base, e.g. Cs_2CO_3, can also provide compounds of intermediates **2cc**. Treatment of **2cc** with hydroxylamine and a base, e.g, sodium hydroxide, provides compounds of Formula (I-s).

Scheme 5. General synthesis of compounds of the Formula (II-f).



wherein L and R are defined as in Formula (II).

[0076] The general way of preparing target molecules of Formula (II-f) by using intermediates **2dd**, **2ee**, **2ff**, **2gg**, **2hh**, **2ii**, and **2jj** is outlined in General Scheme 5. Treatment of 1-(5-bromo-2-hydroxyphenyl)ethan-1-one (**2dd**) with tert-butyl 4-oxopiperidine-1-carboxylate in the presence of a base affords **2ee**, which can be reduced by stepwise treatment with sodium borohydride, followed by triethylsilane and trifluroacetic acid to afford **2gg**. Carbonylation of **2gg** can be achieved by metal exchange, e.g. with n-butyl lithium, followed by treatment with methyl chloroformate, to afford methyl ester **2hh**. Spiro-amine **2ii** can be readily obtained by standard Boc deprotection methods. Addition of the R-L moiety can be achieved via standard

methods of alkylation, arylation, acylation, urea formation, or sulfonation. Treatment of **2jj** with hydroxylamine and a base, e.g, sodium hydroxide, provides compounds of Formula (II-f).

Methods of Using the Disclosed Compounds

[0077] Another aspect of the invention relates to a method of treating a disease associated with HDAC6 modulation in a subject in need thereof. The method involves administering to a patient in need of treatment for diseases or disorders associated with HDAC6 modulation an effective amount of a compound of Formula I or Formula II. In an embodiment, the disease can be, but is not limited to, cancer, neurodegenerative disease, neurodevelopmental disease, inflammatory or autoimmune disease, infection, metabolic disease, hematologic disease, or cardiovascular disease.

[0078] Another aspect of the invention is directed to a method of inhibiting HDAC6. The method involves administering to a patient in need thereof an effective amount of Formula I or Formula II.

[0079] The present invention relates to compositions capable of modulating the activity of (e.g., inhibiting) HDACs, and in particular HDAC6. The present invention also relates to the therapeutic use of such compounds.

[0080] One therapeutic use of the compounds of the present invention is to treat proliferative diseases or disorders such as cancer. Cancer can be understood as abnormal or unregulated cell growth within a patient and can include but is not limited to lung cancer, ovarian cancer, breast cancer, prostate cancer, pancreatic cancer, hepatocellular cancer, renal cancer and leukemias such as acute myeloid leukemia and acute lymphoblastic leukemia. Additional cancer types include T-cell lymphoma (*e.g.*, cutaneous T-cell lymphoma, peripheral T-cell lymphoma), Hodgkin lymphoma, melanoma and multiple myeloma. In other embodiments, treating proliferative diseases or disorders can include any cancer where there is evidence of an increase in Treg/effector T cell ratio or in an absolute Treg number, either in the periphery or in the tumor microenvironment or tertiary lymphoid structures, or increased expression of T cell tolerance-related genes. Such proliferative diseases or disorders can include but are not limited to: any Kras mutant carrying tumor (http://cancerimmunolres.aacrjournals.org/content/early/2016/02/13/2326-6066.CIR-15-0241.long); renal cell carcinoma; lung carcinoma; cervical cancer; prostate cancer; ovarian

cancer; head and neck cancer; lymphoma; colorectal cancer, non-small cell lung carcinoma; breast cancers (Gobert, M. et al. (2009) Cancer Res. 69, 2000–2009); and bladder cancer.

[0081] One therapeutic use of the compounds of the present disclosure is to treat neurological diseases or disorders or neurodegeneration. Neurological disorders are understood as disorders of the nervous system (*e.g.*, the brain and spinal cord). Neurological disorders or neurodegenerative diseases can include but are not limited to epilepsy, attention deficit disorder (ADD), Alzheimer's disease, Parkinson's Disease, Huntington's Disease, amyotrophic lateral sclerosis, spinal muscular atrophy, essential tremor, central nervous system trauma caused by tissue injury, oxidative stress-induced neuronal or axomal degeneration, and multiple sclerosis.

[0082] Another therapeutic use of the compounds of the present disclosure is to treat neurodevelopmental disorders. Neurodevelopmental disorders can include, but are not limited to, Rett syndrome, intellectual disability, intellectual and developmental disability, autism spectrum disorder, fetal alcohol syndrome, developmental coordination disorder, stereotypic movement disorder, Tourette syndrome, cerebral palsy, fragile X syndrome, attention deficit hyperactivity disorder, and Mendelsohnn's syndrome.

[0083] Another therapeutic use of the compounds of the present invention is also to treat inflammatory diseases or disorders. Inflammation can be understood as a host's response to an initial injury or infection. Symptoms of inflammation can include but are not limited to redness, swelling, pain, heat and loss of function. Inflammation may be caused by the upregulation of pro-inflammatory cytokines such as IL-1β, and increased expression of the FOXP3 transcription factor. In some embodiments, the inflammatory diseases include fibrosis or fibrotic diseases. Types of fibrotic diseases include but are not limited to lung fibrosis or pulmonary fibrosis, Liver fibrosis; Heart fibrosis; Mediastinal fibrosis; Retroperitoneal cavity fibrosis; Bone marrow fibrosis; Skin fibrosis; and Scleroderma or systemic sclerosis.

[0084] Another therapeutic use of the compounds of the present invention is also to treat autoimmune diseases or disorders. Autoimmune disorders are understood as disorders wherein a host's own immune system responds to tissues and substances occurring naturally in the host's body. Autoimmune diseases can include but are not limited to rheumatoid arthritis, Crohn's disease, type-1 diabetes, systemic juvenile idiopathic arthritis; inflammatory bowel disease; allograft transplantation; eczema, psoriasis, idiopathic thrombocytopenic purpra, autoimmune thrombocytopenia, acquired immune thrombocytopenia, autoimmune neutropenia, autoimmune

hemolyitic anemia, parvovirus B19-associated red cell aplasia, acquired antifactor VIII autoimmunity, acquired von Willebrand disease, monoclonal gammopathy, aplastic anemia, pure red cell aplasia, Diamond-Blackfan anemia, hemolytic disease of the newborn, immune mediated-refractoriness to platelet transfusion, hemolytic uremic syndrome, Evan's syndrome, Guillain-Barre syndrome, chronic demyelinating polyradiculoneuropathy, paraproteinemic IgM demyelinating polyneuropathy, Lamber-Eaton myasthenic syndrome, myasthenia gravis, multifocal motor neuropathy, stiff man syndrome, paraneoplastic encephalomyelitis, sensory neuropathy with anti-Hu antibodies, myelitis, autoimmune diabetic neuropathy, acute idiopathic neuropathy, toxic epidermal necrolysis, gangrene, granuloma, pemphigus vulgaris, bullous pemphigoid, vitiligo, scleroderma, atomic dermatitis, systemic and diffuse sclerosis, primary biliary cirrhosis, Celiac disease, dermatitis herpetiformis, cryptogenic cirrhosis, reactive arthritis, Hashimoto's thryroditis, Wegner's granulomoatosis, micropolyarterits, Churg-Strauss syndrome Type I and Type II autoimmune polygalndular syndromes, linear IgA disease, epidermolysis bullosa acquisita, erythema nodosa, pemphigoid gestationis, cicatricial pemphigoid, mixed essential cryoglobulinemia, chronic bullous disease of childhood, Goodpasture's syndrome, sclerosis cholangitis, ankylosing spondylitis, Bechet's syndrome temporal arteritis, Takayasu's arteritis, autoimmune urticaria, and Kawasaki's disease.

[0085] Another therapeutic use of the compounds of the present invention is also to treat infectious diseases or disorders. Infections or infectious diseases are caused by the invasion of a foreign pathogen. The infection may be caused by, for instance, a bacteria, a fungus, or virus. Bacterial infections include, but are not limited to streptococcus infections, mycobacterial infections, bacillus infections, Salmonella infections, Vibrio infections, spirochete infections, and Neisseria infections. Viral infections include, but are not limited to herpes virus infections, hepatitis virus infections, west nile virus infections, flavivrus infections, influenza virus infections, rhinovirus infections, papillomavirus infections, paromyxovirus infections, parainfluenza virus infections, and retrovirus infections. In particular embodiments, the compounds of the present invention are useful for treating infections which result in an inflammatory cytokine burst. Nonlimiting examples of such infections include Ebola and othe viral hemorghagic fever-causing viruses, and Malaria.

[0086] Another therapeutic use of the compounds of the present invention is also to treat and/or prevent allergy and unwanted immune responses associated with allergy. A non-limiting list of

allergies and related conditions includes, pollen allergy (e.g. Japanese Cedar Pollen), mold allergy, food allergies (including, but not limited to peanut, tree nut, milk, soy, gluten, and egg allergies), animal allergies (e.g. allergies to dogs, cats, rabbits), dust mite allergy, atopic dermatitis, allergic rhinitis, allergic otitis, allergic asthma, dry eye, ocular allergy, allergic urticaria, contact dermatitis, anaphalaxis, eosinophilic esophagitis.

[0087] Yet another therapeutic use of the compounds of the present invention is also to treat metabolic diseases or disorders. Metabolic diseases can be characterized as abnormalities in the way that a subject stores energy. Metabolic disorders can include but are not limited to metabolic syndrome, diabetes, obesity, high blood pressure, non-alcoholic fatty liver disease and heart failure.

[0088] Yet another therapeutic use of the compounds of the present invention is also to treat hematologic disorders. Hematologic diseases primarily affect the blood. Hematologic disorders can include but are not limited to anemia, multiple myeloma, lymphoma, and leukemia.

[0089] Yet another therapeutic use of the compounds of the present invention is also to prevent and/or treat transplant rejection. Tissues that are transplanted include (but are not limited to) whole organs such as kidney, liver, heart, lung; organ components such as skin grafts and the cornea of the eye; and cell suspensions such as bone marrow cells and cultures of cells selected and expanded from bone marrow or circulating blood, and whole blood transfusions.

[0090] Yet another therapeutic use of the compounds of the present invention is also to treat cardiovascular diseases or disorders. Cardiovascular diseases affect the heart and blood vessels of a patient. Exemplary conditions include but are not limited to cardiovascular stress, pressure overload, chronic ischemia, infarction-reperfusion injury, hypertension, Brain infarct after cerebral artery occlusion; atherosclerosis, peripheral artery disease, cardiac hypertrophy, cardiac arrhythmias, stroke, and heart failure.

[0091] Another therapeutic use of the compounds of the present invention is for purging the reservoir of latently infected memory CD4+ T cells in HIV+ patients (Matalon, et al., Mol Med. 2011; 17(5-6): 466–472).

[0092] The disclosed compound can be administered in effective amounts to treat or prevent a disorder and/or prevent the development thereof in subjects.

[0093] Another aspect of the present disclosure relates to a compound of Formula I or Formula II, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or

tautomer thereof, for use in treating or preventing a disease associated with HDAC6 modulation. In some embodiments, the disease is cancer, neurodegenerative disease, neurodevelopmental disorder, inflammatory or autoimmune disease, infection, metabolic disease, hematologic disease, or cardiovascular disease. In some embodiments, the compound inhibits a histone deacetylase. In another embodiment, the compound inhibits a zinc-dependent histone deacetylase. In another embodiment, the compound inhibits the HDAC6 isozyme zinc-dependent histone deacetylase.

[0094] In another aspect, the present disclosure relates to the use of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating or preventing a disease associated with HDAC6 modulation. In some embodiments, the disease is cancer, neurodegenerative disease, neurodevelopmental disorder, inflammatory or autoimmune disease, infection, metabolic disease, hematologic disease, or cardiovascular disease. In some embodiments, the compound inhibits a histone deacetylase. In another embodiment, the compound inhibits a zinc-dependent histone deacetylase. In another embodiment, the compound inhibits the HDAC6 isozyme zinc-dependent histone deacetylase.

[0095] In some embodiments, the cancer is melanoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, Hodgkin lymphoma, multiple myeloma, leukemia, lung, ovarian, breast, prostate, pancreatic, hepatocellular or renal cancer. In other embodiments, the neurodegenerative disease is Alzheimer's, Huntington's, Parkinson's, Amyotrophic Lateral Sclerosis, or spinal muscular atrophy. In other embodiments, the neurodevelopmental disorder is Rett syndrome. In yet other embodiments, the inflammatory or autoimmune disease is rheumatoid arthritis, spondylitis arthritis, psoriatic arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, graft versus host disease, transplant rejection or fibrotic disease.

[0096] Administration of the disclosed compounds can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

[0097] Depending on the intended mode of administration, the disclosed compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, and all using forms well known to those skilled in the pharmaceutical arts.

[0098] Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising a compound of the disclosure and a pharmaceutically acceptable carrier, such as a) a diluent, e.g., purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil, or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA, or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, e.g., silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, e.g., starches, agar, methyl cellulose, bentonite, xanthan gum, algiic acid or its sodium salt, or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutol, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200.

[0099] Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, the disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles, or serum proteins can be used to solubilize the disclosed compounds.

[00100] The disclosed compounds can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

[00101] The disclosed compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, containing cholesterol, stearylamine or phosphatidylcholines. In some embodiments, a film of lipid components is hydrated with an aqueous solution of drug to a form lipid layer encapsulating the drug, as described in U.S. Pat. No. 5,262,564.

[00102] Disclosed compounds can also be delivered by the use of monoclonal antibodies as individual carriers to which the disclosed compounds are coupled. The disclosed compounds can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspanamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the disclosed compounds can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels. In one embodiment, disclosed compounds are not covalently bound to a polymer, e.g., a polycarboxylic acid polymer, or a polyacrylate.

[00103] Parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

[00104] Another aspect of the invention relates to a pharmaceutical composition comprising a compound of Formula I or Formula II and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier can further include an excipient, diluent, or surfactant.

[00105] Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from

about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of the disclosed compound by weight or volume.

[00106] The dosage regimen utilizing the disclosed compound is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular disclosed compound employed. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[00107] Effective dosage amounts of the disclosed compounds, when used for the indicated effects, range from about 0.5 mg to about 5000 mg of the disclosed compound as needed to treat the condition. Compositions for in vivo or in vitro use can contain about 0.5, 5, 20, 50, 75, 100, 150, 250, 500, 750, 1000, 1250, 2500, 3500, or 5000 mg of the disclosed compound, or, in a range of from one amount to another amount in the list of doses. In one embodiment, the compositions are in the form of a tablet that can be scored.

[00108] Without wishing to be bound by any particular theory, the compounds of the present invention can inhibit HDACs such as HDAC6 by interacting with the zinc (Zn^{2+}) ion in the protein's active site via the hydroxamic acid group bound to the aromatic ring of the compound. The binding can prevent the zinc ion from interacting with its natural substrates, thus inhibiting the enzyme.

Examples

[00109] The disclosure is further illustrated by the following examples and synthesis examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

[00110] The present invention includes a number of unique features and advantages compared with other inhibitors of HDAC enzymes, in particular HDAC6. For instance, the present invention features a unique class of small molecule therapeutic agents of Formula I or Formula

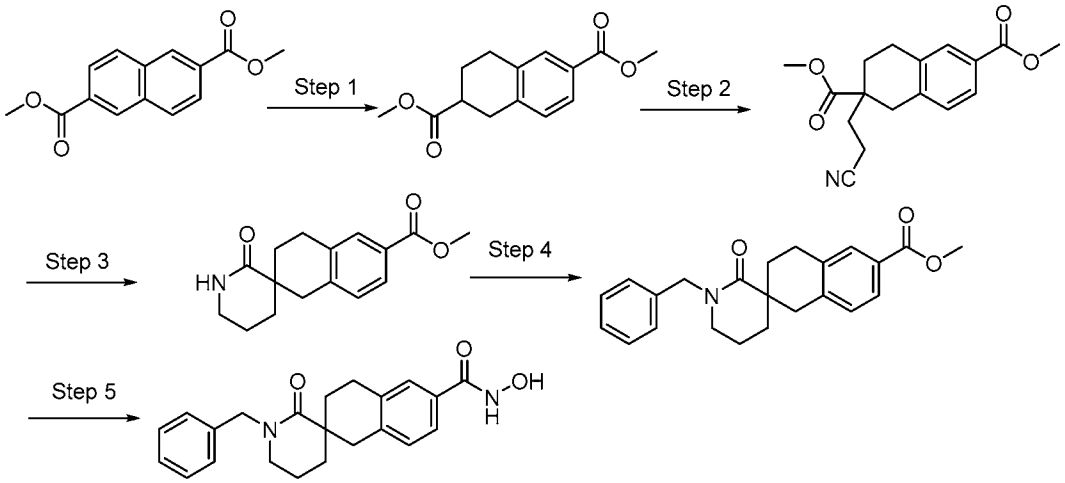
II. The compounds were designed by using crystal structure information of HDAC ligand-protein complexes as well as advanced computational chemistry tools. These techniques led to the development of new chemical scaffolds that were iteratively refined to optimize key recognition features between the ligand and receptor known to be necessary for potency.

[00111] Definitions used in the following examples and elsewhere herein are:

AcOH	Acetic acid
$AlCl_3$	Aluminum chloride
CH_2Cl_2	Methylene chloride, Dichloromethane
CH_3CN	Acetonitrile
CO (g)	Carbon monoxide gas
CH_3I	Iodomethane
CO_2	Carbon dioxide
Cs_2CO_3	Cesium carbonate
$Cu(OAc)_2$	Copper (II) acetate
CuI	Copper (I) iodide
CuBr	Copper (I) bromide
DCE	1,2-Dichloroethane
DMA	Dimethylacetamide
DIEA	Diisopropylethylamine
DMC	2-Chloro-1,3-dimethylimidazolinium chloride
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
h	hours
H_2 (g)	Hydrogen (gas)
H_2O	Water
HBTU	*N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HCl	Hydrochloric acid
K_2CO_3	Potassium carbonate
K_3PO_4	Potassium phosphate tribasic
LDA	Lithium diisopropylamide
m-CPBA	3-Chloroperbenzoic acid
MeOH	Methanol
$MgSO_4$	Magnesium sulfate

min	minutes
$NaBH(OAc)_3$	Sodium triacetoxyborohydride
Na_2CO_3	Sodium carbonate
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4HCO_3	Ammonium bicarbonate
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NH_3	Ammonia
NaI	Sodium iodide
NaOH	Sodium hydroxide
NH_2OH	Hydroxylamine
NMM	4-Methylmorpholine
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(dppf)Cl_2•CH_2Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)-dichloromethane adduct
$Pd(OAc)_2$	Palladium (II) acetate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$POCl_3$	Phosphorus (V) oxychloride
PtO_2	Platinum (IV) oxide
PTSA	p-Toluenesulfonic acid monohydrate
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
RuPhos Pd G2	Chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl) [2-(2′-amino-1,1′-biphenyl)]palladium(II)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSCN	Trimethylsilyl cyanide
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
ZnI_2	Zinc diiodide

Example 1 – Preparation of 1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxamide (I-176)



***Step-1*: Dimethyl 1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate**

[00112] Into a 2-L pressure tank reactor was placed 2,6-dimethyl naphthalene-2,6-dicarboxylate (50 g, 204.71 mmol, 1 equiv) in isopropanol (1.2 L), palladium on carbon (9.5 g) and acetic acid (5 g, 83.26 mmol, 0.41 equiv). Hydrogen gas (50 atm) was introduced. The resulting solution was stirred for 2 days at 40 °C. The solids were filtered off. The filter cake was washed with 2x200 mL of CH_2Cl_2 and 2x200 mL of MeOH. The combined filtrate was concentrated under vacuum. The residue was dissolved with 300 mL of EtOAc. The pH was adjusted to 8 using aq. Na_2CO_3. The organic layer was washed with 3x100 mL of H_2O and dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 40 g (79% yield) of the title compound as a white solid. MS: (ES, *m/z*): 249 $[M+H]^+$.

***Step-2*: Dimethyl 2-(2-cyanoethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate**

[00113] Into a 500-mL 3-necked round-bottom flask purged and maintained with N_2, was placed dimethyl 1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (6 g, 24.17 mmol, 1 equiv) in THF (50 mL, 1 equiv). The solution was cooled to -78 °C and LDA (2M in THF/hexanes, 24.2 mL 2 equiv) was added dropwise to the stirring solution. After 30 min, 3-bromopropanenitrile (4.8 g, 35.83 mmol, 1.5 equiv) was added at -78 °C. The resulting solution was stirred for additional 2 h. The reaction was then quenched by the addition of 30 mL of NH_4Cl. The resulting solution was extracted with 3x20 mL of EtOAc. The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1/1). The collected fractions

were concentrated to give 1.6 g (22% yield) of the title compound as a white solid. MS: (ES, *m/z*): 302 $[M+H]^+$.

***Step-3*: Methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate**

[00114] Into a 250-mL 3-necked round-bottom flask was placed dimethyl 2-(2-cyanoethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (1.6 g, 5.31 mmol, 1 equiv) in MeOH (50 mL), PtO_2 (0.4 g) and NH_3/MeOH (8 mL). To the above mixture, H_2 (g) was introduced and the resulting mixture was stirred for 16 h at room temperature under H_2 atmosphere. The solids were filtered out and the filtrate was concentrated under vacuum. The crude product was purified by re-crystallization from EtOAc. This provided 1 g (69% yield) of the title compound as an off-white solid. MS: (ES, *m/z*): 274 $[M+H]^+$.

***Step-4*: Methyl 1'-benzyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate**

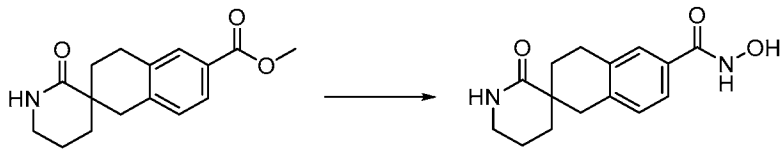
[00115] Into a 100-mL round-bottom flask was placed methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate (100 mg, 0.37 mmol, 1 equiv) in DMF (5 mL, 1 equiv). The resulting mixture was cooled to 0 °C in an ice-water bath. NaH (60% dispersion in oil, 29.3 mg, 1.22 mmol, 3 equiv) was added and the mixture stirred at 0 °C for 30 min. Then (bromomethyl)benzene (68.4 mg, 0.40 mmol, 1.1 equiv) was added to the reaction. The resulting mixture was stirred for 1h at room temperature. The reaction was then quenched by the addition of 10 mL of water and was extracted with 3x10 mL of EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 120 mg (90% yield) of the title compound as a yellow solid. MS: (ES, m/z): 364$[M+H]^+$.

***Step-5*: 1'-Benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

[00116] Into a 50-mL round-bottom flask was placed methyl 1'-benzyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate (120 mg, 0.33 mmol, 1 equiv), THF/MeOH (4:1, 2 mL), NH_2OH (50% in water, 326.7 mg, 30 equiv), and 1N aq. NaOH (26.4 mg, 2 equiv). The resulting solution was stirred for 1h at room temperature. The pH of the solution was adjusted to 6 with 1N aq. HCl. The crude product was purified by Prep-HPLC with the following conditions: Column: Waters HSS C18, 2.1x50 mm, 1.8 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 0.7mL/min; Gradient: 5%B to 95%B in 2.0 min, hold 0.6 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 18.1

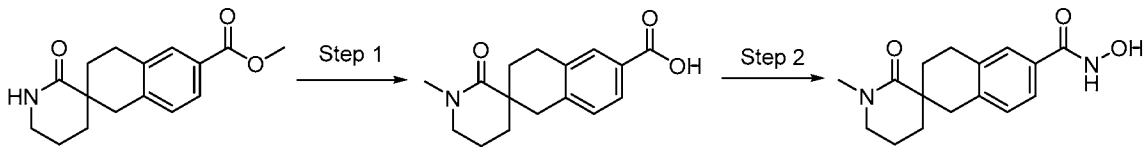
mg (15% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.09 (s, 1H), 7.51 (s, 1H), 7.46-7.48 (d, *J* = 8 Hz, 1H), 7.34-7.38 (m, 2H), 7.21-7.29 (m, 3H), 7.14-7.16 (d, *J* = 8 Hz, 1H), 4.53 (s, 2H), 3.15-3.25 (m, 3H), 2.70-2.80 (m, 3H), 2.08-2.18 (m, 1H), 1.74-1.77 (m, 3H), 1.58-1.61 (m, 2H). MS: (ES, *m/z*): 365[M+H]$^+$.

Example 2 – Preparation of N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-177)



[00117] Into an 8-mL vial, was placed a solution of methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]- 6-carboxylate (70 mg, 0.26 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL), NH_2OH (50% in water, 0.51 mL, 2 equiv) and 1N aq. NaOH (0.51 mL, 30 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Sunfire C18, 19x150, 5 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 25 mL/min; Gradient: 5% B to 52% B in 6 min); Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 39.2 mg (56% yield) of the title compound as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.08 (br s, 1H), 7.50-7.41 (m, 3H), 7.13-7.12 (m, 1H), 3.16-3.06 (m, 3H), 2.82-2.71 (m, 2H), 2.70-2.65 (m, 1H), 2.08-2.00 (m,1H), 1.70-1.66 (m, 3H), 1.59-1.58 (m, 2H). MS: (ES, *m/z*): 275 [M+H]$^+$.

Example 3 – Preparation of N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxamide (I-178)



***Step-1*: 1'-Methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylic acid**

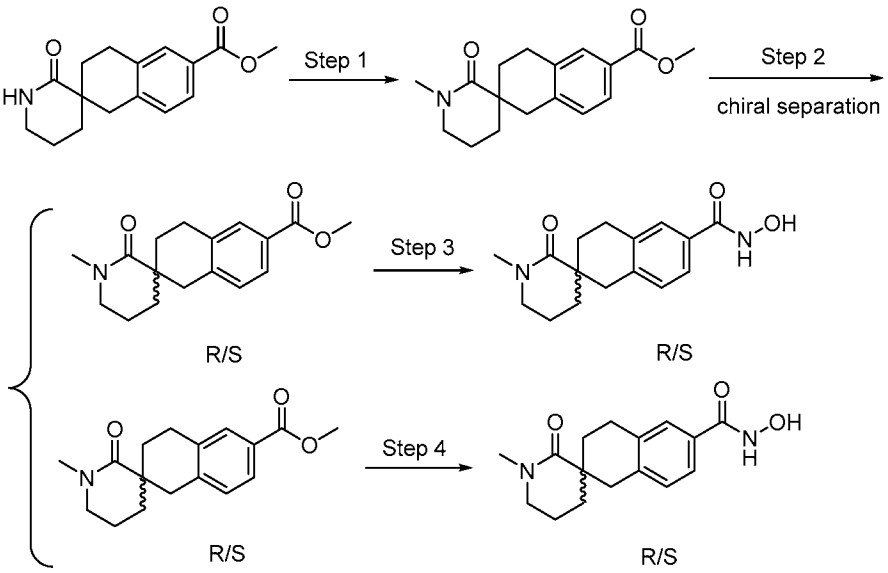
[00118] Into an 8-mL vial, was placed a solution of methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate (100 mg, 0.37 mmol, 1 equiv) in DMF (4 mL). This was followed by the addition of NaH (60% dispersion in oil, 44 mg, 1.83 mmol, 3 equiv), in

portions at 0 °C over 10 min. To this was added CH_3I (104 mg, 0.73 mmol, 2 equiv). The resulting mixture was stirred for 18 h at room temperature. The reaction was then quenched by the addition of 10 mL of NH_4Cl (aq.) at 0 °C. The resulting solution was extracted with 2x20 mL of EtOAc. The aqueous layers were combined and the pH of the solution was adjusted to 4 with 1N aq. HCl. The resulting solution was extracted with 3x30 mL of CH_2Cl_2, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to give 137.6 mg (crude) of the title compound as a light yellow oil which was used in the next step without purification. MS: (ES, *m/z*): 274 $[M+H]^+$.

***Step-2*: N-Hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

[00119] Into an 8-mL vial, was placed a solution of 1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylic acid (135 mg, 0.49 mmol, 1 equiv) in DMA (3 mL). This was followed by the addition of isopropyl chloroformate (311 mg, 2.47 mmol, 5 equiv) and NMM (250 mg, 2.47 mmol, 5 equiv) at 0°C over 10 min. To this was added a solution of NH_2OH•HCl (173 mg, 2.47 mmol, 5 equiv) in DMA (1.5 mL). The resulting solution was stirred for 18 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Sunfire C18, 5 μm, 19x100mm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 25 mL/min; Gradient: 5% B to 52% B in 6 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 46.4 mg (33% yield) of the title compound as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.08 (br s, 1H), 7.50-7.45 (m, 2H), 7.12-7.10 (d, J = 8.0 Hz, 1H), 3.32-3.25 (m, 2H), 3.11-3.07 (m, 1H), 2.83 (s, 3H), 2.79-2.69 (m, 2H), 2.66-2.62 (m, 1H), 2.10-2.02 (m, 1H), 1.79-1.78 (m, 2H), 1.74-1.63 (m, 1H), 1.62-1.53 (m, 2H). MS: (ES, *m/z*): 289 $[M+H]^+$.

Example 4 – Preparation of (R)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxamide (I-179) and (S)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxamide (I-180)



***Step-1*: Methyl 1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate**

[00120] Into an 8-mL vial, was placed a solution of methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate (100 mg, 0.37 mmol, 1 equiv) in DMF (4 mL). This was followed by the addition of NaH (60% dispersion in oil, 44 mg, 1.83 mmol, 3 equiv), in portions at 0 °C over 10 min. To this was added CH_3I (104 mg, 0.73 mmol, 2 equiv). The resulting solution was stirred for 18 h at room temperature. The reaction was then quenched by the addition of 10 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x30 mL of CH_2Cl_2. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to provide 137.6 mg (crude) of the title compound as a light yellow oil. MS: (ES, *m/z*): 288 $[M+H]^+$.

***Step-2*: Chiral separation of the racemate to obtain methyl (R)-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate and methyl (S)-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate**

[00121] The racemate of methyl 1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate (137.6 mg, 47.9 mmol, 1 equiv) was purified by Prep-SFC with the following conditions: Column: Chiralpak IC 2x25cm, 5 μm; Mobile Phase A: Hexanes, Mobile Phase B: EtOH; Flow rate: 18 mL/min; Gradient: 25% B in 26 min; Detector: UV 254 nm,220

nm. The first peak (Rt 18.65 min) was collected and concentrated to give 60 mg of a yellow solid which was assigned as the R isomer of methyl 1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate. MS: (ES, *m/z*): 288 $[M+H]^+$. The second peak (Rt 22.25 min) was collected and concentrated to give 40 mg of a yellow solid which was assigned as the S isomer of methyl 1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate. MS: (ES, *m/z*): 288 $[M+H]^+$.

***Step-3*: (R)-N-Hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

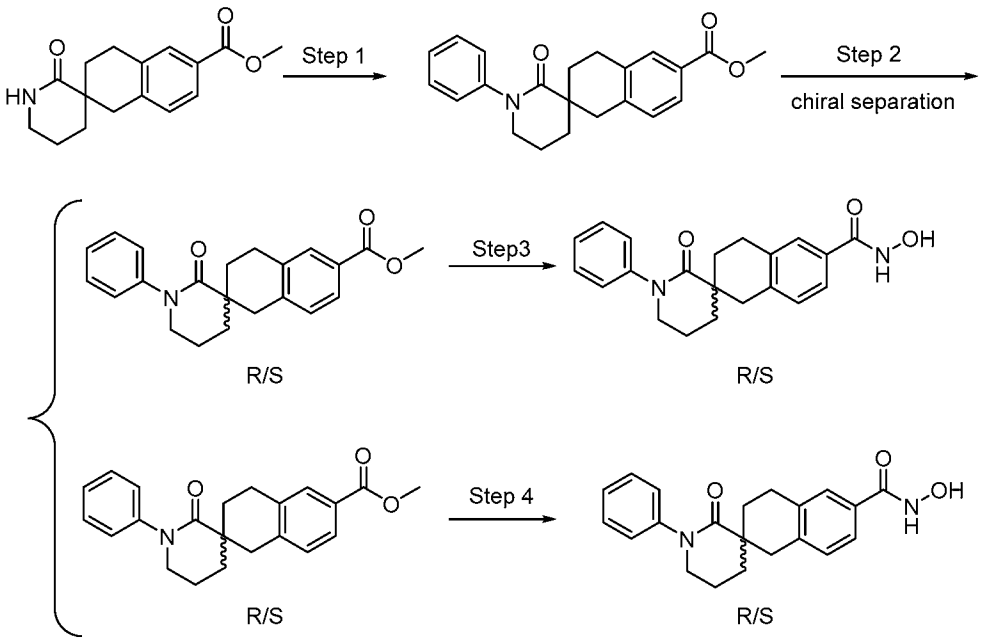
[00122] Into an 8-mL vial, was placed a solution of the first eluted isomer from Step 2, which was assigned as methyl (R)-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (60 mg, 0.21 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL), NH_2OH (50% in water, 0.41 mL, 30 equiv) and 1N aq. NaOH (0.42 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 19x150mm, 5 μm; Mobile Phase A: Water/0.1% Formic Acid, Mobile Phase B: CH_3CN/0.1% Formic Acid; Flow rate: 20 mL/min; Gradient: 5%B to 40%B in 8 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 38.7 mg (64% yield) of the title compound as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.08 (br s, 1H), 8.94 (br s, 1H), 7.50-7.45 (m, 2H), 7.12-7.10 (m, 1H), 3.32-3.25 (m, 2H), 3.12-3.07 (m, 1H), 2.83-2.2.79 (m, 3H), 2.78-2.76 (m, 2H), 2.74-2.72 (m, 1H), 2.10-2.02 (m, 1H), 1.79-1.73 (m, 2H), 1.69-1.61 (m, 1H), 1.59-1.51 (m, 2H). MS: (ES, *m/z*): 289 $[M+H]^+$.

***Step-4*: (S)-N-Hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

[00123] Into an 8-mL vial, was placed a solution of the second eluted isomer from Step 2, which was assigned as methyl (S)-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (40 mg, 0.14 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL), NH_2OH (50% in water, 0.27 mL, 30 equiv) and 1N aq. NaOH (0.29 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 19x150mm, 5 μm; Mobile Phase A: Water/0.1% Formic Acid, Mobile Phase B: CH_3CN/0.1% Formic Acid; Flow rate: 20 mL/min; Gradient: 5% B to 40% B in 8 min; Detector: UV 254 nm, 220 nm. The

collected fractions were lyophilized to give 33.7 mg (84% yield) of the title compound as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.06 (br s, 1H), 8.92 (br s, 1H), 7.48-7.43 (m, 2H), 7.10-7.08 (m, 1H), 3.31-3.25 (m, 2H), 3.10-3.06 (m, 1H), 2.81-2.61 (m, 6H), 2.08-2.00 (m, 2H), 1.78-1.72 (m, 2H), 1.68-1.64 (m, 1H), 1.57-1.50 (m, 2H). MS: (ES, *m/z*): 289 $[M+H]^+$.

Example 5 – Preparation of (R)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxamide (I-181) and (S)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxamide (I-182)



***Step-1*: Methyl 2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate**

[00124] Into a 25-mL round-bottom flask, was placed methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate (500 mg, 1.83 mmol, 1 equiv) in DMSO (8 mL), iodobenzene (448 mg, 2.20 mmol, 1.2 equiv), CuI (70 mg, 0.37 mmol, 0.2 equiv), Cs_2CO_3 (1.78 g, 5.46 mmol, 3 equiv), and methyl[2-(methylamino)ethyl]amine (65 mg, 0.74 mmol, 0.4 equiv). The resulting mixture was stirred overnight at 130 °C. The reaction was then quenched by the addition of 20 mL of water, extracted with 3x50 mL of CH_2Cl_2, washed with 100 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with EtOAc/petroleum ether

(1:5). The collected fractions were concentrated under vacuum to give 150 mg (23% yield) of the title compound as an off- white solid. MS: (ES, *m/z*): 350 $[M+H]^+$.

***Step-2*: Chiral separation of methyl (R)-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate and methyl (S)-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate**

[00125] The racemate was purified by Chiral-HPLC with the following conditions: Column: CHIRALPAK IC 2x25cm, 5 μm; Mobile Phase A: Hexanes, Mobile Phase B: EtOH; Flow rate: 15 mL/min; Gradient: 50% B to 50% B in 21 min; Detector: UV 254 nm, 220 nm. The first eluting isomer (Rt 12.37 min) was collected and concentrated under vacuum to give 55 mg (37% yield) of an off-white solid which was assigned as the R isomer of methyl 2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate. MS: (ES, *m/z*): 350 $[M+H]^+$. The second eluting isomer (Rt 15.78 min) was collected and concentrated under vacuum to give 48 mg (32% yield) of an off-white solid which was assigned as the S isomer of methyl 2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate. MS: (ES, *m/z*): 350 $[M+H]^+$.

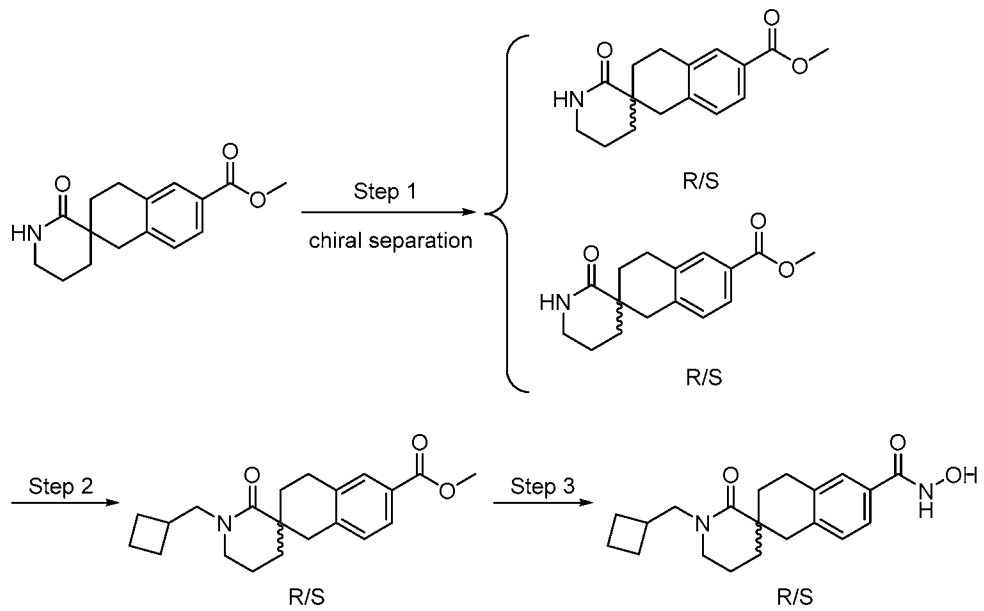
***Step-3*: (R)-N-Hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxamide**

[00126] Into a 25-mL round-bottom flask, was placed the first eluted isomer from Step 2, which was assigned as methyl (R)-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (55 mg, 0.16 mmol, 1 equiv), THF/MeOH (4:1, 3 mL), NH_2OH (50% in H_2O, 1560 mg, 30.56 mmol, 150 equiv) and 1N aq. NaOH (0.3 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The solids were filtered out and the crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 5 μm, 19x150mm; Mobile Phase A: Water/0.01% NH_4HCO_3, Mobile Phase B: CH_3CN; Gradient: 15% B to 60% B in 6 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 38.6 mg (70% yield) of the title compound as an off-white solid. ^{1}H-NMR (300 MHz, DMSO-d6) δ(ppm): 10.56 (s, 1H), 8.95 (s, 1H), 7.52-7.47 (t, *J* = 8.3 Hz, 2H), 7.41-7.36 (m, 2H), 7.27-7.22 (m, 3H), 7.16-7.14 (d, *J* = 8 Hz, 1H), 3.66-3.62 (t, *J* = 5.9 Hz, 2H), 3.19-3.14 (d, *J* = 16.8 Hz, 1H), 2.88-2.73 (m, 3H), 2.18-2.08 (m, 1H), 1.96-1.70 (m, 5H). MS: (ES, *m/z*): 351 $[M+H]^+$.

***Step-4*: (S)-N-Hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

[00127] Into a 25-mL round-bottom flask, was placed the second eluted isomer from Step 2, which was assigned as methyl (S)-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (43 mg, 0.12 mmol, 1 equiv), THF/MeOH (4:1, 2 mL), NH_2OH (50% in H_2O, 1220 mg, 23.90 mmol, 150 equiv), 1N aq. NaOH (0.25 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The solids were filtered out and the crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 5 μm, 19x150mm; Mobile Phase A: Water/0.01% NH_4HCO_3, Mobile Phase B: CH_3CN; Gradient: 15% B to 60% B in 6 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 39.4 mg (91% yield) of the title compound as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.07 (br s, 1H), 8.97 (s, 1H), 7.53 (s, 1H), 7.50-7.48 (d, J = 8 Hz, 1H), 7.42-7.38 (t, J = 7.8 Hz, 2H), 7.28-7.24 (m, 3H), 7.17-7.15 (d, J = 8 Hz, 1H), 3.67-3.64 (t, J = 6 Hz, 2H), 3.19-3.15 (d, J = 16.8 Hz, 1H), 2.88-2.75 (m, 3H), 2.18-2.09 (m, 1H), 1.96-1.84 (m, 3H), 1.79-1.66 (m, 2H). MS: (ES, *m/z*): 351 $[M+H]^+$.

Example 6 – Preparation of (R)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-185)



***Step-1*: Chiral separation of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate and methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate**

[00128] 5 g of the racemate methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate was purified by Prep-SFC with the following conditions: Column: CHIRALPAK IA-SFC-02, 5cmx25cm; Mobile Phase A: CO_2: 50%, Mobile Phase B: MeOH/CH_2Cl_2 (1:1) 50%; Flow rate: 180 mL/min; Detector: UV 220 nm. The first eluting isomer (Rt 3.53 min) was collected and concentrated under vacuum to give 2.4 g (29% yield) of a white solid which was assigned as the R isomer of methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as a white solid. MS: (ES, *m/z*): 274 [M+H]+. The second eluting isomer (Rt 4.49 min) was collected and concentrated under vacuum to give 2.4 g (29% yield) of a white solid which was assigned as the S isomer of methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as a white solid. MS: (ES, *m/z*): 274 [M+H]+.

***Step-2*: Methyl (R)-1'-(cyclobutylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxylate**

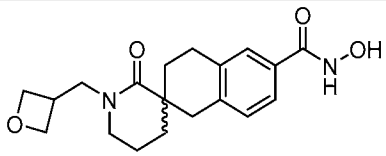
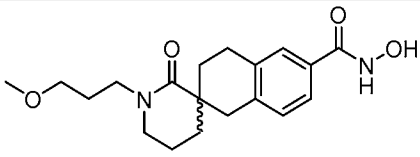
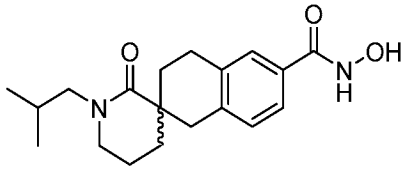
[00129] Into a 25-mL round-bottom flask, was placed the first eluted isomer from Step 1, which was assigned as methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (120 mg, 0.44 mmol, 1 equiv) in DMF (5 mL). This was followed by the addition of NaH (60% dispersion in oil, 70 mg, 2.92 mmol, 4 equiv) at 0 °C. The mixture was stirred for 30 min at room temperature. Then (bromomethyl)cyclobutane (262 mg, 1.76 mmol, 1 equiv) was added. The resulting solution was stirred for 5 h at room temperature. The reaction was then quenched by the addition of 20 mL of water, extracted with 3x30 mL of CH_2Cl_2, washed with 50 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with EtOAc/petroleum ether (1:1). The collected fractions were concentrated under vacuum to give 60 mg (40% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 342 $[M+H]^+$.

***Step-3*: (R)-1'-(Cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

[00130] Into a 10-mL sealed tube, was placed a solution of the product from Step 2, which was assigned as methyl (R)-1'-(cyclobutylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (60 mg, 0.18 mmol, 1 equiv) in THF/MeOH (4:1, 4 mL), NH_2OH (50% in H_2O, 1394 mg, 42.20 mmol, 120 equiv), 1N aq. NaOH (0.35 mL, 2 equiv). The resulting solution was stirred for 2 h at 28 °C. The solids were filtered out. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18

OBD, 5 μm,19x150mm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN; Gradient: 5% B to 65% B in 8 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 34.8 mg (58% yield) of the title compound as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d6), δ (ppm): 11.09 (s, 1H), 8.94 (s, 1H), 7.50-7.45 (t, *J* = 18.8 Hz, 2H), 7.13-7.11 (d, *J* = 8 Hz, 1H), 3.45-3.40 (m, 1H), 3.32-3.25 (m, 3H), 3.13-3.08 (d, *J* = 20 Hz, 1H), 2.74-2.65 (m, 2H), 2.61-2.51 (m, 2H), 2.08-2.06 (t, *J* = 8 Hz, 1H), 1.99-1.96 (m, 2H), 1.85-1.80 (m, 2H), 1.79-1.64 (m, 5H), 1.57-1.51(m, 2H). MS: (ES, *m/z*): 343 $[M+H]^+$.

Table-1: The following compounds were prepared according to the method of Example 6 using the first eluted enantiomer from Step 1.

Ex.	**Structure**	**^{1}H-NMR δ (ppm)**	**Found (ES, *m/z*) $[M+H]^+$**
I-196	 R/S	(300 MHz, DMSO-d6): 9.57 (s, 1H), 7.49-7.45 (t, *J* = 14.1 Hz, 2H), 7.12-7.09 (t, *J* = 8.1 Hz, 1H), 4.64-61 (t, *J* = 7.2 Hz, 2H), 4.37-4.31 (m, 2H), 3.70-3.51(m, 2H), 3.32-3.19 (m, 3H), 3.12-3.06 (d, *J* = 16.5 Hz, 1H), 2.76-2.71 (m, 2H), 2.65-2.60 (d, *J* = 16.5 Hz, 1H), 2.08-2.00 (m, 1H), 1.78-1.61 (m, 3H), 1.57-1.50 (m, 2H)	345
I-187	 R/S	(300 MHz, DMSO-d6): 7.47-7.43 (t, *J* = 12 Hz, 2H), 7.13-7.10 (d, *J* = 7.8 Hz, 1H), 3.63-3.32 (m, 6H), 3.30-3.27 (m, 3H), 3.23-3.14 (t, *J* = 13.7 Hz, 1H), 2.89-2.76 (m, 2H), 2.71-2.66 (d, *J* = 16.8 Hz, 1H), 2.24-2.13 (m, 1H), 1.89-1.68 (m, 5H), 1.67-1.51 (m, 2H)	347
I-189	 R/S	(400 MHz, DMSO-d6): 11.09 (s, 1H), 8.95 (s, 1H), 7.50 (s, 1H), 7.47-7.45 (d, *J* = 8 Hz, 1H), 7.13-7.11 (d, *J* = 7.6 Hz, 1H), 3.32-3.26 (m, 2H), 3.25-3.18 (m, 1H), 3.14-3.02 (m, 2H), 2.77-2.73 (t, *J* = 8.4 Hz, 2H), 2.70-2.63 (d, *J* = 16.8 Hz, 1H), 2.12-2.04 (m, 1H), 1.99- 1.92	331

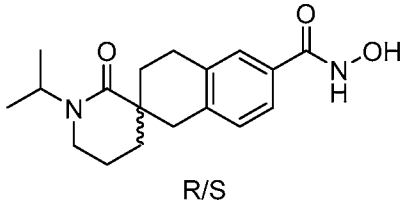
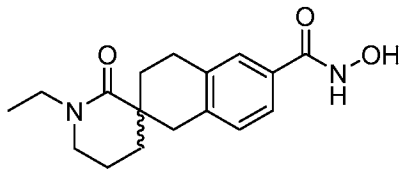
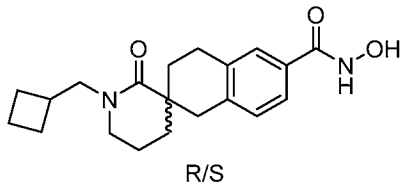
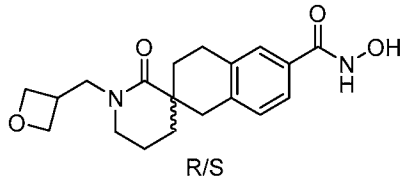
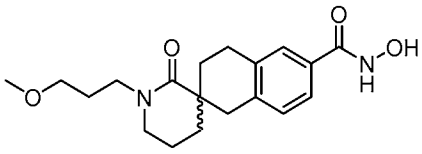
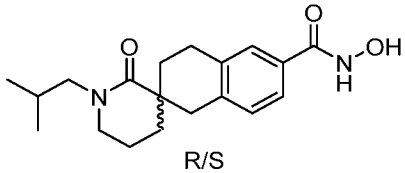
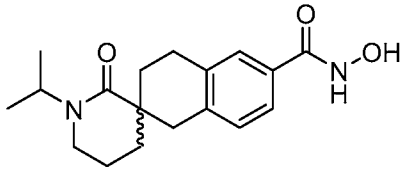
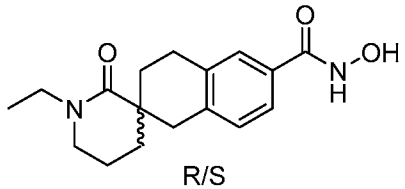
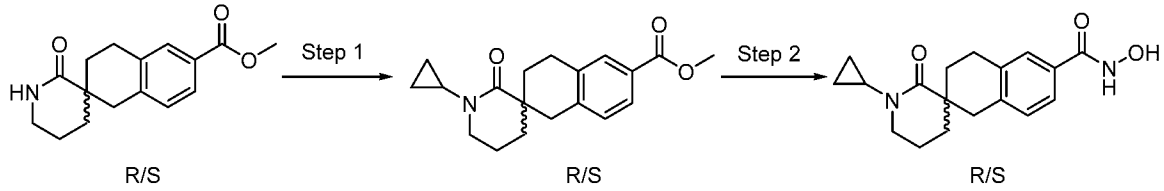
		(m, 1H), 1.78-1.74 (m, 2H), 1.69-1.62 (t, *J* = 15.6 Hz, 1H), 1.60-1.52 (m, 2H), 0.86-0.83 (t, *J* = 2.8 Hz, 6H)	
I-191	 R/S	(300 MHz, DMSO-d6): 11.07 (s, 1H), 8.94 (s, 1H), 7.50-7.44 (t, *J* = 15.3 Hz, 2H), 7.12-7.10 (t, *J* = 8.1 Hz, 1H), 4.72-4.63 (m, 1H), 3.31-3.08 (m, 3H), 2.77-2.60 (m, 3H), 2.12-2.01 (m, 1H), 1.69-1.48 (m, 5H), 1.06-1.04 (d, *J* = 6.9 Hz, 6H)	317
I-194	 R/S	(400 MHz, DMSO-d6): 11.08 (s, 1H), 8.92 (s, 1H), 7.48-7.43 (t, *J* = 9.6 Hz, 2H), 7.11-7.09 (d, *J* = 7.6 Hz, 1H), 3.30-3.25 (m, 4H), 3.11-3.06 (d, *J* = 16.8 Hz, 1H), 2.77-2.60 (m, 3H), 2.08-2.00 (m, 1H), 1.77-1.71 (m, 2H), 1.66-1.59 (m, 1H), 1.57-1.48 (m, 2H), 1.03-1.00 (t, *J* = 7.2 Hz, 3H)	303

Table-2: The following compounds were prepared according to the method of Example 6, with the following modification: In Step 2, the second eluted product from Step 1 was used.

Ex.	**Structure**	**^{1}H-NMR δ (ppm)**	**Found (ES, *m/z*) $[M+H]^+$**
I-186	 R/S	(300 MHz, DMSO-d6): 11.06 (s, 1H), 8.93 (s, 1H), 7.49-7.44 (m, 2H), 7.12-7.10 (m, 1H), 3.46-3.39 (m, 1H), 3.31-3.24 (m, 3H), 3.12-3.07 (m, 1H), 2.82-2.71 (m, 2H), 2.64-2.50 (m, 2H), 2.27-1.95 (m, 3H), 1.87-1.60 (m, 7H), 1.57-1.46 (m, 2H)	343

I-195	 R/S	(400 MHz, DMSO-d6): 8.94 (br s, 1H), 7.49-7.45 (m, 2H), 7.11-7.09 (d, *J* = 7.6 Hz, 1H), 4.63-4.59 (m, 2H), 4.37-4.32 (m, 2H), 3.69-3.64 (m, 1H), 3.58-3.52 (m, 1H), 3.27-3.19 (m, 3H), 3.11-3.06 (d, *J* = 16.8 Hz, 1H), 2.80-2.73 (m, 2H), 2.64-2.60 (d, *J* = 16.4 Hz, 1H), 2.10-2.01 (m, 1H), 1.75-1.72 (m, 2H), 1.70-1.61 (m, 1H), 1.58-1.54 (m, 2H)	345
I-188	 R/S	(300 MHz, CD_3OD): 7.50-7.46 (m, 2H), 7.16-7.13 (m, 1H), 3.51-3.38 (m, 6H), 3.33-3.31 (m, 3H), 3.26-3.21 (m, 1H), 2.91-2.83 (m, 2H), 2.75-2.70 (m, 2H), 2.27-2.16 (m, 1H), 1.88-1.77 (m, 7H)	347
I-190	 R/S	(300 MHz, DMSO-d6): 11.06 (br s, 1H), 8.93 (br s, 1H), 7.49-7.41 (m, 2H), 7.13-7.10 (d, *J* = 8.10 Hz, 1H), 3.28-3.14 (m, 3H), 3.08-3.01 (m, 2H), 2.76-2.61 (m, 3H), 2.12-1.90 (m, 2H), 1.78-1.51 (m, 5H), 0.92-0.82 (m, 6H)	331
I-192	 R/S	(300 MHz, DMSO-d6): 11.07 (s, 1H), 8.93 (s, 1H), 7.49-7.44 (m, 2H), 7.12-7.10 (m, 1H), 4.72-4.62 (m, 1H), 3.31-3.08 (m, 3H), 2.81-2.60 (m, 3H), 2.12-2.01 (m, 1H), 1.73-1.54 (m, 5H), 1.10-1.00 (m, 6H)	317
I-184	 R/S	(300 MHz, DMSO-d6): 11.04 (s, 1H), 8.94 (s, 1H), 7.50-7.45 (m, 2H), 7.12-7.10 (m, 1H), 3.32-3.25 (m, 4H), 3.13-3.07 (m, 1H), 2.81-2.66 (m, 2H), 2.60-2.50 (m, 1H), 2.11-2.00 (m, 1H), 1.80-1.58 (m, 5H), 1.08-0.96 (m, 3H)	303

Example 7 – Preparation of (R)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- piperidine]-6-carboxamide (I-193)



***Step-1*: Methyl (R)-1'-cyclopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxylate**

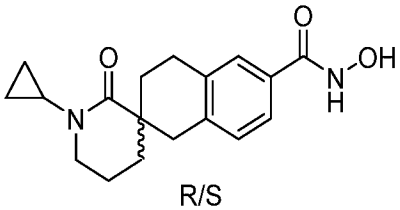
[00131] Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of O_2, was placed the first eluted isomer from Example 6, Step 1, which was assigned as methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (100 mg, 0.37 mmol, 1 equiv) in THF (5 mL), $Cu(OAc)_2$ (80 mg, 0.44 mmol, 1 equiv), Et_3N (120 mg, 1.19 mmol, 3 equiv), pyridine (40 mg, 0.51 mmol, 1.5 equiv), and cyclopropylboronic acid (105 mg, 1.22 mmol, 3 equiv). The resulting solution was stirred overnight at 60 °C. The solids were filtered out and the filtrate was quenched by the addition of 50 mL of water, extracted with 3x20 mL of CH_2Cl_2, washed with 100 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with CH_2Cl_2/MeOH (10:1). The collected fractions were concentrated under vacuum to give 90 mg (78% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 314 $[M+H]^+$.

***Step-2*: (R)-1'-Cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

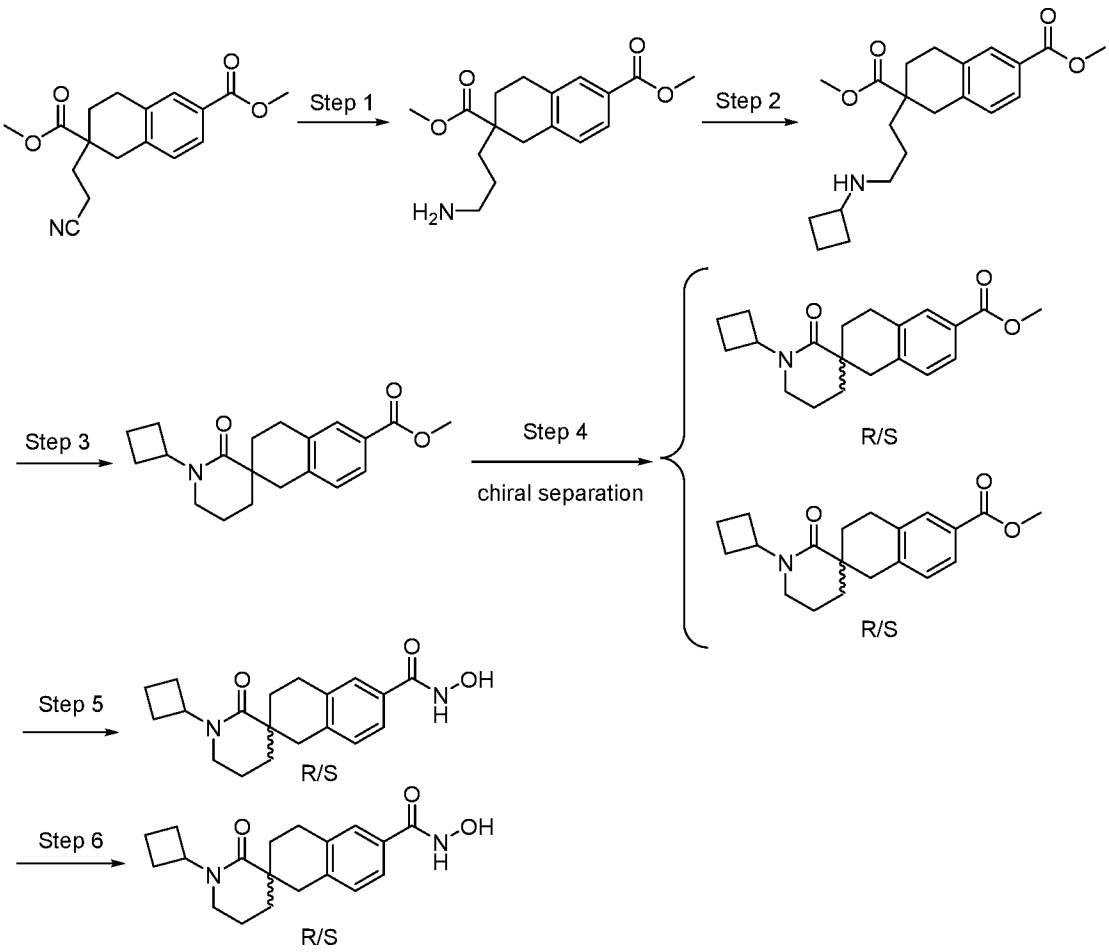
[00132] Into a 25-mL round-bottom flask, was placed a solution of the product from Step 1, which was assigned as methyl (R)-1'-cyclopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (70 mg, 0.22 mmol, 1 equiv) in THF/MeOH (4:1, 3 mL), NH_2OH (50% in H_2O, 1771 mg, 53.62 mmol, 120 equiv), 1N aq. NaOH (5 mL, 2 equiv). The resulting solution was stirred for 2 h at 28 °C. The solids were filtered out and the crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 5 μm,19x150mm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN; Flow rate: 20 mL/min; Gradient: 28% B to 39% B in 8 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 22.2 mg (32% yield) of the title compound as an off-

white solid. ^{1}H-NMR (300 MHz, DMSO-d6) δ(ppm): 11.04 (s, 1H), 8.92 (s, 1H), 7.49-7.44 (t, *J* = 14.4 Hz, 2H), 7.12-7.09 (d, *J* = 7.8 Hz, 1H), 3.31-3.18 (m, 2H), 3.10-3.05 (d, *J* = 16.8 Hz, 1H), 2.75-2.59 (m, 4H), 2.08-1.98 (m, 1H), 1.73-1.58 (m, 3H), 1.54-1.48 (m, 2H), 0.72-0.61 (m, 2H), 0.56-0.48 (m, 2H). MS: (ES, *m/z*): 315 $[M+H]^+$.

Table-3: The following compound was prepared according to the method of Example 7, with the following modification: In Step 1, the second eluted product from Example 6, Step 1 was used.

Ex.	**Structure**	**^{1}H-NMR δ (ppm)**	**Found (ES, *m/z*) $[M+H]^+$**
I-183	 R/S	(300 MHz, DMSO-d6): 11.06 (s, 1H), 8.96-8.89 (m, 1H), 7.52-7.40 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 1H), 3.20 (t, *J* = 6.1 Hz, 2H), 3.07 (d, *J* = 16.7 Hz, 1H), 2.86-2.52 (m, 4H), 2.11-1.94 (m, 1H), 1.80-1.48 (m, 3H), 1.47-1.40 (m, 2H), 0.75-0.58 (m, 2H), 0.57-0.42 (m, 2H)	315

Example 8 – Preparation of (R)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-197) and (S)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-198)



***Step-1*: Dimethyl 2-(3-aminopropyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate**

[00133] Into a 100-mL round-bottom flask, was placed dimethyl 2-(2-cyanoethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (250 mg, 0.83 mmol, 1 equiv), MeOH (25 mL), AcOH (8 mL), and PtO_2 (135 mg). H_2 (g) was introduced into the flask. The resulting solution was stirred for 1 h at 25 °C. The solid was filtered out and the filtrate was concentrated under vacuum to give 200 mg (74% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 306 $[M+H]^+$.

***Step-2*: Dimethyl 2-(3-(cyclobutylamino)propyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate**

[00134] Into a 25-mL round-bottom flask, was placed dimethyl 2-(3-aminopropyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (200 mg, 0.65 mmol, 1 equiv) in CH_2Cl_2 (6 mL), AcOH

(0.2 mL) and cyclobutanone (46 mg, 0.66 mmol, 1 equiv). The resulting solution was stirred for 1 h at 28 °C. Then $NaBH(OAc)_3$ (695 mg, 3.28 mmol, 5 equiv) was added. The resulting solution was allowed to stir for an additional 2 h at 28 °C. The reaction was then quenched by the addition of 15 mL of water. The solids were filtered out and the filtrate was extracted with 3x30 mL of CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with EtOAc/petroleum ether (1:2). The collected fractions were concentrated under vacuum to give 97 mg (41% yield) of the title compound as an off-white solid. MS: (ES, *m/z*): 360 $[M+H]^+$.

***Step-3*: Methyl 1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate**

[00135] Into a 20-mL pressure tank reactor, was placed a solution of dimethyl 2-(3-(cyclobutylamino)propyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (200 mg, 0.56 mmol, 1 equiv) in NH_3(g)/MeOH (7M, 10 mL). The resulting solution was stirred overnight at 90 °C. The reaction was then cooled to room temperature and quenched by the addition of 15 mL of water. The resulting solution was extracted with 3x30 mL of CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with EtOAc/petroleum ether (1:1). The collected fractions were concentrated under vacuum to give 80 mg (44% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 328 $[M+H]^+$.

***Step-4*: Chiral separation of methyl (R)-1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxylate and methyl (S)-1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6- carboxylate**

[00136] Methyl 1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate was separated by Chiral-Prep-HPLC with the following conditions: Column: Chiralpak IC, 2x25cm, 5 μm; Mobile Phase A: hexanes, Mobile Phase B: isopropanol; Gradient: hold 30% B over 36 min; Detector: UV 254 nm, 220 nm. The first eluting isomer (Rt 4.876 min) was collected and concentrated under vacuum to give 32 mg (40% yield) of an off-white solid which was assigned as the R isomer of methyl 1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate. MS: (ES, *m/z*): 328 $[M+H]^+$. The second eluting isomer (Rt 6.071 min) was collected and concentrated under vacuum to give 33 mg (41%

yield) of an off-white solid which was assigned as the S isomer of methyl 1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate. MS: (ES, *m/z*): 328 $[M+H]^+$.

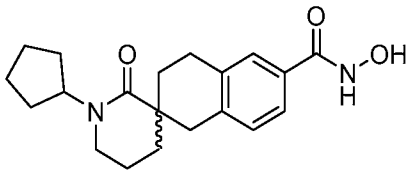
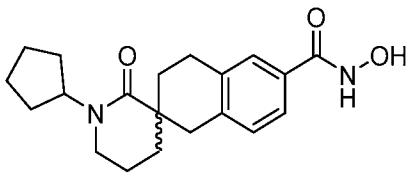
***Step-5*: (R)-1'-Cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

[00137] Into a 10-mL vial, was placed a solution of the first eluted isomer from Step 4, which was assigned as methyl (R)-1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (30 mg, 0.09 mmol, 1 equiv) in THF/MeOH (4:1, 3 mL), NH_2OH (50% in H_2O, 691 mg, 20.92 mmol, 120 equiv), and 1N aq. NaOH (0.2 mL, 2 equiv). The resulting solution was stirred for 2 h at 28 °C. The solids were filtered out and the crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 5 μm, 19x150mm; Mobile Phase A: Water/0.01% NH_4HCO_3, Mobile Phase B: CH_3CN; Gradient: 5% B to 60% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 15.9 mg (53% yield) of the title compound as an off-white solid. ^{1}H-NMR (300 MHz, DMSO-d6), δ (ppm): 10.88 (s, 1H), 8.94-8.92 (d, *J* = 5.4 Hz, 1H), 7.49-7.44 (t, *J* = 7.2 Hz, 2H), 7.11-7.08 (d, *J* = 7.8 Hz, 1H), 4.81-4.75 (t, *J* = 9 Hz, 1H), 3.28-3.24 (t, *J* = 6.6 Hz, 2H), 3.09-3.04 (d, *J* = 16.5 Hz, 1H), 2.76-2.60 (m, 3H), 2.17-1.97 (m, 5H), 1.76 (s, 2H), 1.66-1.58 (m, 3H), 1.54-1.42 (m, 2H). MS: (ES, *m/z*): 329 $[M+H]^+$.

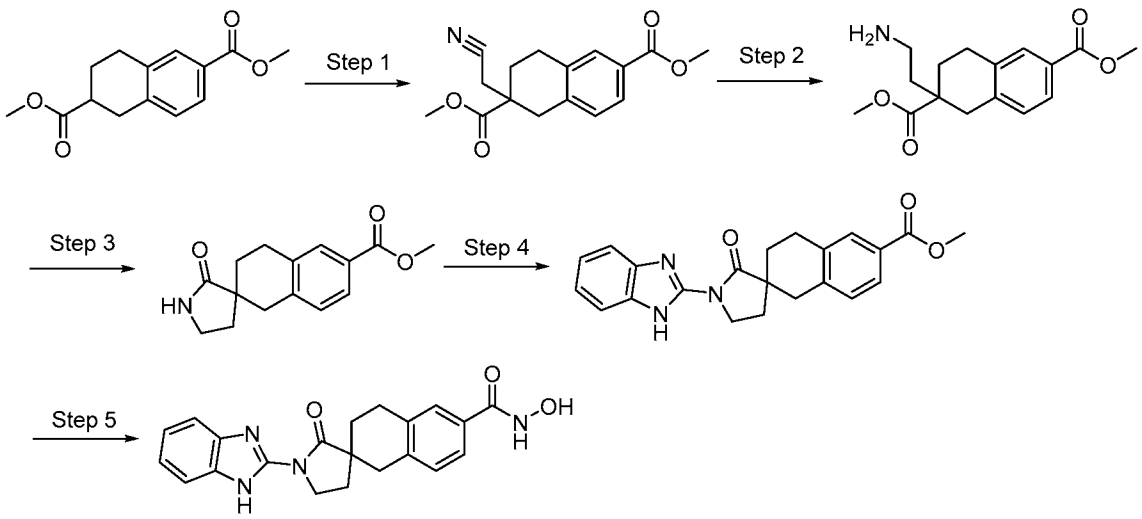
***Step-6*: (S)-1'-Cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide**

[00138] Into a 8-mL vial, was placed a solution of the second eluted isomer from Step 4, which was assigned as methyl (S)-1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxylate as described above, (34 mg, 0.10 mmol, 1 equiv) in THF/MeOH (4:1, 2.0 mL), NH_2OH (50% in water, 0.21 mL, 30 equiv) and 1N aq. NaOH (0.21 mL, 2 equiv). The resulting solution was stirred for 1 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 19x150mm, 5 μm; Mobile Phase A: Water/0.1% Formic acid; Mobile Phase B: CH_3CN; Flow rate: 20 mL/min; Gradient: 5% B to 64% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 19.5 mg (57% yield) of title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 11.05 (s, 1H), 8.92 (s, 1H), 7.45-7.43 (m, 2H), 7.10-7.08 (m, 1H), 4.80-4.70 (m, 1H), 3.36-3.19 (m, 1H), 3.07-3.03 (d, *J* = 16.7 Hz, 1H), 2.75-2.59 (m, 3H), 2.14-1.96 (m, 5H), 1.74-1.71 (m, 2H), 1.64-1.56 (m, 3H), 1.53-1.47 (m, 2H). MS: (ES, *m/z*): 329 $[M+H]^+$.

Table-4: The following compounds were prepared according to the method of Example 8.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-199	 R/S	(300 MHz, DMSO-d6): 11.06 (s, 1H), 8.96 (s, 1H), 7.50-7.44 (t, *J* = 7.7 Hz, 2H), 7.12-7.10 (d, *J* = 7.8 Hz, 1H), 4.81-4.75 (t, *J* = 7.8Hz, 1H), 3.22-3.07 (m, 3H), 2.81-2.61 (m, 3H), 2.12-2.01 (m, 1H), 1.72-1.53 (m, 13H)	343
I-200	 R/S	(300 MHz, DMSO-d6): 11.07 (s, 1H), 8.95 (s, 1H), 7.50-7.44 (t, *J* = 8 Hz, 2H), 7.12-7.10 (d, *J* = 8.1 Hz, 1H), 4.81-4.76 (d, *J* = 7.2 Hz, 1H), 3.22-3.07 (m, 3H), 2.77-2.61 (m, 3H), 2.12-2.01 (m, 1H), 1.72-1.51 (m, 13H)	343

Example 9 – Preparation of 1'-(1H-benzo[d]imidazol-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-5)



***Step-1*: Dimethyl 2-(cyanomethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate**

[00139] Into a 1-L 3-necked round-bottom flask was placed dimethyl 1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (20 g, 80.56 mmol, 1 equiv) in THF (400 mL). This was followed by the dropwise addition of LDA (2 M in THF, 53 mL, 106 mmol, 1.32 equiv)

with stirring at -78 °C over 30 min. To this was added 2-bromoacetonitrile (9 mL, 129 mmol, 1.6 equiv) dropwise with stirring at -78 °C over 30 min. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by adding 300 mL of H_2O. The resulting solution was extracted with 3x300 mL of EtOAc. The combined organics were washed with 2x300 mL of H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (3:20). The collected fractions were concentrated to give 14 g (60% yield) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.83 (dq, *J* = 3.5, 1.7 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 3.42 (d, *J* = 16.9 Hz, 1H), 3.06-2.83 (m, 3H), 2.69 (s, 2H), 2.39-2.23 (m, 1H), 2.15-2.00 (m, 1H).

***Step-2*: Dimethyl 2-(2-aminoethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate**

[00140] Into a 1000-mL 3-necked round-bottom flask was placed dimethyl 2-(cyanomethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (14 g, 48.73 mmol, 1 equiv) in MeOH (440 mL), acetic acid (220 mL) and PtO_2 (6 g). Hydrogen gas was introduced. The resulting solution was stirred overnight at room temperature. The solids were filtered out. The filter cake was washed with 2x100 mL of MeOH and 100 mL of CH_2Cl_2. The combined filtrate was concentrated under vacuum. The residue was dissolved in 200 mL of EtOAc and the pH was adjusted to 9 with aq. Na_2CO_3. The resulting solution was extracted with 3x200 mL of EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 10 g (70% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 292 $[M+H]^+$.

***Step-3*: Methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00141] Into a 500-mL round-bottom flask was placed dimethyl 2-(2-aminoethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (10 g, 34.32 mmol, 1 equiv) in MeOH (80 mL) and NH_3 (7M in MeOH, 40 mL). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum to give 9.1 g (crude) of the title compound as a solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.81 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 1H), 3.90 (s, 3H), 3.41-3.37 (t, *J* = 6.6 Hz, 2H), 3.16-2.65 (m, 4H), 2.14-1.78 (m, 4H). MS: (ES, *m/z*): 260 $[M+H]^+$.

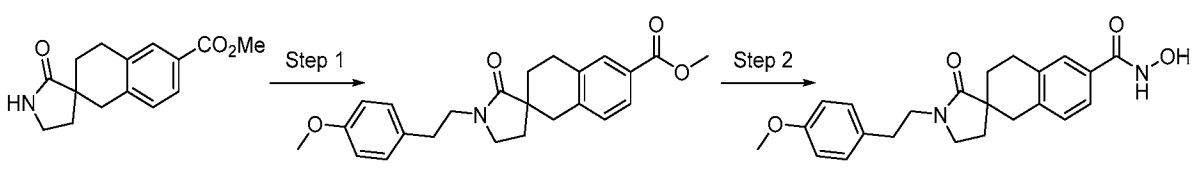
***Step-4*: Methyl 1'-(1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxylate**

[00142] Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (150 mg, 0.58 mmol, 1 equiv), 2-bromo-1H-1,3-benzodiazole (171 mg, 0.87 mmol, 1.5 equiv), CuI (220 mg, 1.16 mmol, 2 equiv), K_3PO_4 (492 mg, 2.32 mmol, 4.01 equiv), 1-N,2-N-dimethylcyclohexane-1,2-diamine (124 mg, 0.87 mmol, 1.51 equiv), and DMF (3 mL). The resulting solution was degassed three times with N_2, and stirred overnight at 100 °C. The reaction was quenched by adding 50 mL of H_2O. The resulting solution was extracted with 3x50 mL of EtOAc. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:9). The collected fractions were concentrated to give 63 mg (29% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 376 $[M+H]^+$.

***Step-5*: 1'-(1H-Benzo[d]imidazol-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00143] Into a 50-mL round-bottom flask was placed methyl 1'-(1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (63 mg, 0.17 mmol, 1 equiv), THF/MeOH (4:1, 2.5 mL), NH_2OH (50% in water, 498 mg, 15.08 mmol, 89.85 equiv), and 1N aq. NaOH (0.5 mL, 2.94 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Xbridge C18, 19x150mm; Mobile phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/ 0.05% TFA; Gradient: 19% B to 51% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 23.6 mg (37% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.11 (br s, 1H), 7.56-7.50 (m, 4H), 7.22-7.15 (m, 3H), 4.08-4.05 (t, *J* = 6 Hz, 2H), 3.05-2.88 (m, 4H) , 2.19-1.93 (m, 4H). MS: (ES, *m/z*): 377 $[M+H]^+$.

Example 10 – Preparation of N-hydroxy-1'-(4-methoxyphenethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-4)



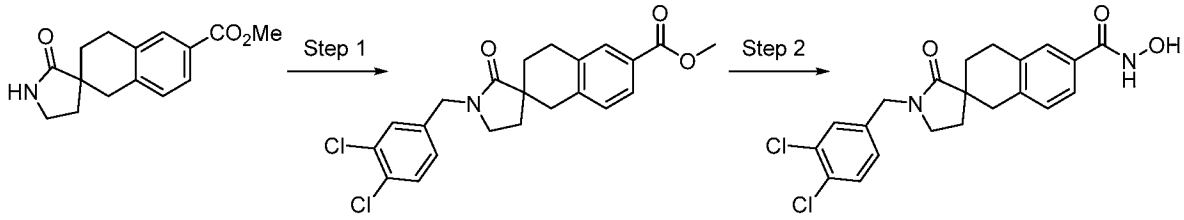
***Step-1*: Methyl 1'-(4-methoxyphenethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate**

[00144] Into a 10 mL microwave vial was added methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (50.2 mg, 0.194 mmol, 1 equiv) and 1-(2-bromoethyl)-4-methoxybenzene (45.8 mg, 0.213 mmol, 1.1 equiv) in DMF (1.5 mL). Next, sodium bis(trimethylsilyl)amide (1M in THF, 0.25 mL, 1.3 equiv) was added and the mixture was heated in the microwave at 150 °C for 20 min. Water was added and the reaction mixture was extracted with three portions of EtOAc. The organic phases were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (Biotage SP1, 10 g Snap column, 10-50% EtOAc/hexanes) to afford 15.8 mg (21% yield) of the title compound as a colorless oil. MS: (ES *m/z*) 394 $[M+H]^+$.

***Step-2*: N-hydroxy-1'-(4-methoxyphenethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00145] Methyl 1'-(4-methoxyphenethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate (20 mg, 0.051 mmol, 1 equiv) was dissolved in a solution of THF/MeOH (4:1, 1.38 mL). NH_2OH (50% in water, 0.279 mL, 4.6 mmol, 90 equiv) was added followed by 2N aq. NaOH (0.076 mL, 3 equiv). The reaction was stirred at room temperature for 48 h and was purified directly by reverse-phase chromatography using the following conditions: Column: XTerra Prep MS C18 OBD, 5 mM, 19x100 mm; Mobile Phase A: Water/0.05% Formic Acid, Mobile Phase B: CH_3CN/0.05% Formic Acid; Flow rate: 20 mL/min; Gradient: 15% B to 85% B in 10 min; Detector: UV 254 nm, 220 nm. Combined fractions were lyophilized to afford 6.2 mg (31% yield) the title compound. ^1H NMR (300 MHz, DMSO-d6) δ (PPM): 11.10 (br s, 1H), 8.97 (br s, 2H), 7.34-7.54 (m, 2H), 6.97-7.29 (m, 3H), 6.86 (d, J = 8.5 Hz, 2H), 3.73 (s, 3H), 3.30-3.52 (m, 4H), 3.10-3.30 (m, 2H), 2.62-2.97 (m, 4H), 1.47-1.85 (m, 4H). MS: (ES *m/z*) 395 $[M+H]^+$.

Example 11 – Preparation of 1'-(3,4-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-6)



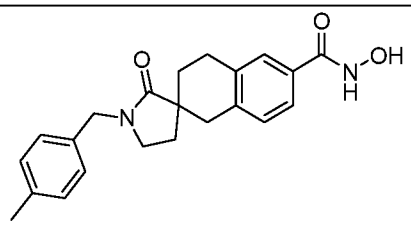
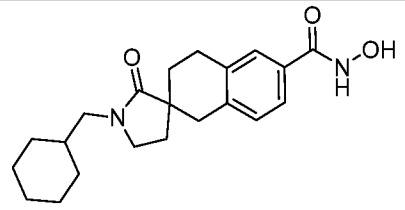
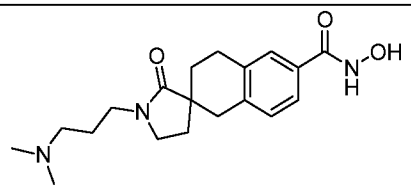
***Step-1*: Methyl 1'-(3,4-dichlorobenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate**

[00146] Into a 100-mL round-bottom flask was placed methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (150 mg, 0.58 mmol, 1 equiv), DMF (5 mL), NaH (29 mg, 1.21 mmol, 2.09 equiv), and 4-(bromomethyl)-1,2-dichlorobenzene (193 mg, 0.80 mmol, 1.39 equiv). The resulting solution was stirred for 3 h at room temperature. The resulting mixture was quenched with 30 mL of H_2O and extracted with 2x50 mL of EtOAc. The combined organics were washed with 2x30 mL of H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:3). The collected fractions were concentrated to give 277 mg (crude) of the title compound as a yellow solid. MS: (ES, *m/z*): 418 $[M+H]^+$.

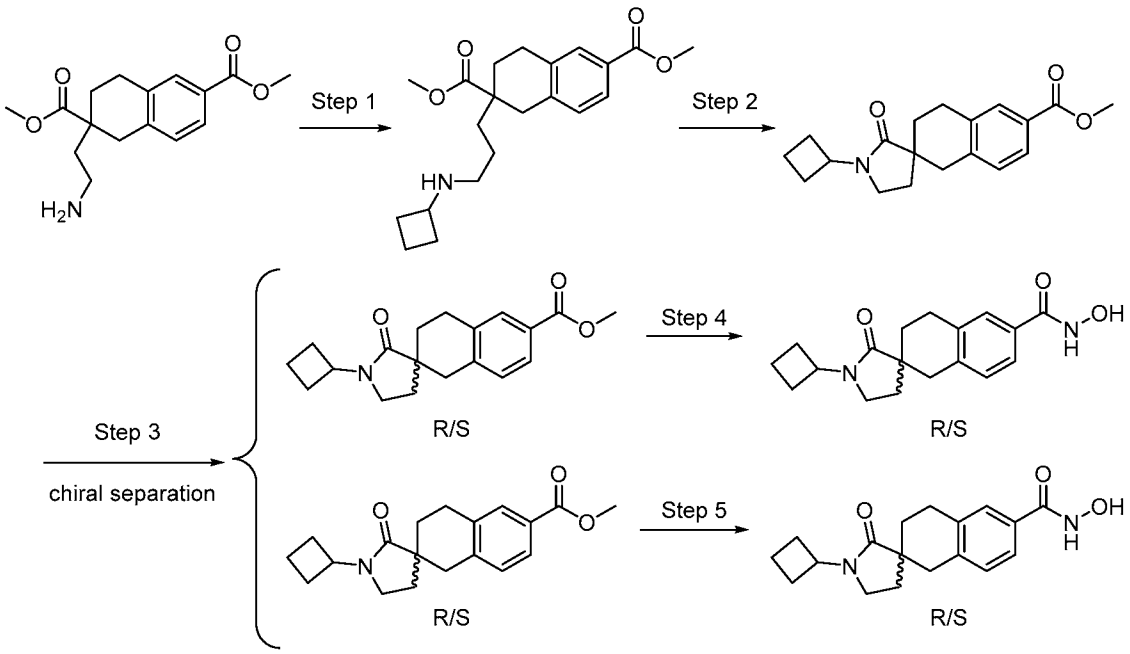
***Step-2*: 1'-(3,4-Dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00147] Into a 100-mL round-bottom flask was placed methyl 1'-(3,4-dichlorobenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate (277 mg, 0.66 mmol, 1 equiv), THF/MeOH (4:1, 2.5 mL), NH_2OH (50% in water, 4.57 g, 68.55 mmol, 104 equiv), and 1N aq. NaOH (1 mL, 1.51 equiv). The resulting solution was stirred for 5 h at room temperature. The pH of the solution was adjusted to 6 with 4N aq. HCl. The crude product was purified by Prep-HPLC with the following conditions: Column: SunFire Prep C18, 5 μm, 19x100mm; Mobile Phase A: Water/10% NH_4HCO_3, Mobile Phase B: CH_3CN/10% NH_4HCO_3; Gradient: 10% B to 50% B in 6 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 30.2 mg (10% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.10 (br s, 1H), 8.96 (br s, 1H), 7.65-7.63 (d, J = 8 Hz, 1H), 7.53-7.44 (m, 3H), 7.26-7.12 (m, 2H), 4.43 (s, 2H), 3.27-3.24 (t, J = 8 Hz, 2H), 2.95-2.77 (m, 3H), 2.67-2.61 (m, 1H), 1.95-1.82 (m, 2H), 1.73-1.63 (m, 2H). MS: (ES, *m/z*): 419 $[M+H]^+$.

Table-5: The following compounds were prepared according to the method of Example 11.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-8		(400 MHz, DMSO-d6): 11.09 (br s, 1H), 9.12-8.78 (br s, 1H), 7.53-7.46 (m, 2H), 7.18-7.11 (m, 5H), 4.37(s, 2H), 3.20-3.16 (t, *J* = 8 Hz, 2H), 2.93-2.76 (m, 3H), 2.62-2.58 (m, 1H), 2.33 (s, 3H), 1.92-1.83 (m, 2H), 1.71-1.63 (m, 2H).	365
I-7		(400 MHz, DMSO-d6): 11.09 (br s, 1H), 7.51-7.45 (m, 2H), 7.15-7.13 (d, *J* = 8 Hz, 1H), 3.32-3.29 (t, *J* = 4 Hz, 2H), 3.06-3.04 (d, *J* = 8 Hz, 2H), 2.91-2.74 (m, 3H), 2.62-2.55 (m, 1H), 1.91-1.78 (m, 2H), 1.71-1.57 (m, 7H), 1.27-1.11 (m, 3H), 0.92-0.83 (m, 2H).	357
I-9		(300 MHz, DMSO-d6): 11.10 (br s, 1H), 10.28-9.82 (m, 2H), 9.05-8.95 (br, 1H), 7.54-7.44 (m, 2H), 7.15-7.12 (d, *J* = 9 Hz, 1H), 3.37-3.27 (m, 4H), 3.02-2.96 (m, 2H), 2.96-2.83 (m, 3H), 2.77 (s, 6H), 2.68-2.59 (m, 1H), 1.96-1.59 (m, 6H).	346

Example 12 – Preparation of (R)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-171) and (S)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-172)



***Step-1*: Dimethyl 2-(2-(cyclobutylamino)ethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate**

[00148] Into a 250-mL round-bottom flask, was placed a mixture of 2,6-dimethyl 2-(2-aminoethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (2 g, 6.86 mmol, 1 equiv) and cyclobutanone (433.3 mg, 6.18 mmol, 0.9 equiv) in CH_2Cl_2 (50 mL) and AcOH (1 mL). The mixture was stirred for 15 min at 0 °C. After that $NaBH(OAc)_3$ (4.37 g, 20.58 mmol, 3 equiv) was slowly added at 0 °C. The resulting solution was stirred overnight while the temperature warmed to room temperature. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with CH_2Cl_2/MeOH (92:8). The collected fractions were concentrated to give 800 mg (34% yield) of the title compound as a light yellow oil. MS: (ES, *m/z*): 346 $[M+H]^+$.

***Step-2*: Methyl 1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00149] Into a 100-mL round-bottom flask, was placed a solution of dimethyl 2-(2-(cyclobutylamino)ethyl)-1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (700 mg, 2.03 mmol, 1 equiv) and 7M NH_3 in MeOH (20 mL, 8 equiv). The resulting solution was stirred for 18 h at 25

°C. The resulting mixture was concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel column with EtOAc/petroleum ether (1:5). The collected fractions were concentrated to give 300 mg (47% yield) of the title compound as a light yellow oil. MS: (ES, *m/z*): 314 $[M+H]^+$.

***Step-3*: Chiral separation of methyl (R)-1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate and methyl (S)-1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate**

[00150] The racemate of methyl 1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (300 mg) was purified by Prep-SFC with the following conditions: Column: Chiralpak AS-H 2x25cm; Mobile Phase A: CO_2 (70%), Mobile Phase B: isopropanol (30%); Flow rate: 40 mL/min; Detector: UV 220 nm. The first eluting isomer (Rt 4.22 min) was collected and concentrated to give 120 mg of a white solid which was tentatively assigned as the R isomer of methyl 1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate. MS: (ES, *m/z*): 314 $[M+H]^+$. The second eluting isomer (Rt 6.06 min) was collected and concentrated to give 130 mg of a white solid which was tentatively assigned as the S isomer of methyl 1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate. MS: (ES, *m/z*): 314 $[M+H]^+$.

***Step-4*: (R)-1'-Cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

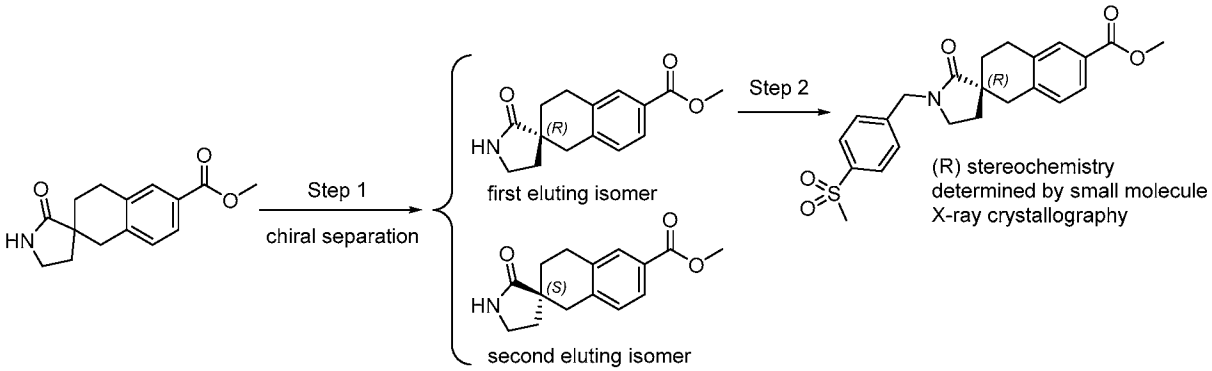
[00151] Into a 25-mL round-bottom flask, was placed a solution of the first eluted isomer from Step 3, which was assigned as methyl (R)-1'-cyclobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (50 mg, 0.16 mmol, 1 equiv), NH_2OH (50% in water, 1.2 mL, 120 equiv) and 1N aq. NaOH (0.32 mL, 2 equiv) in THF/MeOH (5:1, 1.25 mL). The reaction was stirred for 5 h at 25 °C. The resulting mixture was concentrated under vacuum. The residue was dissolved in 3 mL of THF and purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 5 μm, 19x150mm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN/0.1% Formic Acid; Gradient: 20% B to 38% B in 8 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 25 mg (50% yield) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 1.68-1.70 (m, 4H), 1.78-1.90 (m, 2H), 2.00-2.01 (m, 2H), 2.04-2.24 (m, 2H), 2.59 (d, J = 6 Hz, 1H), 2.81 (d, J = 12 Hz, 3H), 3.41 (t, J = 12 Hz, 2H), 4.47-4.52 (m,

1H), 7.13 (m, J = 6 Hz, 1H), 7.46-7.51 (m, 2H), 8.95 (s, 1H), 11.10 (s, 1H). MS: (ES, *m/z*): 315 $[M+H]^+$.

***Step-5*: (S)-1'-Cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00152] (S)-1'-Cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxamide was prepared according to the method of (R)-1'-Cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 1.56-1.69 (m, 4H), 1.70-1.86 (m, 2H), 1.96-2.01 (m, 2H), 2.17-2.22 (m, 2H), 2.55-2.60 (m, 1H), 2.77-2.83 (m, 3H), 3.33-3.39 (m, 2H), 4.46-4.49 (m, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.46-7.49 (m, 2H), 8.93 (br s, 1H), 11.09 (br s, 1H). MS: (ES, *m/z*): 315 $[M+H]^+$.

Example 13 – Preparation of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate and methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate



***Step-1*: Chiral separation of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate and methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

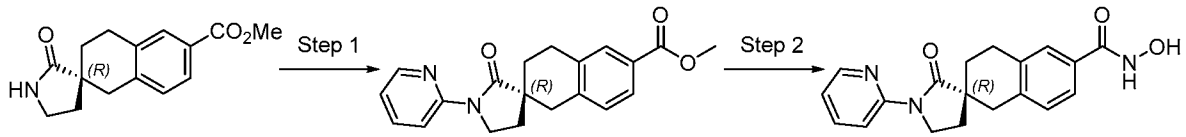
[00153] The racemate of methyl 2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (22 g, 75.51 mmol, 1 equiv) was purified by Prep-SFC with the following conditions: Column: Chiralpak AS-H, 5x25cm, 5 μm; Mobile Phase: CO_2 (50%), MeOH: CH_2Cl_2 (2:1)/0.2% DIEA; Detector: UV 220 nm. The first eluting isomer (Rt 6.56 min) was collected and concentrated to give 10 g of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ(ppm): 7.74-7.64 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 3.21 (t, J = 6.8 Hz, 2H), 2.99-2.75 (m, 3H), 2.71-2.62 (m, 1H), 1.93 (m, 1H), 1.87-1.59 (m, 3H). MS: (ES, *m/z*): 260 $[M+H]^+$. The second eluting isomer

(Rt 8.26 min) was collected and concentrated to give 10 g of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ(ppm): 7.74-7.64 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 1H), 3.21 (t, *J* = 6.8 Hz, 2H), 2.98-2.75 (m, 3H), 2.71-2.62 (m, 1H), 1.93 (m, 1H), 1.87-1.59 (m, 3H). MS: (ES, *m/z*): 260 $[M+H]^+$.

***Step-2*: Determination of the absolute stereochemistry of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00154] Into a 50-mL round-bottom flask, was placed a solution of the first eluting isomer from Step 1 (400 mg, 1.54 mmol, 1 equiv) in DMF (5 mL). This was followed by the addition of NaH (124 mg, 5.17 mmol, 1.5 equiv) at 0 °C over 10 min. To this was added 1-(bromomethyl)-4-methanesulfonylbenzene (572 mg, 2.30 mmol, 2 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 2 h at 0 °C in a water-ice bath. The reaction was then quenched by the addition of 40 mL of water. The resulting solution was extracted with 3x100 mL of EtOAc and the combined organic layers were concentrated. The residue was purified on a C18 column eluting with 45% CH_3CN/water/0.05% TFA to afford 501 mg (60% yield) of a single isomer of methyl 1'-[(4-methanesulfonylphenyl)methyl]-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate•TFA as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 7.92-7.94 (dd, J = 8 Hz, 2H), 7.70-7.72 (m, 2H), 7.49-7.51 (dd, *J* = 8 Hz, 2H), 7.23-7.25 (dd, *J* = 8 Hz, 1H), 4.53 (s, 2H), 3.82 (s, 3H), 3.28-3.24 (t, *J* = 8 Hz, 2H), 3.22 (s, 3H), 2.92-2.97 (m, 2H), 2.80-2.89 (m, 1H), 2.70-2.74 (m, 1H), 1.84-1.97 (m, 2H), 1.76-1.74 (m, 2H). MS: (ES, *m/z*): 428 $[M+H]^+$. A sample was recrystallized from EtOAc/hexanes (~1:1) and submitted for small molecule X-ray crystallography, which showed the material to be methyl (R)-1'-[(4-methanesulfonylphenyl)methyl]-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (see Example 52). Thus, the first eluting isomer of Step 1 was assigned as methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate and the second eluting isomer of Step 1 was assigned as methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate.

Example 14 – Preparation of (R)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-20)



***Step-1*: Methyl (R)-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

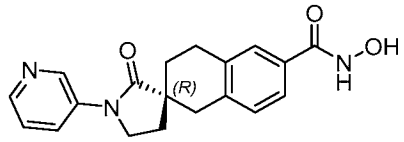
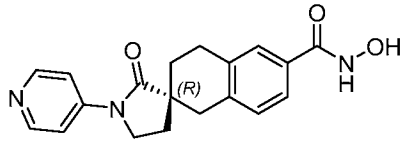
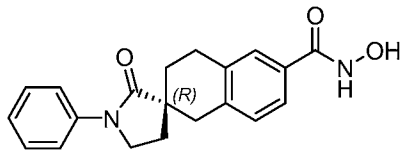
[00155] Into a 100-mL round-bottom flask maintained with the atmosphere of nitrogen, was placed methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (100 mg, 0.39 mmol, 1 equiv) in toluene (5 mL), $Pd_2(dba)_3$ (7.9 mg, 0.01 mmol, 0.02 equiv), XantPhos (66.0 mg, 0.11 mmol, 0.3 equiv), Cs_2CO_3 (248.0 mg, 0.76 mmol, 1.97 equiv), and 2-bromopyridine (91.0 mg, 0.58 mmol, 1.49 equiv). The resulting mixture was stirred overnight at 110 °C and then concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:5). The collected fractions were concentrated to give 40 mg (31% yield) of the title compound as a white solid. MS: (ES, *m/z*): 337 $[M+H]^+$.

***Step-2*: (R)-N-Hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

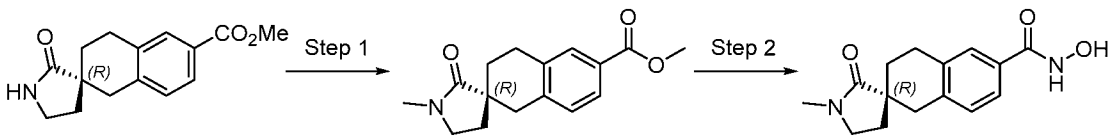
[00156] Into a 100-mL round-bottom flask was placed methyl (R)-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate (40 mg, 0.12 mmol, 1 equiv) in THF/MeOH (4:1, 1.25 mL), NH_2OH (50% in water, 786 mg, 23.8 mmol, 200 equiv) and 1N aq. NaOH (0.2 mL, 1.67 equiv). The resulting solution was stirred for 4 h at room temperature. The resulting mixture was adjusted to pH 7 with 4N aq. HCl . The crude product was purified by Prep-HPLC with the following conditions: Column: X Bridge C18, 19x150 mm, 5 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 28 mL/min; Gradient: 10% B to 40% B in 7 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 36 mg (90% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.10 (br s, 1H), 8.42-8.33 (m, 2H), 7.86-7.82 (m, 1H), 7.55-7.49 (m, 2H), 7.18-7.15 (m, 2H), 4.03-3.96 (m, 2H) , 2.98-2.80 (m, 4H), 2.07-1.80 (m, 4H). MS: (ES, *m/z*): 338 $[M+H]^+$.

Table-6: The following compounds were prepared according to the method of Example 14.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$

I-10		(400 MHz, DMSO-d6): 11.13 (s, 1H), 9.08 (s, 1H), 8.47-8.46 (d, *J* = 4.4 MHz, 1H), 8.35-8.33 (d, *J* = 7.2 MHz, 1H), 7.66-7.49 (m, 3H), 7.23-7.11 (m, 1H), 3.94-3.91 (t, *J* = 7.2 MHz, 2H), 2.98-2.80 (m, 4H), 2.14-1.82 (m, 4H).	338
I-16		(300 MHz, DMSO-d6): 11.14 (s, 1H), 8.78 (s, 2H), 8.19 (s, 2H), 7.56-7.50 (m, 2H), 7.18-7.16 (d, *J* = 7.8 Hz, 1H), 4.02-3.97 (t, *J* = 6.9 Hz, 2H), 3.01-2.84 (m, 4H), 2.18-2.11 (m, 1H), 2.09-1.92 (m, 3H).	338
I-26		(400 MHz, DMSO-d6): 11.10 (br s, 1H), 7.73-7.71 (d, *J* = 8 Hz, 2H), 7.58-7.38 (m, 4H), 7.18-7.12 (m, 2H), 3.88-3.86 (t, *J* = 4 Hz, 2H), 2.97-2.78 (m, 4H), 2.09-2.02 (m, 1H), 1.96-1.79 (m, 3H).	337

Example 15 – Preparation of (R)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-104)



***Step-1*: Methyl (R)-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

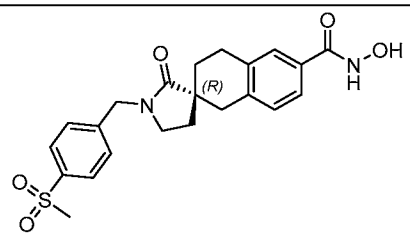
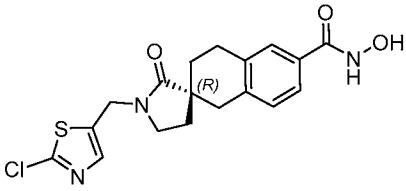
[00157] Into a 100-mL round-bottom flask was placed a solution of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (200 mg, 0.77 mmol, 1 equiv) in DMF (5 mL). NaH (60 mg, 2.50 mmol, 2 equiv) was added in portions at 0 °C. After stirring for 10 min, iodomethane (219mg, 1.54 mmol, 2 equiv) was added dropwise at 0 °C. The resulting solution was stirred for 2.5 h at 0 °C. The reaction was quenched with 30 mL of water. The resulting solution was extracted 3x100 mL with EtAOc. The organic layers were combined and concentrated under reduced pressure. The crude product was purified by normal phase column

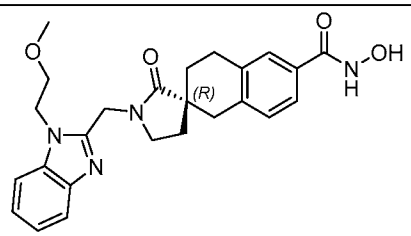
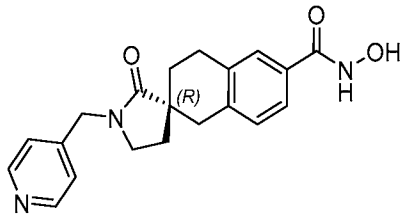
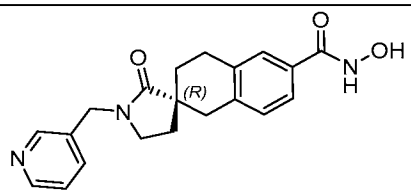
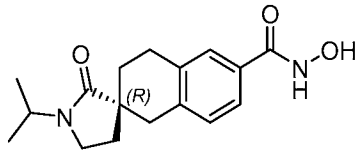
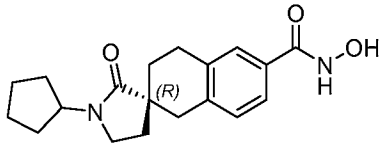
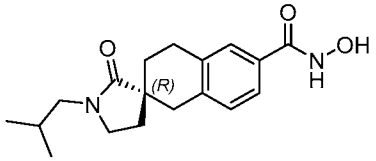
chromatography on silica gel with EtOAc/petroleum ether (1:5). The collected fractions were concentrated to give 230 mg of the title compound as a yellow oil. MS: (ES, *m/z*): 274 $[M+H]^+$.

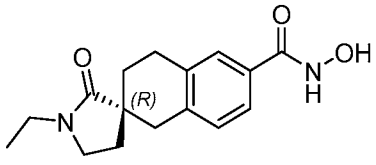
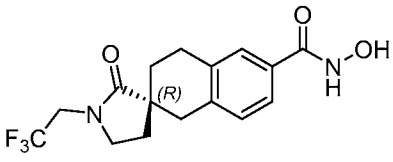
***Step-2*: (R)-N-Hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00158] Into a 50-mL round-bottom flask was placed a solution of methyl (R)-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (130 mg, 0.48 mmol, 1 equiv) in THF (2.0 mL), NH_2OH (50% in water, 1.87 mL, 60 equiv) and 1N aq. NaOH (0.95 mL, 2 equiv). The resulting solution was stirred for 4 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: X-bridge C18 190x50mm 5 μm; Mobile Phase A: Water/0.05%TFA, Mobile Phase B: CH_3CN/0.05% TFA; Gradient: 20% B to 60% B in 7 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 43.5 mg (24% yield) of the title compound as a light yellow solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ(ppm): 11.09 (s, 1H), 8.95 (s, 1H), 7.45-7.51 (m, 2H), 7.11-7.13 (d, *J* = 8 Hz, 1H), 3.28-3.32 (t, *J* = 8 Hz, 2H), 2.76-2.89 (m, 6H), 2.50-2.56 (m, 1H), 1.81-1.90 (m, 2H), 1.63-1.80 (m, 2H). MS: (ES, *m/z*): 275 $[M+H]^+$.

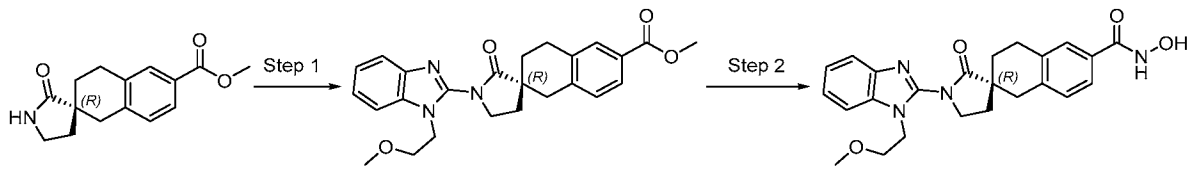
Table-7: The following compounds were prepared according to the method of Example 15, with the following modification: In Step 1, the halide can be an iodide, a chloride, or a bromide.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-88		(400 MHz, DMSO-d6): 11.09 (s, 1H), 9.00 (s, 1H), 7.92-7.94 (dd, *J* = 8 Hz, 2H), 7.46-7.52 (m, 4H), 7.15-7.17 (dd, *J* = 8 Hz, 1H), 4.54(s, 2H), 3.22-3.28 (m, 5H), 2.81-2.95 (m, 3H), 2.65-2.70 (m, 1H), 1.86-1.97 (m, 2H), 1.60-1.71 (m, 2H)	429
I-30		(400 MHz, DMSO-d6): 11.09 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.45-7.47 (dd, *J* = 8Hz, 1H), 7.13-7.15 (dd, *J* = 8 Hz, 1H), 4.60 (s, 2H), 3.29-3.22 (t, *J* = 6.8 Hz, 2H), 2.79-2.90 (m, 3H), 2.50-2.58 (m, 1H), 1.90-1.94 (m, 1H), 1.80-	392

		1.89 (m, 1H), 1.77-1.80 (m, 2H)	
I-22		(400 MHz, DMSO-d6): 11.11 (br s, 1H), 7.79-7.72 (m, 2H), 7.532-7.37 (m, 4H), 7.17-7.15 (d, *J* = 8.0 Hz, 1H), 4.88 (s, 2H), 4.60 (s, 2H), 3.70-3.67 (t, *J* = 6 Hz, 2H), 3.45-3.41 (t, J = 8 Hz, 2H), 3.24 (s, 3H), 2.94-2.73 (m, 4H), 1.98-1.72 (m, 4H)	449
I-14		(300 MHz, DMSO-d6): 11.14 (br s, 1H), 8.78-8.76 (d, *J* = 6 Hz 2H), 7.65-7.63 (d, *J* = 6 Hz, 2H), 7.56-7.48 (m, 2H), 7.18-7.15 (d, *J* = 9 Hz 1H), 4.64 (s, 2H) 3.37-3.32 (t, *J* = 7.5 Hz, 2H), 2.96-2.70 (m, 4H), 2.04-1.72 (m, 4H)	352
I-18		(300 MHz, DMSO-d6): 11.12 (br s, 1H), 8.71-8.67 (m, 2H), 8.04-8.01 (d, *J* = 9 Hz, 1H), 7.76-7.71 (m, 1H), 7.53-7.42 (m, 2H), 7.16-7.13 (d, *J* = 9 Hz, 1H), 4.56 (s, 2H), 3.32-3.28 (t, *J* = 6 Hz, 2H), 2.94-2.75 (m, 3H), 2.70-2.64 (m, 1H), 1.98-1.81 (m, 2H), 1.77-1.60 (m, 2H)	352
I-24		(400 MHz, DMSO-d6): 11.08 (s, 1H), 7.51-7.46 (m, 2H), 7.15-7.09 (m, 1H), 4.18-4.10 (m, 1H), 3.28-3.24 (t, 2H, *J* = 6.8 Hz), 2.89-2.60 (m, 4H), 1.88-1.58 (m, 4H), 1.15-1.05 (m, 6H)	303
I-163		(400 MHz, DMSO-d6): 11.09 (s, 1H), 8.95 (s, 1H), 7.46-7.51 (m, 2H), 7.12-7.14 (d, *J* = 8.0 Hz, 1H), 4.31-4.35 (m, 1H), 3.27-3.32 (m, 2H), 2.75-2.89 (m, 3H), 2.57-2.61 (m, 1H), 1.69-1.89 (m, 12H)	329
I-159		(400 MHz, DMSO-d6): 11.09 (br s, 1H), 8.95 (br s, 1H), 7.51 (s, 1H), 7.47 (d, *J* = 8 Hz, 1H), 7.14 (d, *J* = 8 Hz, 1H), 2.32-2.29 (m, 2H), 3.04-3.01 (m, 2H), 2.88-2.78 (m, 2H), 2.61 (d, *J* = 16	317

		Hz, 1H), 1.93-1.78 (m, 3H), 1.71-1.60 (m, 2H), 1.86 (d, *J* = 7 Hz, 6H)	
I-161		(400 MHz, DMSO-d6): 11.08 (br s, 1H), 8.95 (br s, 1H), 7.51 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8 Hz, 1H), 3.33-3.29 (m, 2H), 3.27-3.23 (m, 2H), 2.89-2.75 (m, 3H), 2.59 (d, *J* = 17 Hz, 1H), 1.90-1.76 (m, 2H), 1.70-1.65 (m, 2H), 1.05 (t, *J* = 8.0 Hz, 3H)	289
I-165		(400 MHz, DMSO-d6): 11.08 (s, 1H), 8.97 (s, 1H), 7.47-7.52 (m, 2H), 7.15 (d, *J* = 8 Hz, 1H), 4.06-4.15 (m, 2H), 3.45-3.49 (m, 2H), 2.77-2.92 (m, 3H), 2.66 (d, *J* = 16 Hz, 3H), 1.95-2.00 (m, 1H), 1.77-1.95 (m, 3H)	343

Example 16 – Preparation of (R)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-12)



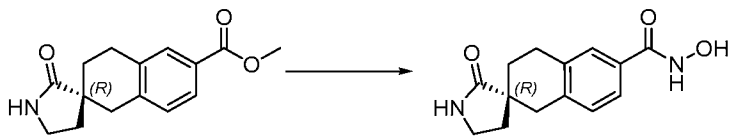
***Step-1*: Methyl (R)-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00159] Into a 10-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (60 mg, 0.23 mmol, 1 equiv), 2-bromo-1-(2-methoxyethyl)-1H-1,3-benzodiazole (103 mg, 0.40 mmol, 1.5 equiv) in toluene (4 mL), CuI (5 mg, 0.03 mmol, 0.1 equiv), Cs_2CO_3 (263 mg, 0.81 mmol, 3 equiv), and (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (8 mg, 0.06 mmol, 0.2 equiv). The resulting mixture was stirred for 10 h at 110 °C in an oil bath. The reaction mixture was cooled to 20 °C with a water bath. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:1). The collected fractions were concentrated to give 50 mg (50% yield) of the title compound as a colorless oil. MS: (ES, *m/z*): 434 $[M+H]^+$.

***Step-2*: (R)-N-Hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00160] Into a 10-mL round-bottom flask was placed methyl (R)-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (50 mg, 0.12 mmol, 1 equiv), THF/MeOH (4:1, 2.5 mL), NH_2OH (50% in water, 0.5 mL, 63 equiv), and 1N aq. NaOH (0.3 mL, 2.5 equiv). The resulting solution was stirred for 3 h at room temperature. The reaction mixture was cooled to 0 °C with an ice-water bath. The pH of the solution was adjusted to 7 with 1N aq. HCl. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge C18,19x150 mm, 5 μm; Mobile Phase A: Water/10% NH_4HCO_3, Mobile Phase B: CH_3CN/10% NH_4HCO_3; Flow rate: 25 mL/min; Gradient: 5% B to 47% B in 7 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 38.4 mg (77% yield) of the title compound as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.14 (br s, 1H), 7.65-7.48 (m, 4H), 7.31-7.18 (m, 3H), 4.35-4.32 (t, *J* = 6 Hz, 2H), 3.99-3.89 (m, 2H), 3.62-3.59 (t, *J* = 6 Hz, 2H), 3.20 (s, 3H), 3.01-2.86 (m, 4H), 2.22-2.16 (m, 1H), 2.02-1.98 (m, 3H). MS: (ES, *m/z*): 435 $[M+H]^+$.

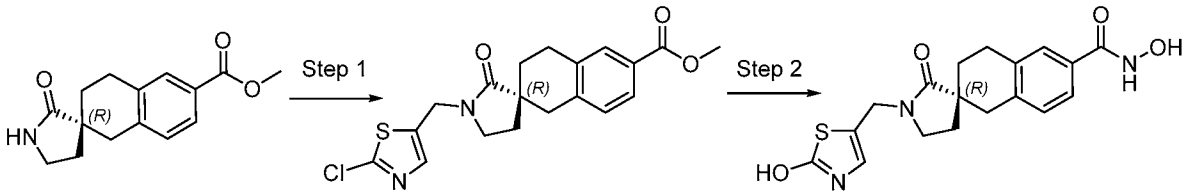
Example 17 – Preparation of (R)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxamide (I-27)



[00161] Into a 50-mL round-bottom flask was placed a solution of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (100 mg, 0.39 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL), NH_2OH (50% in water, 1.52 mL, 60 equiv), and 1N aq. NaOH (0.77 mL, 2 equiv). The resulting solution was stirred for 1.5 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Waters HSS C18, 2.1x50 mm, 1.8 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 0.7mL/min; Gradient: 5% B to 95% B in 2.0 min hold 0.6 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 40.6 mg (28% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.09 (s, 1H), 8.94 (s, 1H), 7.66 (s, 1H), 7.45-7.50 (m, 2H), 7.13-7.15 (d, *J* = 8 Hz, 1H), 318-3.22 (t, *J* = 7 Hz, 2H), 2.74-2.90 (m, 3H), 2.63-

2.67 (m, 1H), 1.90-1.95 (m, 1H), 1.68-1.80 (m, 2H), 1.60-1.64 (m, 1H). MS: (ES, *m/z*): 261 $[M+H]^+$.

Example 18 – Preparation of (R)-N-hydroxy-1'-((2-hydroxythiazol-5-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro [naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-31)



***Step-1*: Methyl (R)-1'-((2-chlorothiazol-5-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxylate**

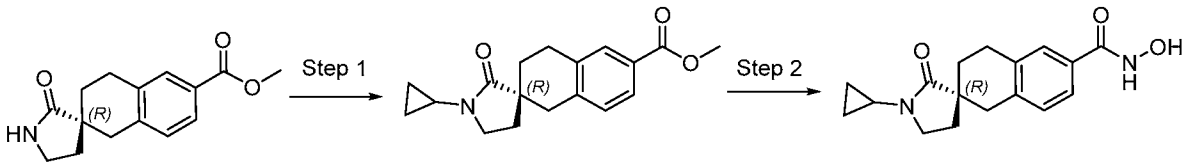
[00162] Into a 100-mL round-bottom flask was placed a solution of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (250 mg, 0.96 mmol, 1 equiv) in DMF (5 mL). NaH (75 mg, 3.12 mmol, 2 equiv) and 2-chloro-5-(chloromethyl)-1,3-thiazole (242 mg, 1.44 mmol, 1.5 equiv) were added at 0 °C. The resulting solution was stirred for 2.5 h at 0 °C. The residue was purified by reverse-phase purification using the following conditions: C18 column; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Gradient: 50% B to 60% B; Detector: UV 254 nm. The collected fractions were lyophilized to give 265 mg (54% yield) of the title compound as a light yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.80-7.82 (m, 2H), 7.50 (s, 1H), 7.14-7.16 (dd, *J* = 8 Hz, 1H), 6.81 (s, 1H), 4.65 (s, 2H), 3.92 (s, 3H), 3.36-3.39 (t, *J* = 12 Hz, 2H), 3.12-3.16 (m, 1H), 2.98-3.06 (m, 1H), 2.82-2.90 (m, 1H), 2.60-2.64 (m, 1H), 2.14-2.11 (m, 1H), 1.95-2.00 (m, 1H), 1.84-1.89 (m, 1H), 1.70-1.76 (m, 1H). MS: (ES, *m/z*): 391 $[M+H]^+$.

***Step-2*: (R)-N-Hydroxy-1'-((2-hydroxythiazol-5-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro [naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00163] Into a 50-mL round-bottom flask was placed a solution of methyl (R)-1'-((2-chlorothiazol-5-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxylate (150 mg, 0.38 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL), NH_2OH (50% in water, 1.6 mL, 60 equiv) and 1N aq. NaOH (1.0 mL, 3 equiv). The reaction was stirred for 6 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: X-bridge C18 19x150mm, Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Gradient: 5% B to 70% B in 7 min; Detector: UV 254 nm. The collected

fractions were lyophilized to give 4.9 mg (4% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.02-11.09 (m, 2H), 8.94 (s, 1H), 7.50-7.54 (m, 2H), 7.13-7.15 (d, *J* = 8 Hz, 1H), 6.84 (s, 1H), 4.30 (s, 2H), 3.23-3.26 (t, *J* = 7.2 Hz, 2H), 2.80-2.89 (m, 3H), 2.57-2.66 (m, 1H), 1.80-1.92 (m, 2H), 1.71-1.79 (m, 2H). MS: (ES, *m/z*): 374 $[M+H]^+$.

Example 19 – Preparation of (R)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-109)



***Step-1*: Methyl (R)-1'-cyclopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate**

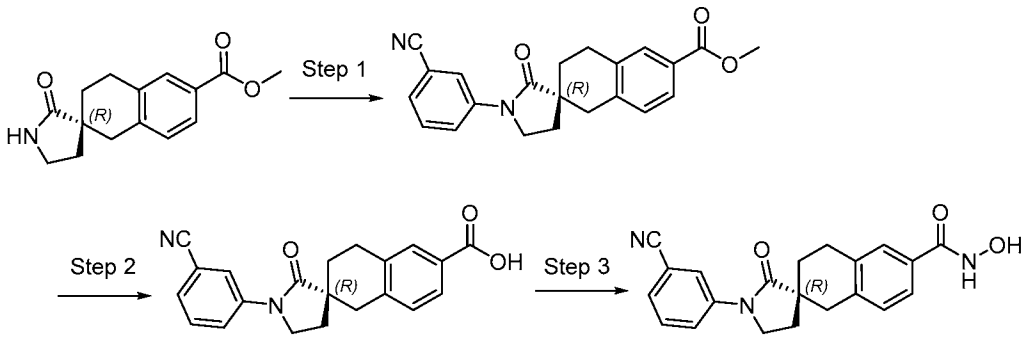
[00164] A 4 mL vial with a Teflon screw-cap was charged with a solution of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (0.2M in 4:1 toluene/pyridine, 0.15 mL, 0.03 mmol, 1 equiv). Then $Cu(OAc)_2$ (11 mg, 0.06 mmol, 2 equiv) was added, followed by Cs_2CO_3 (20 mg, 0.06 mmol, 2 equiv). Lastly a solution of 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.2 M in toluene, 0.3 mL, 0.6 mmol, 2 equiv) was added. The vial was purged with O_2 and sealed. The vial was heated at 110 °C for 72 h. Then reaction mixture was then cooled to room temperature and diluted with 2 mL of EtOAc and 1 mL of 1N aq. HCl. The vial was shaken and the organic layer was separated. The aqueous layer was extracted once more with 2mL EtOAc. The combined organic layers were washed with brine and concentrated to dryness. The title compound was carried forward as a residue without further purification. MS: (ES, *m/z*): 300 $[M+H]^+$.

***Step-2*: (R)-1'-Cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00165] Into a vial was placed methyl (R)-1'-cyclopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate in THF/MeOH (3:1, 0.2 mL), NH_2OH (50% in water, 0.15 mL, 76 equiv), and 1N aq. NaOH (0.1 mL, 3.3 equiv). The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was concentrated and purified by Prep-HPLC using the following conditions: Column: Waters Sunfire C18, 5μm, 19x50mm; Mobile Phase A: Water/0.1% Formic Acid, Mobile Phase B: CH_3CN/0.1% Formic Acid; Flow rate: 23

mL/min; Gradient 15% B to 100% B in 6 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to afford 4 mg (37% yield) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.10 (s, 1H), 9.00 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 3.20 (t, *J* = 8.0 Hz, 2H), 2.95-2.77 (m, 2H), 2.85 (d, *J* = 16 Hz, 1H), 2.66–2.61 (m, 2H), 1.95-1.89 (m, 1H), 1.83-1.69 (m, 2H), 1.66-1.60 (m, 1H) 0.79-0.73 (m, 2H), 0.70-0.66 (m, 2H). MS: (ES, *m/z*): 301 $[M+H]^+$.

Example 20 – Preparation of (R)-1'-(3-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-112)



***Step-1*: Methyl-(R)-1'-(3-cyanophenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00166] A 7-mL vial with Teflon screw top and magnetic stir bar was charged with methyl-(R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (41 mg, 0.160 mmol, 1 equiv), Cs_2CO_3 (210 mg, 0.640 mmol, 4 equiv), and a solution of 3-bromobenzonitrile in 1,4-dioxane (0.2M, 0.880 mL, 0.176 mmol, 1.1 equiv). The vial was sealed and brought into a nitrogen-filled glovebox where a solution of CuI and N,N'-dimethylethylenediamine in DMA (0.2M, 0.40 mL, 0.80 mmol, 0.5 equiv) was added. The vial was sealed and heated at 100 °C for 16 h. The reaction mixture was then cooled to room temperature and diluted with 30 mL of EtOAc and washed with sat. NH_4Cl (2 x 30 mL) and brine (1 x 30 mL). The organic phase was dried with Na_2SO_4, filtered and evaporated to dryness in vacuo to afford a pale yellow residue which was carried forward without any further purification (51 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07-8.05 (m, 1H), 7.99-7.96 (m, 1H), 7.88-7.82 (m, 1H), 7.80-7.77 (m, 1H), 7.49 (t, *J* = 8.2 Hz, 1H), 7.41 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 3.91, (s, 3H), 3.86 (t, *J* = 6.6 Hz, 2H), 3.20 (d, *J* = 17 Hz, 1H), 3.12-3.05 (m, 1H), 2.99-2.90 (m, 1H), 2.78 (d, *J* = 17 Hz, 1H), 2.24-2.00 (m, 3H), 1.92-1.86 (m, 1H). MS: (ES, *m/z*) 361 $[M+H]^+$.

***Step-2*: (R)-1'-(3-Cyanophenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylic acid**

[00167] Methyl-(R)-1'-(3-cyanophenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (51 mg, 0.140 mmol, 1 equiv) was dissolved in THF (1.0 mL). A solution of LiOH in water (0.2 M, 1.0 mL, 0.200 mmol, 1.42 equiv) was added and the reaction mixture stirred at room temperature for 16 h. The mixture was diluted with 30 mL of EtOAc and 10 mL of 1M HCl. The layers were separated and the organic layer was evaporated to dryness in vacuo to afford a white solid. The solid was recrystallized from 2-methyltetrahydrofuran/hexane (43 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.04-8.00 (m, 2H), 7.92-7.87 (m, 2H), 7.52-7.43 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.24 (d, *J* = 17 Hz, 1H), 3.12-3.05 (m, 1H), 2.99-2.90 (m, 1H), 2.80 (d, *J* = 17 Hz, 1H), 2.24-2.00 (m, 3H), 1.92-1.86 (m, 1H). MS: (ES, *m/z*): 347 $[M+H]^+$.

***Step-3*: (R)-1'-(3-Cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00168] (R)-1'-(3-cyanophenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylic acid (10 mg, 0.030 mmol, 1 equiv) was dissolved in 0.150 mL of CH_3CN. N-methylmorpholine (0.011 mL, 0.100 mmol, 3.33 equiv) was added followed by propylphosphonic anhydride solution (50% by weight in EtOAc, 0.070 mL, 7.8 equiv). The mixture stirred for 15 min at 50 °C, then NH_2OH HCl (25 mg, 0.370 mmol, 12.33 equiv) was added. The mixture stirred vigorously at 50 °C for 48 h. The reaction mixture was then diluted with 3 mL of EtOAc and 2 mL of 1N aq HCl. The layers were separated and the organic layer was washed with 1N aq HCl once more. The organic layer was dried and the residue was purified by reverse-phase chromatography Prep-HPLC using the following conditions: Column: Waters Sunfire C18, 5μm, 19x50mm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN/0.1% Formic acid; Gradient: 15% B to 100% B in 6 min; Flow rate: 23 mL/min; Detector: UV 254 nm, 220 nm. The product containing fractions were combined and concentrated to afford 0.6 mg (5.5% yield) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (br s, 2H), 8.04-8.00 (m, 2H), 7.92-7.87 (m, 2H), 7.52-7.43 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.24 (d, *J* = 17 Hz, 1H), 3.12-3.05 (m, 1H), 2.99-2.90 (m, 1H), 2.80 (d, *J* = 17 Hz, 1H), 2.24-2.00 (m, 3H), 1.92-1.86 (m, 1H). MS: (ES, *m/z*): 362 $[M+H]^+$.

Table-8: The following compound was prepared according to the method of Example 20.

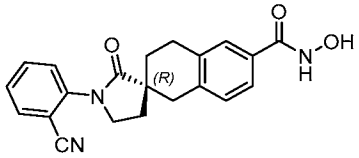
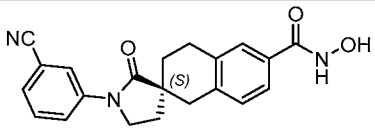
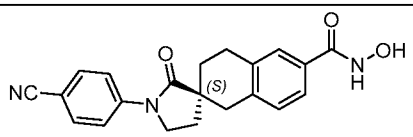
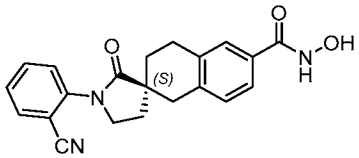
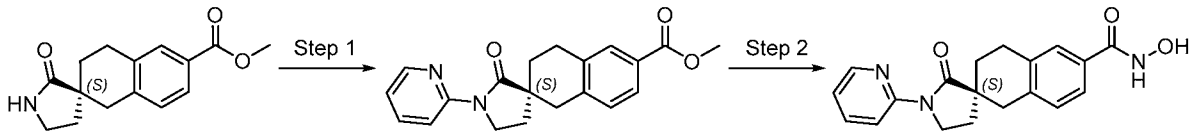
Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-175		(400 MHz, $CDCl_3$): 11.08 (br s, 1H), 8.91 (br s, 1H), 7.91 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 12 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 3.97-3.89 (m, 2H), 3.30 (d, *J* = 17 Hz, 1H), 3.13-3.06 (m, 1H), 3.00-2.93 (m, 1H), 2.88 (d, *J* = 17 Hz, 1H), 2.27-2.04 (m, 3H), 2.00-1.94 (m, 1H)	362

Table-9: The following compounds were prepared according to the method of Example 20, using methyl-(S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate in Step 1.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-116		(400 MHz, $CDCl_3$): 11.08 (br s, 1H), 8.90 (br s, 1H), 8.04-8.00 (m, 2H), 7.92-7.87 (m, 2H), 7.52-7.43 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 3.87 (t, *J* = 6.6 Hz, 2H), 3.24 (d, *J* = 17 Hz, 1H), 3.12-3.05 (m, 1H), 2.99-2.90 (m, 1H), 2.80 (d, *J* = 17 Hz, 1H), 2.24-2.00 (m, 3H), 1.92-1.86 (m, 1H)	362
I-173		(400 MHz, $CDCl_3$): 8.13 (br s, 2H), 7.90-7.85 (m, 4H), 7.69-7.66 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 3.88 (t, *J* = 6.8 Hz, 2H), 3.23 (d, *J* = 17 Hz, 1H), 3.11-3.03 (m, 1H), 2.98-2.89 (m, 1H), 2.79 (d, *J* = 17 Hz, 1H), 2.22-1.99 (m, 3H), 1.91-1.85 (m, 1H)	362
I-174		(400 MHz, $CDCl_3$): 11.08 (br s, 1H), 8.90 (br s, 1H), 7.91 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 12 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 3.97-3.89 (m, 2H), 3.30 (d, *J* = 17 Hz, 1H), 3.13-3.06 (m, 1H), 3.00-2.93 (m, 1H), 2.88 (d, *J* = 17 Hz, 1H), 2.27-2.04 (m, 3H), 2.00-1.94 (m, 1H)	362

Example 21 – Preparation of (S)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-21)



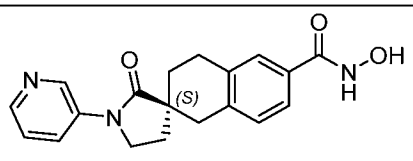
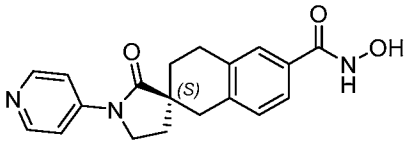
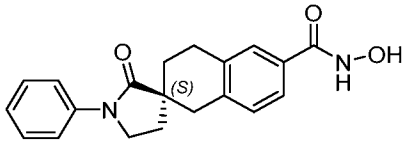
***Step-1*: Methyl (S)-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate**

[00169] Into a 100-mL round-bottom flask maintained with the atmosphere of nitrogen, was placed methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (100 mg, 0.39 mmol, 1 equiv) in toluene (5 mL), $Pd_2(dba)_3$ (7.9 mg, 0.01 mmol, 0.02 equiv), XantPhos (66 mg, 0.11 mmol, 0.3 equiv), Cs_2CO_3 (250 mg, 0.77 mmol, 1.99 equiv), and 2-bromopyridine (91 mg, 0.58 mmol, 1.49 equiv). The resulting solution was stirred overnight at 110 °C. The solids were filtered out. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:5). The collected fractions were concentrated to give 60 mg (46% yield) of the title compound as a white solid. MS: (ES, *m/z*): 337 $[M+H]^+$.

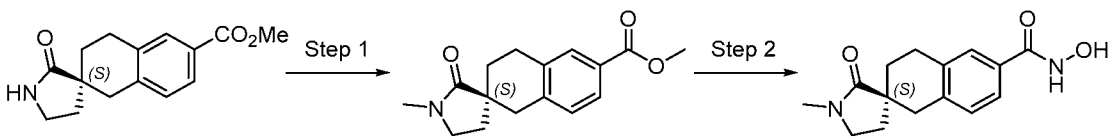
***Step-2*: (S)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00170] Into a 100-mL round-bottom flask was placed methyl (S)-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate (60 mg, 0.18 mmol, 1 equiv), THF/MeOH (4:1, 1.25 mL), NH_2OH (50% in water, 1.18 g, 35.73 mmol, 60 equiv) and 1N aq. NaOH (0.4 mL, 2 equiv). The resulting solution was stirred for 5 h at room temperature. The resulting mixture was adjusted to pH 7 with 4N aq. HCl. The crude product was purified by Prep-HPLC with the following conditions: Column: Waters HSS C18, 2.1x50 mm, 1.8 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2.0 min, hold 0.6 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 33 mg (55% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.10 (s, 1H), 8.42-8.33 (m, 2H), 7.86-7.82 (m, 1H), 7.55-7.49 (m, 2H), 7.18-7.15 (m, 2H), 4.03-3.96 (m, 2H), 2.98-2.80 (m, 4H), 2.07-1.81 (m, 4H). MS: (ES, *m/z*): 338 $[M+H]^+$.

Table-10: The following compounds were prepared according to the method of Example 21.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-11		(300 mHz, DMSO-d6): 11.13 (s, 1H), 9.09 (s, 1H), 8.47-8.46 (d, *J* = 4.4 Hz, 1H), 8.35-8.32 (d, *J* = 7.2 Hz, 1H), 7.67-7.49 (m, 3H), 7.23-7.11 (m, 1H), 3.94-3.91 (t, *J* = 7.2 Hz, 2H), 2.98-2.80 (m, 4H), 2.14-1.82 (m, 4H)	338
I-17		(300 mHz, DMSO-d6): 11.14 (s, 1H), 8.77-8.75 (d, *J* = 9.9 Hz, 2H), 8.18-8.15 (d, *J* = 6.9 Hz, 2H), 7.56-7.50 (m, 2H), 7.18-7.13 (m, 1H), 4.01-3.97 (t, *J* = 6.9 Hz, 2H), 3.01-2.84 (m, 4H), 2.18-2.09 (m, 1H), 1.98-1.91 (m, 3H)	338
I-29		(400 mHz, DMSO-d6): 11.14 (br s, 1H), 7.73-7.71 (d, *J* = 8 Hz, 2H), 7.55-7.36 (m, 4H), 7.20-7.12 (m, 2H), 3.88-3.86 (t, *J* = 4 Hz, 2H), 2.97-2.78 (m, 4H), 2.08-2.02 (m, 1H), 1.96-1.79 (m, 3H)	337

Example 22 – Preparation of (S)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxamide (I-105)



***Step-1*: Methyl (S)-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

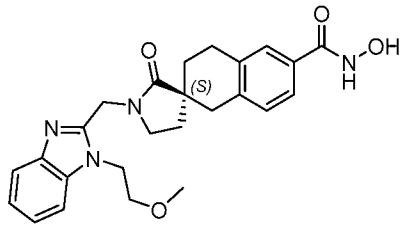
[00171] Into a 50-mL round-bottom flask, was placed a solution of methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (100 mg, 0.39 mmol, 1 equiv) in DMF (5 mL). This was followed by the addition of NaH (60% dispersion in oil, 30 mg, 1.25 mmol, 2 equiv) at 0 °C over 10 min. Then CH_3I (109 mg, 0.77 mmol, 2 equiv) was added at 0 °C. The resulting mixture was stirred for 2.5 h at the same temperature. The reaction was then quenched by the addition of 30 mL of water. The resulting solution was extracted with 3x80 mL

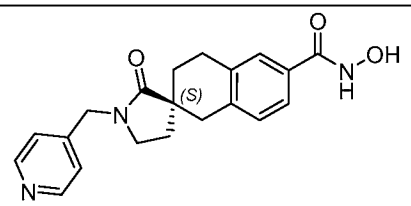
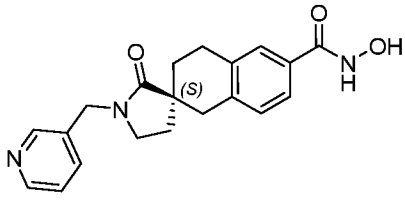
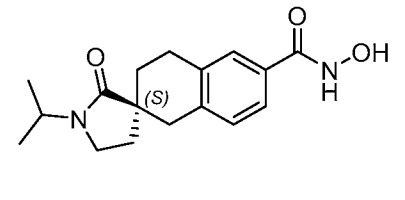
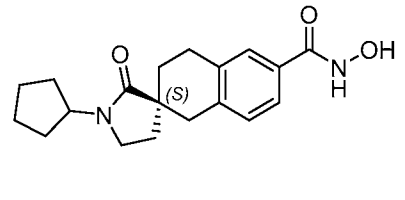
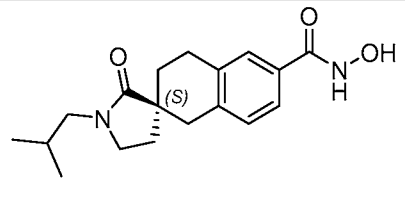
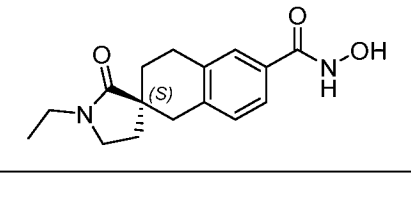
of EtOAc. The organic layers were combined and concentrated. The residue was purified by normal phase chromatography on silica gel and eluted with EtOAc/petroleum ether (1:5). The collected fractions were concentrated to give 70 mg (66% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 274 $[M+H]^+$.

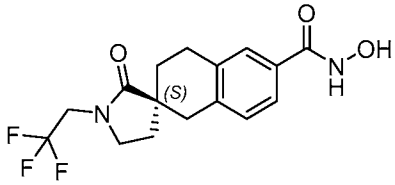
***Step-2*: (S)-N-Hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00172] Into a 50-mL round-bottom flask, was placed a solution of methyl (S)-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (130 mg, 0.48 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), NH_2OH (50% in water, 0.1.87 mL, 28.8 mmol, 60 equiv), and 1N aq. NaOH (0.95 mL, 0.95 mmol, 2 equiv). The resulting solution was stirred for 4 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge C18, 19x150 mm, 5 μm; Mobile Phase A: Water/0.05 % TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 25 mL/min; Gradient: 20% B to 60% B in 7.0 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 47.7 mg (26% yield) of the title compound as a light yellow solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.09 (s, 1H), 8.95 (s, 1H), 7.45-7.51 (m, 2H), 7.11-7.13 (d, *J* = 8 Hz, 1H), 3.28-3.32 (t, *J* = 8 Hz, 2H), 2.76-2.89 (m, 6H), 2.50-2.56 (m, 1H), 1.81-1.91 (m, 2H), 1.65-1.80 (m, 2H). MS: (ES, *m/z*): 275 $[M+H]^+$.

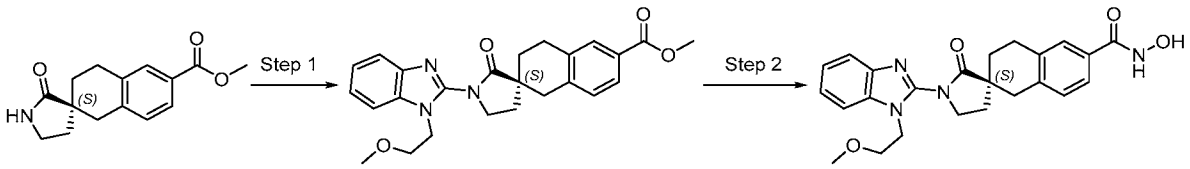
Table-11: The following compounds were prepared according to the method of Example 22, with the following modification: In Step 1, the halide can be an iodide, a chloride, or a bromide.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-23		(400 MHz, DMSO-d6): 11.12 (br s, 1H), 7.88-7.74 (m ,2H), 7.54-7.40 (m, 4H), 7.16-7.14 (d, *J* = 8 Hz, 1H), 4.94-4.89 (br, 2H), 4.64-4.56 (br, 2H), 3.70 (s, 2H), 3.45-3.43 (t, *J* = 4 Hz, 2H), 3.24 (s, 3H), 2.94-2.79 (m, 3H), 2.78-2.66 (m, 1H), 2.01-1.69 (m, 4H)	449

I-15		(300 MHz, DMSO-d6): 11.14 (br s, 1H), 8.76-8.74 (d, *J* = 6 Hz, 2H), 7.62-7.60 (d, *J* = 6 Hz, 2H), 7.53-7.47 (m, 2H), 7.18-7.15 (d, *J* = 9 Hz 1H), 4.62 (s, 2H), 3.36-3.32 (t, *J* = 6 Hz, 2H), 2.96-2.67 (m, 4H), 2.07-1.72 (m, 4H)	352
I-19		(300 MHz, DMSO-d6): 11.11 (br s, 1H), 8.73-8.63 (m, 2H), 8.03-8.01 (d, *J* = 6 Hz, 1H), 7.75-7.71 (t, J = 6 Hz, 1H), 7.54-7.42 (m, 2H), 7.16-7.13 (d, *J* = 9 Hz, 1H), 4.56 (s, 2H), 3.32-3.28 (t, *J* = 6 Hz, 2H), 2.94-2.81 (m, 3H) 2.72-2.63 (m, 1H), 1.98-1.81 (m, 2H), 1.77-1.68 (m, 2H)	352
I-25		(400 MHz, DMSO-d6): 11.09 (br s, 1H), 8.95 (br s, 1H), 7.53-7.45 (m, 2H), 7.14-7.12 (d, *J* = 8 Hz, 1H), 4.18-4.11 (m, 1H), 3.27-3.23 (t, *J* = 8 Hz, 2H), 2.92-2.76 (m, 3H), 2.62-2.54 (m, 1H), 1.88-1.68 (m, 2H), 1.66-1.57 (m, 2H), 1.11-1.08 (m, 6H)	303
I-164		(400 MHz, DMSO-d6): 11.09 (s, 1H), 8.96 (s, 1H), 7.47(d, *J* = 27 Hz, 2H), 7.12 (d, *J* = 9 Hz, 1H), 4.29-4.36 (m, 1H), 329-3.34 (m, 2H), 3.27-3.33 (m, 3H), 2.53 (d, *J* = 18 Hz, 1H), 1.68-1.89 (m, 12H)	329
I-160		(400 MHz, DMSO-d6): 11.08 (s, 1H), 8.96 (s, 1H), 7.43-7.50 (m, 2H), 7.15 (d, *J* = 9 Hz, 1H), 3.29-3.34 (m, 2H), 3.03 (d, *J* = 6 Hz, 2H), 2.80-2.89 (m, 3H), 2.51 (d, *J* = 3 Hz, 1H), 1.89-1.90 (m, 3H) 1.64-1.73 (m, 2H) 0.85(d, *J* = 15 Hz, 6H)	317
I-162		(400 MHz, DMSO-d6): 11.05 (m, 1H), 9.03 (m, 1H), 7.46-7.44 (m, 2H), 7.12-7.10 (m, 1H), 3.31-3.30 (m, 2H), 3.28-3.20 (m, 2H), 2.88-2.78 (m, 3H), 2.59-	289

		2.49 (m, 1H), 1.89-1.76 (m, 2H), 1.74-1.56 (m, 2H), 1.04-1.01 (m, 3H)	
I-166		(400 MHz, DMSO-d6): 11.03 (s, 1H), 7.50-7.44 (m, 2H), 7.14-7.11 (m, 1H), 4.11-4.02 (m, 2H), 3.46-3.43 (m, 2H), 2.90-2.75 (m, 3H), 2.65-2.61 (m, 1H), 1.97-1.91 (m, 1H), 1.85-1.70 (m, 2H), 1.66-1.63 (m, 1H)	343

Example 23 – Preparation of (S)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-13)



***Step-1*: Methyl (S)-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro [naphthalene-2,3'-pyrrolidine]-6-carboxylate**

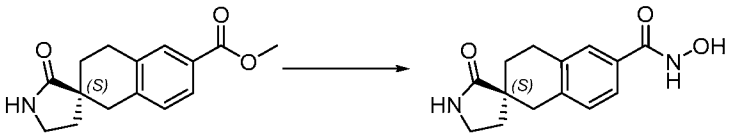
[00173] Into a 10-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (60 mg, 0.23 mmol, 1 equiv), 2-bromo-1-(2-methoxyethyl)-1H-1,3-benzodiazole (103 mg, 0.40 mmol, 1.5 equiv), CuI (5.0 mg, 0.03 mmol, 0.1 equiv), Cs_2CO_3 (263 mg, 0.81 mmol, 3 equiv), toluene (2 mL), and (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (8 mg, 0.06 mmol, 0.2 equiv). The resulting solution was stirred for 10 h at 110 °C in an oil bath. The reaction mixture was cooled to 20 °C in a water bath. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:1). The collected fractions were concentrated to give 30 mg (30% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 434 $[M+H]^+$.

***Step-2*: (S)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00174] Into a 10-mL round-bottom flask was placed methyl (S)-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (30 mg, 0.07 mmol, 1 equiv), THF/MeOH (4:1, 2.5 mL), NH_2OH (50% in water, 0.5 mL, 108 equiv), and 1N aq. NaOH (0.3 mL, 4.29 equiv). The resulting solution was stirred for 3 h at room

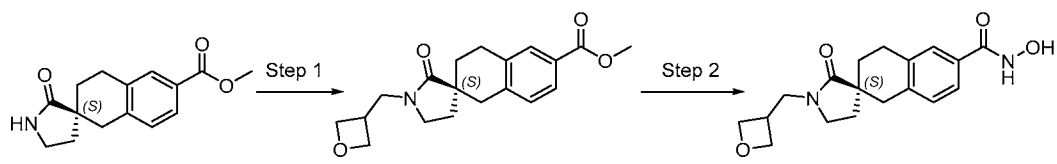
temperature. The reaction mixture was cooled to 0 °C in an ice-water bath. The pH of the solution was adjusted to 7 with 1N aq. HCl. The crude product was purified by Prep-HPLC with the following conditions: Column: X Bridge C18, 19x150 mm, 5 μm; Mobile Phase A: Water/10% NH_4HCO_3, Mobile Phase B: CH_3CN/10% NH_4HCO_3; Flow rate: 25 mL/min; Gradient: 5% B to 47% B in 7.0 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 29.6 mg (98% yield) of the title compound as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.14 (br s, 1H), 7.65-7.48 (m, 4H), 7.28-7.17 (m, 3H), 4.35-4.33 (t, *J* = 4 Hz, 2H), 3.99-3.89 (m, 2H), 3.62-3.60 (t, *J* = 4 Hz, 2H), 3.20 (s, 3H), 3.02-2.86 (m, 4H), 2.22-2.15 (m, 1H), 2.02-1.97 (m, 3H). MS: (ES, *m/z*): 435 $[M+H]^+$.

Example 24 – Preparation of (S)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxamide (I-28)



[00175] Into a 50-mL round-bottom flask was placed a solution of methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (100 mg, 0.39 mmol, 1 equiv) in THF/MeOH (4:1, 1.25 mL), NH_2OH (50% in water, 1.52 mL, 60 equiv), and 1N aq. NaOH (0.77 mL, 2 equiv). The resulting solution was stirred for 1.5 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Waters HSS C18, 2.1x50 mm, 1.8 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2.0 min hold 0.6 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 37.5 mg (38% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 1.74-1.80 (m, 1H), 1.81-1.90 (m, 2H), 1.92-1.95 (m, 1H), 2.63-2.67 (m, 1H), 2.74-2.90 (m, 3H), 3.18-3.22 (t, *J* = 7 Hz, 2H), 7.13-7.15 (d, *J* = 8 Hz, 1H), 7.43-7.50 (m, 2H), 7.66 (s, 1H), 8.94 (s, 1H), 11.09 (s, 1H). MS: (ES, *m/z*): 261 $[M+H]^+$.

Example 25 – Preparation of (S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-122)



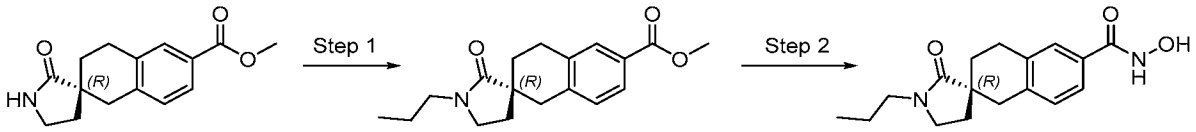
***Step-1*: Methyl (S)-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00176] A 4-mL vial charged with methyl-(S)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (10 mg, 0.040 mmol) was dissolved in 0.20 mL of anhydrous DMA. Then NaH (60% dispersion in oil, 1 mg, 0.043 mmol, 1.1 equiv) was added. The reaction mixture was stirred for 5 min at room temperature. Next, a solution of 3-(bromomethyl)oxetane (0.20 mL, 0.040 mmol, 1 equiv) in CH_3CN was added. The reaction mixture was stirred at room temperature overnight. The solvent was removed under a stream of N_2. The residue was diluted with brine (0.50 mL) and extracted with EtOAc (2 x 0.50 mL). The combined organic layers were dried under a stream of N_2 and carried forward without further purification

***Step-2*: (S)-N-Hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide**

[00177] Methyl (S)-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate was dissolved in THF/MeOH (3:1, 200 µL). The vial was sealed and shaken at 50°C for 15 min to dissolve the residue, then cooled to room temperature. NH_2OH (50% v/v in water, 0.150 mL) was added, followed by 1N aq NaOH (0.10 mL, 0.10 mmol, 2.5 equiv). The mixture was sealed and then shaken at room temperature for 18 h. The reaction mixture was concentrated under a stream of N_2 at room temperature, then dissolved in 0.50 mL of DMSO and purified by reverse-phase chromatography Prep-HPLC Column: Waters Sunfire C18, 5µm, 19x50mm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN/0.1% Formic acid; gradient: 15% B to 100% B in 6 min; Flow rate: 23 mL/min; Detector: UV 254 nm, 220 nm. The product-containing fractions were combined and concentrated in to afford 0.6mg (5% yield) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.10 (s, 1H), 9.00 (s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 4.80 (dd, J = 7.4, 6.3 Hz, 2H), 4.41 (t, J = 6.2 Hz, 2H), 3.64 (d, J = 7.8 Hz, 2H), 3.37-3.25 (m, 1H), 3.23 (d, J = 17 Hz, 1H), 3.11-3.03 (m, 1H), 2.98–2.89 (m, 1H), 2.79 (d, J = 17 Hz, 1H), 2.22-1.99 (m, 3H), 1.91-1.85 (m, 1H). MS: (ES, *m/z*) 331 $[M+H]^+$.

Example 26 – Preparation of (R)-N-hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-32)



***Step-1*: Methyl (R)-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

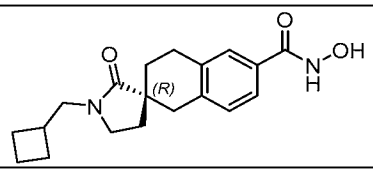
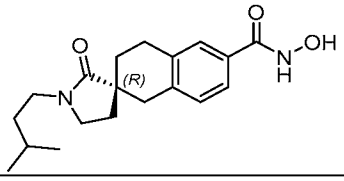
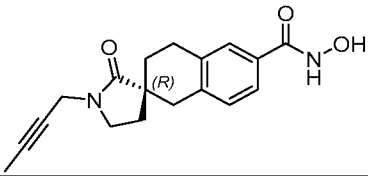
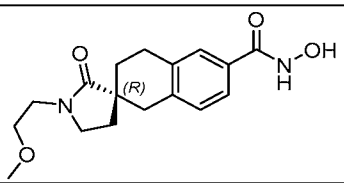
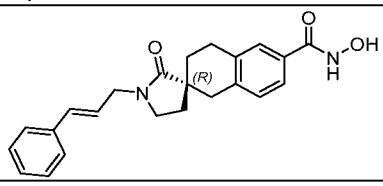
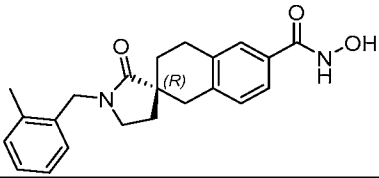
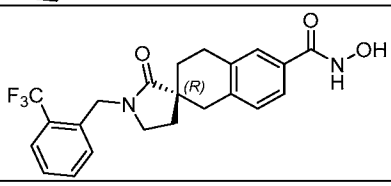
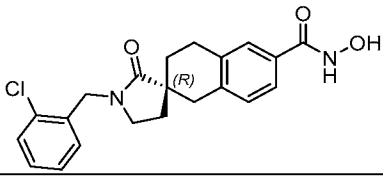
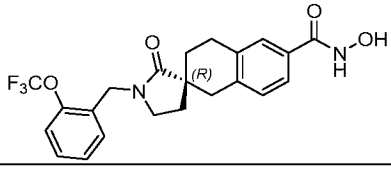
[00178] A solution of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (350 mg, 1.35 mmol, 1 equiv) in anhydrous DMF (6.75 mL) was deprotonated with NaH (60% dispersion in oil, 54 mg, 1.35mmol, 1 equiv). This solution (0.15 mL, 0.30 mmol) was added to a solution of 1-iodopropane (0.2 M in acetonitrile, 0.30 mL, 0.06 mmol, 2 equiv) in a 2 dram vial. NaI (18 mg, 0.12 mmol, 4 equiv) was added and the vial was sealed and shaken at 80 °C for 48 h. The solvent was removed and the residue was diluted with brine (0.5 mL) and extracted with EtOAc (2 x 0.5 mL). The combined organic layers were concentrated under vacuum.

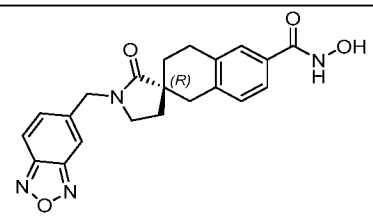
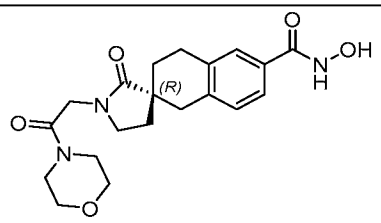
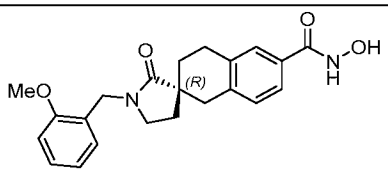
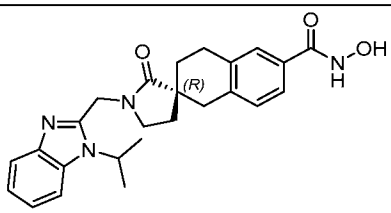
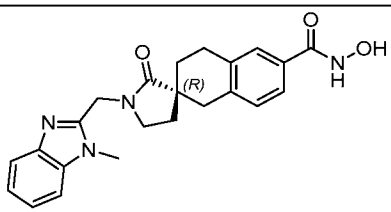
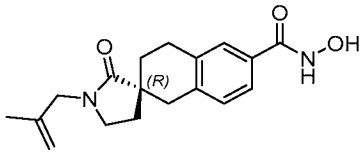
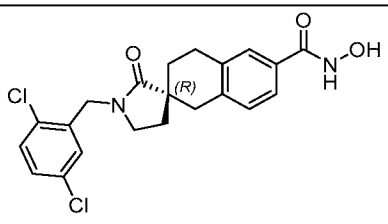
***Step-2*: (R)-N-Hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

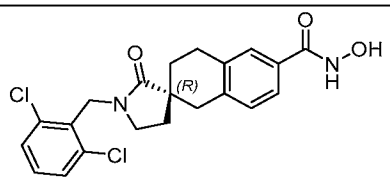
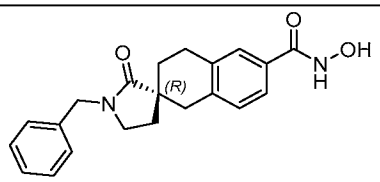
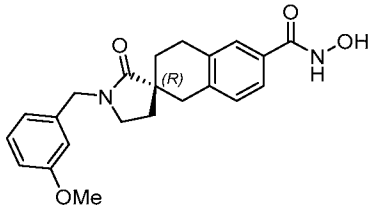
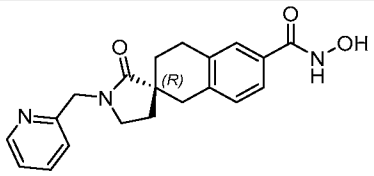
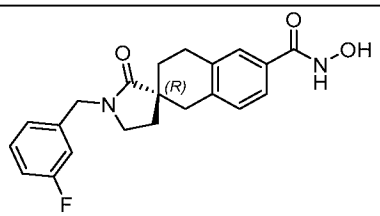
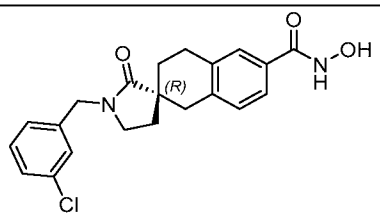
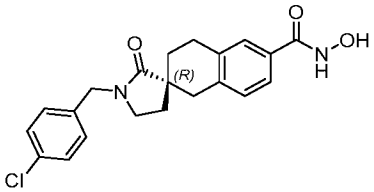
[00179] The residue was dissolved in a solution of THF/MeOH (3:1, 0.2 mL). NH_2OH (50% in water, 0.15 mL, 76 equiv) was added, followed by addition of 1N aq NaOH (0.10 mL, 3.3 equiv). The mixture was sealed and shaken at room temperature for 18 h. The reaction mixture was concentrated and purified by reversed-phase chromatography Prep-HPLC Column: Waters Sunfire C18, 5µm, 19x50mm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN/0.1% Formic acid; Gradient: 15% B to 100% B in 6 min; Flow rate: 23 mL/min; Detector: UV 254 nm, 220 nm. The product-containing fractions were combined and concentrated to afford 3 mg (33% yield) of the title compound. MS: (ES, *m/z*) 303 $[M+H]^+$.

Table-12: The following compounds were prepared according to the parallel synthesis method of Example 26.

Ex.	Name	Structure	Found (ES, *m/z*) $[M+H]^+$

I-33	(*R*)-1'-(cyclobutylmethyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		329
I-34	(*R*)-*N*-hydroxy-1'-isopentyl-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		331
I-35	(*R*)-1'-(but-2-yn-1-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		313
I-36	(*R*)-N-hydroxy-1'-(2-methoxyethyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		319
I-37	(*R*)-1'-cinnamyl-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		377
I-38	(*R*)-*N*-hydroxy-1'-(2-methylbenzyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		365
I-39	(*R*)-*N*-hydroxy-2'-oxo-1'-(2-(trifluoromethyl)benzyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		419
I-40	(*R*)-1'-(2-chlorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-41	(*R*)-*N*-hydroxy-2'-oxo-1'-(2-(trifluoromethoxy)benzyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		435

I-42	(*R*)-1'-(benzo[*c*][1,2,5]oxadiazol-5-ylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		393
I-43	(*R*)-*N*-hydroxy-1'-(2-morpholino-2-oxoethyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		388
I-44	(*R*)-*N*-hydroxy-1'-(2-methoxybenzyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381
I-45	(*R*)-*N*-hydroxy-1'-((1-isopropyl-1*H*-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		433
I-46	(*R*)-*N*-hydroxy-1'-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		405
I-47	*(R)*-*N*-hydroxy-1'-(2-methylallyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		315
I-48	(*R*)-1'-(2,5-dichlorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		419

I-49	(*R*)-1'-(2,6-dichlorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		419
I-50	(*R*)-1'-benzyl-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		351
I-51	(*R*)-*N*-hydroxy-1'-(3-methoxybenzyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381
I-52	(*R*)-*N*-hydroxy-2'-oxo-1'-(pyridin-2-ylmethyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-53	(*R*)-1'-(3-fluorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		369
I-54	(*R*)-1'-(3-chlorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-55	(*R*)-1'-(4-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385

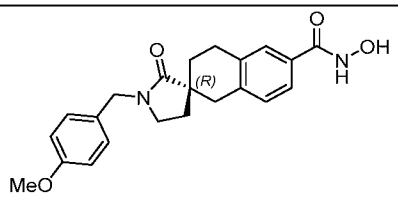
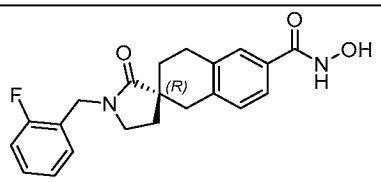
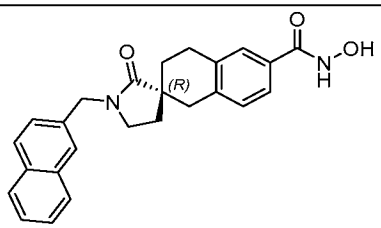
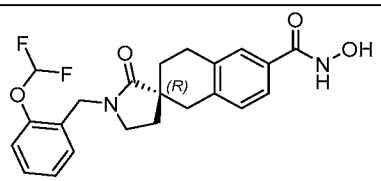
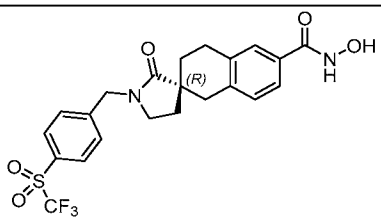
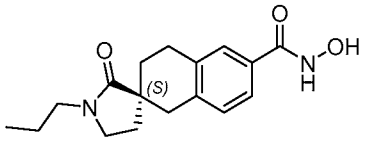
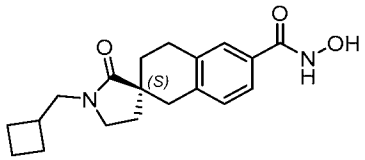
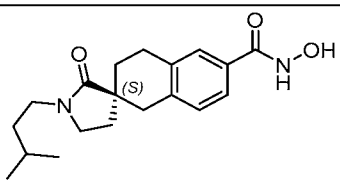
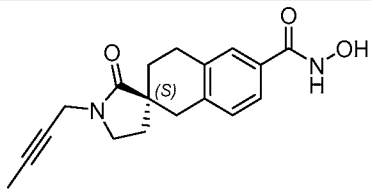
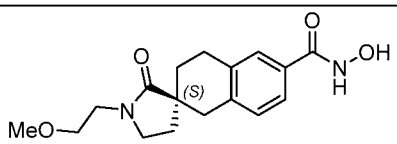
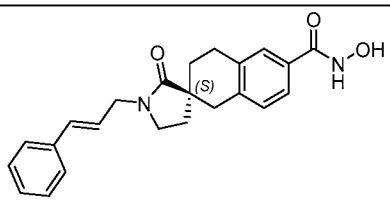
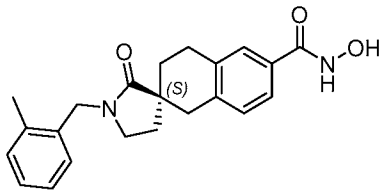
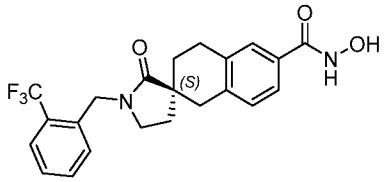
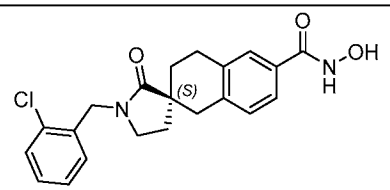
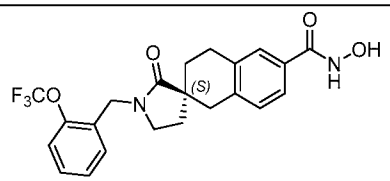
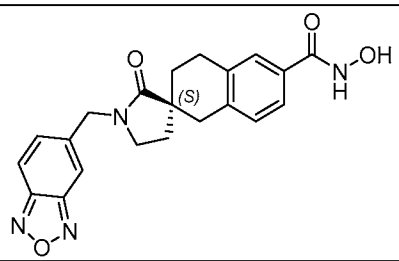
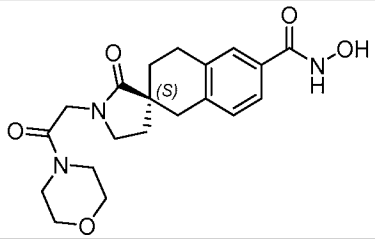
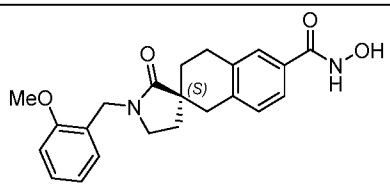
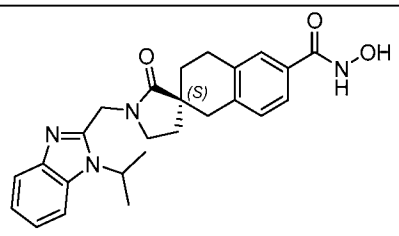
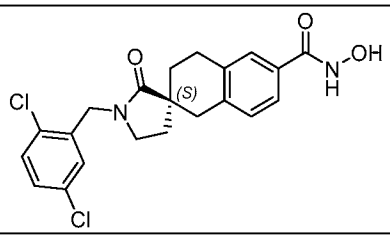
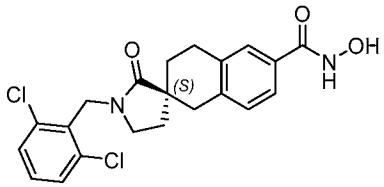
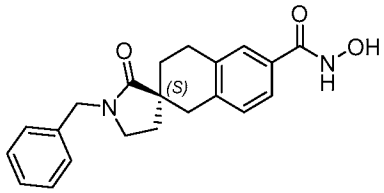
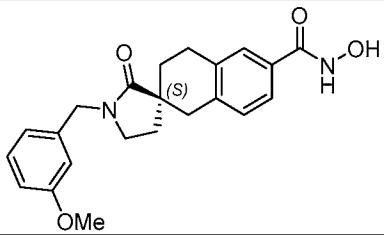
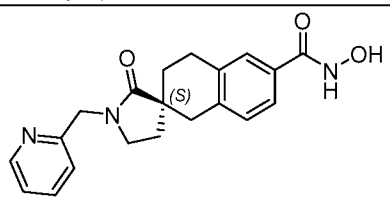
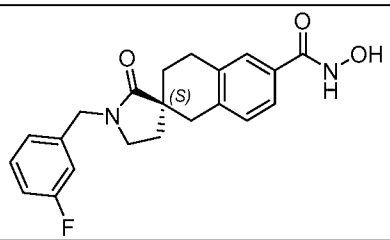
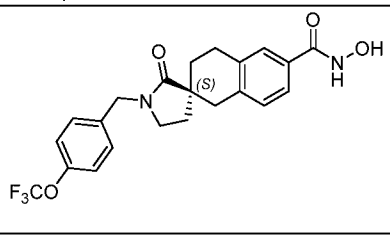
I-56	(*R*)-*N*-hydroxy-1'-(4-methoxybenzyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381
I-57	(*R*)-1'-(2-fluorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		369
I-58	(*R*)-*N*-hydroxy-1'-(naphthalen-2-ylmethyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		401
I-59	(*R*)-1'-(2-(difluoromethoxy)benzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		417
I-106	(*R*)-*N*-hydroxy-2'-oxo-1'-(4-((trifluoromethyl)sulfonyl)benzyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		483

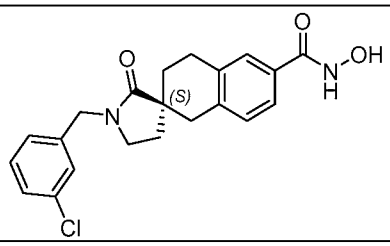
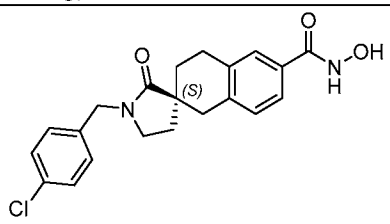
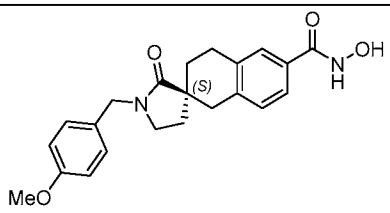
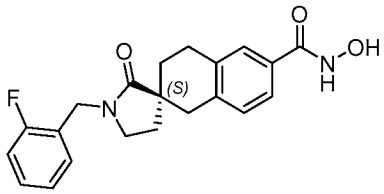
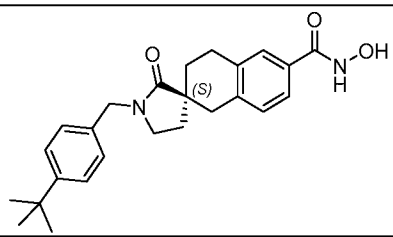
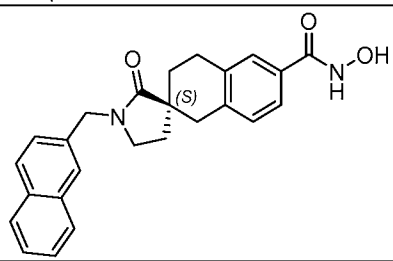
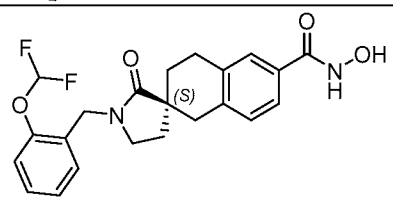
Table-13: The following compounds were prepared according to the synthesis method of Example 26, using methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate in Step 1.

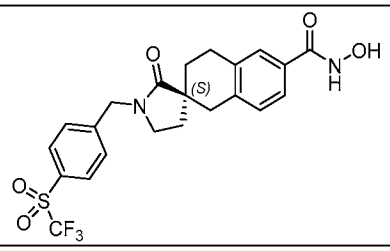
Ex.	**Name**	**Structure**	**Found (ES, *m/z*) $[M+H]^+$**

I-60	(*S*)-*N*-hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		303
I-61	(*S*)-1'-(cyclobutylmethyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		329
I-62	(*S*)-*N*-hydroxy-1'-isopentyl-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		331
I-63	(*S*)-1'-(but-2-yn-1-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		313
I-64	(*S*)-*N*-hydroxy-1'-(2-methoxyethyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		319
I-65	(*S*)-1'-cinnamyl-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		377
I-66	(*S*)-*N*-hydroxy-1'-(2-methylbenzyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		365

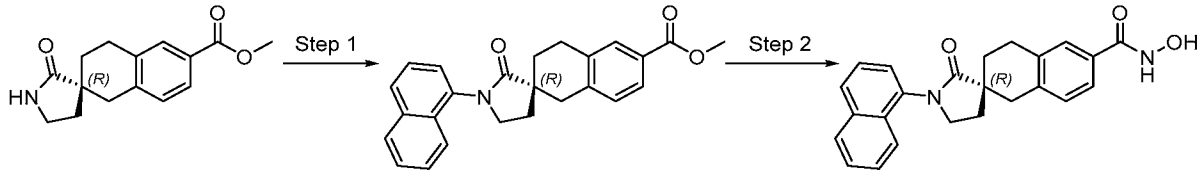
I-67	(*S*)-*N*-hydroxy-2'-oxo-1'-(2-(trifluoromethyl)benzyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		419
I-68	(*S*)-1'-(2-chlorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-69	(*S*)-*N*-hydroxy-2'-oxo-1'-(2-(trifluoromethoxy)benzyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		435
I-70	(*S*)-1'-(benzo[*c*][1,2,5]oxadiazol-5-ylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		393
I-71	(*S*)-*N*-hydroxy-1'-(2-morpholino-2-oxoethyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		388
I-72	(*S*)-*N*-hydroxy-1'-(2-methoxybenzyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381
I-73	(*S*)-*N*-hydroxy-1'-((1-isopropyl-1*H*-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		433

I-74	(*S*)-1'-(2,5-dichlorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		419
I-75	(*S*)-1'-(2,6-dichlorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		419
I-76	(*S*)-1'-benzyl-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		351
I-77	(*S*)-*N*-hydroxy-1'-(3-methoxybenzyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381
I-78	(*S*)-*N*-hydroxy-2'-oxo-1'-(pyridin-2-ylmethyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-79	(*S*)-1'-(3-fluorobenzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		369
I-80	(*S*)-*N*-hydroxy-2'-oxo-1'-(4-(trifluoromethoxy)benzyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		435

I-81	*(S)*-1'-[(3-chlorophenyl)methyl]-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-82	(*S*)-1'-(4-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-83	(*S*)-*N*-hydroxy-1'-(4-methoxybenzyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381
I-84	(*S*)-1'-(2-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		369
I-85	(*S*)-1'-(4-(tert-butyl)benzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		407
I-86	(*S*)-*N*-hydroxy-1'-(naphthalen-2-ylmethyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		401
I-87	(*S*)-1'-(2-(difluoromethoxy)benzyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		417

I-107	(*S*)-*N*-hydroxy-2'-oxo-1'-(4-((trifluoromethyl)sulfonyl)benzyl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		483

Example 27 – Preparation of (R)-N-hydroxy-1'-(naphthalen-1-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-89)



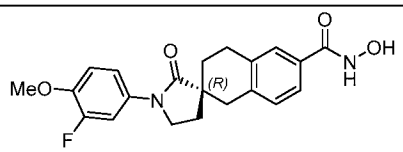
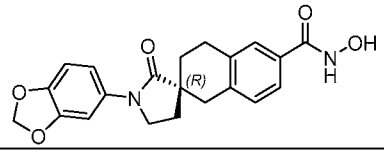
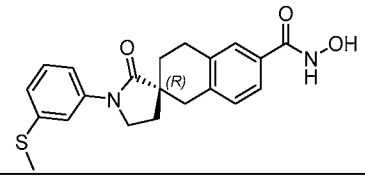
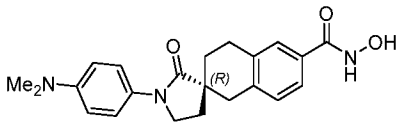
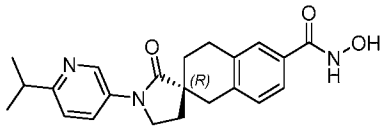
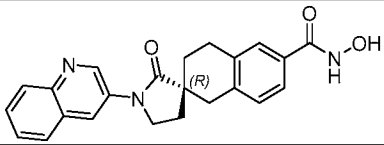
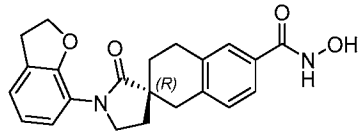
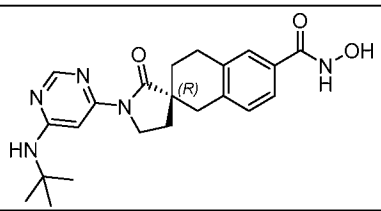
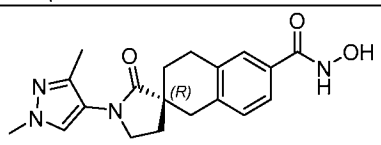
***Step-1*: Methyl (R)-1'-(naphthalen-1-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate**

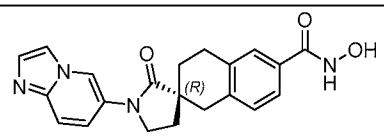
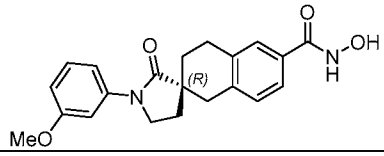
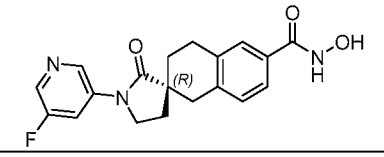
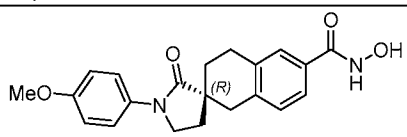
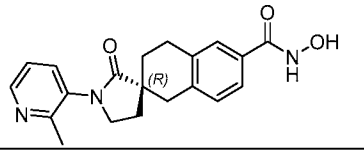
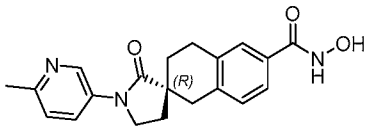
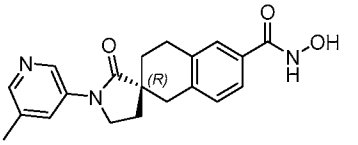
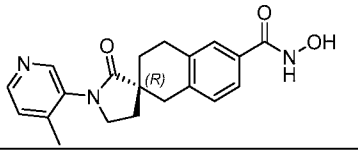
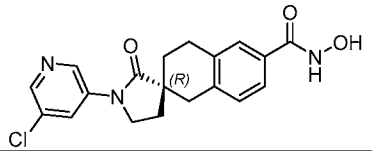
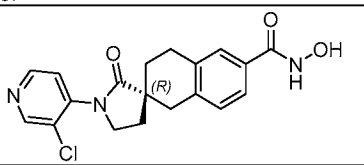
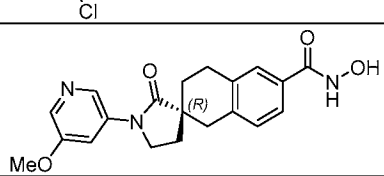
[00180] A 2-mL vial was charged with methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (0.2 M in 1,4-dioxane, 0.15 mL, 0.03 mmol, 1 equiv) and Cs_2CO_3 (39 mg, 0.12 mmol, 4 equiv). Then a solution of 1-bromonaphthalene (0.2 M in 1,4-dioxane, 0.30 mL, 0.06 mmol, 2 equiv) was added. The vial was sealed and brought into a glovebox. A degassed solution of CuBr (10 mol %) and *N,N*-dimethylethane-1,2-diamine (0.02 M in DMA, 0.15 mL, 0.003 mmol, 20 mol %) was added. The vial was sealed and heated at 110 °C for 18 h. The solvent was removed and the residue was diluted with brine (0.5 mL) and extracted with EtOAc (2 x 0.5 mL). The combined organic layers were concentrated under vacuum.

***Step-2*: (R)-N-Hydroxy-1'-(naphthalen-1-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00181] The residue was dissolved in THF/MeOH (3:1, 0.2 mL) and NH_2OH (50% in water, 0.15 mL, 76 equiv) was added, followed by addition of 1N aq NaOH (0.1 mL, 3.3 equiv). The mixture was sealed and then shaken at room temperature for 18 h. The reaction mixture was concentrated and purified by reverse-phase Prep-HPLC Column: Waters Sunfire C18, 5μm, 19x50mm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN/0.1% Formic acid; Gradient: 15% B to 100% B in 6 min; Flow rate: 23 mL/min; Detector: UV 254 nm/220 nm. The product-containing fractions were combined and concentrated to afford 1 mg (8.6% yield) of the title compound. MS: (ES, *m/z*) 387 $[M+H]^+$.

Table-14: The following compounds were prepared according to the parallel synthesis method of Example 27.

Ex.	Name	Structure	Found (ES, *m/z*) $[M+H]^+$
I-90	(*R*)-1'-(3-fluoro-4-methoxyphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-91	(*R*)-1'-(benzo[*d*][1,3]dioxol-5-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381
I-92	(*R*)-*N*-hydroxy-1'-(3-(methylthio)phenyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		383
I-93	(*R*)-1'-(4-(dimethylamino)phenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		380
I-94	(*R*)-*N*-hydroxy-1'-(6-isopropylpyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		380
I-95	(*R*)-*N*-hydroxy-2'-oxo-1'-(quinolin-3-yl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		388
I-96	(*R*)-1'-(2,3-dihydrobenzofuran-7-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		379
I-97	(*R*)-1'-(6-(*tert*-butylamino)pyrimidin-4-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		410
I-98	(*R*)-1'-(1,3-dimethyl-1*H*-pyrazol-4-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		355

I-99	(*R*)-*N*-hydroxy-1'-(imidazo[1,2-a]pyridin-6-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		377
I-108	(*R*)-*N*-hydroxy-1'-(3-methoxyphenyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		367
I-110	(*R*)-1'-(5-fluoropyridin-3-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		356
I-124	(*R*)-*N*-hydroxy-1'-(4-methoxyphenyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		367
I-131	(*R*)-*N*-hydroxy-1'-(2-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-133	(*R*)-*N*-hydroxy-1'-(6-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-135	(*R*)-*N*-hydroxy-1'-(5-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-136	(*R*)-N-hydroxy-1'-(4-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-139	(*R*)-1'-(5-chloropyridin-3-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		372
I-140	(*R*)-1'-(3-chloropyridin-4-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		372
I-143	(*R*)-*N*-hydroxy-1'-(5-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368

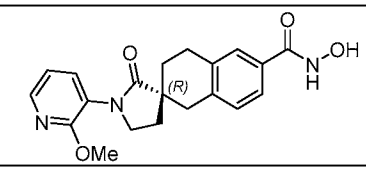
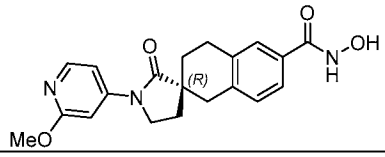
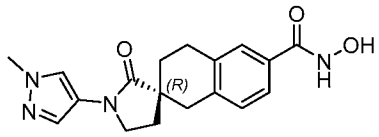
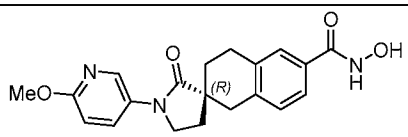
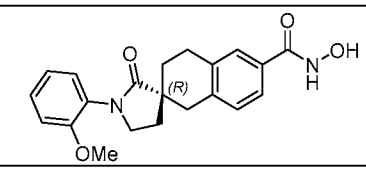
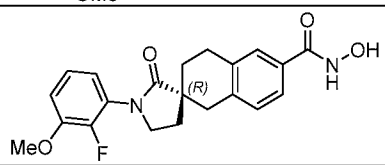
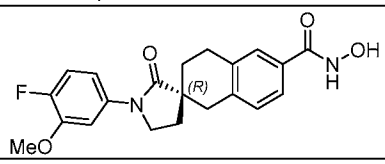
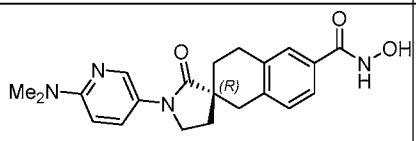
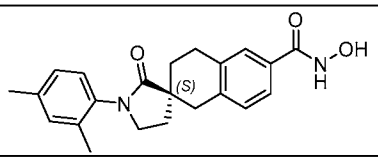
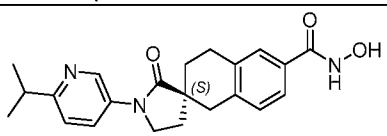
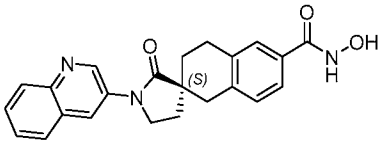
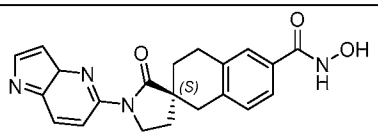
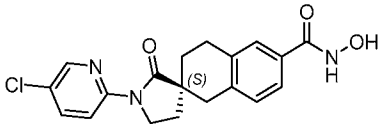
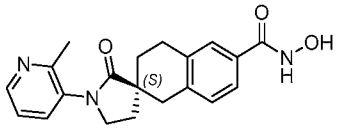
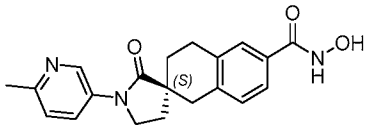
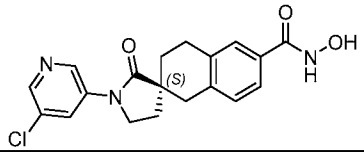
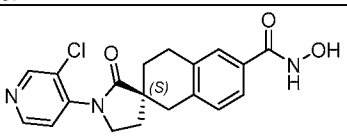
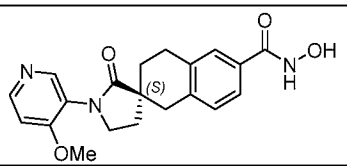
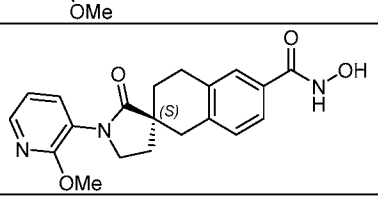
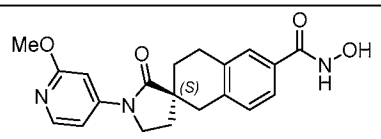
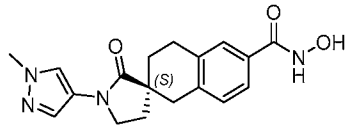
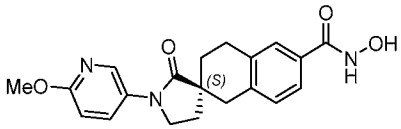
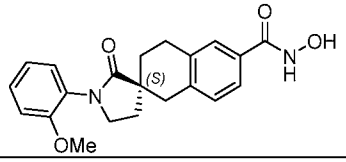
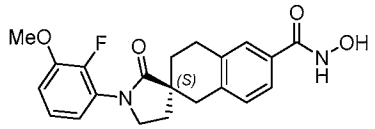
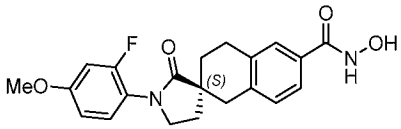
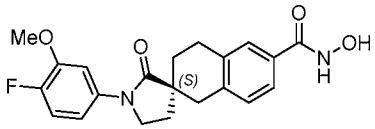
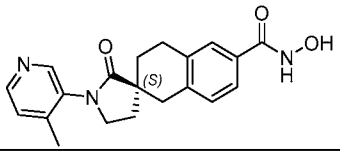
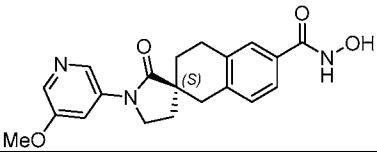
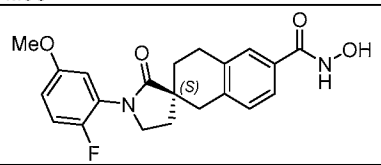
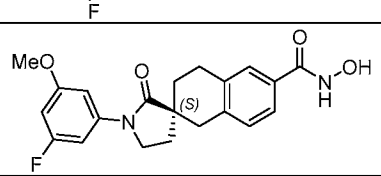
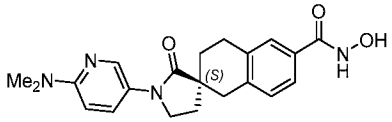
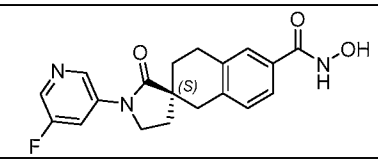
I-145	(*R*)-*N*-hydroxy-1'-(2-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368
I-149	(*R*)-*N*-hydroxy-1'-(2-methoxypyridin-4-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368
I-168	(*R*)-*N*-hydroxy-1'-(1-methyl-1H-pyrazol-4-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		341
I-114	(*R*)-*N*-hydroxy-1'-(6-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368
I-111	(*R*)-*N*-hydroxy-1'-(2-methoxyphenyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		367
I-125	(2*R*)-1'-(2-fluoro-3-methoxyphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-128	(2*R*)-1'-(4-fluoro-3-methoxyphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-151	(2*R*)-1'-[6-(dimethylamino)pyridin-3-yl]-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381

Table-15: The following compounds were prepared according to the parallel synthesis method of Example 27, using methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate in Step 1.

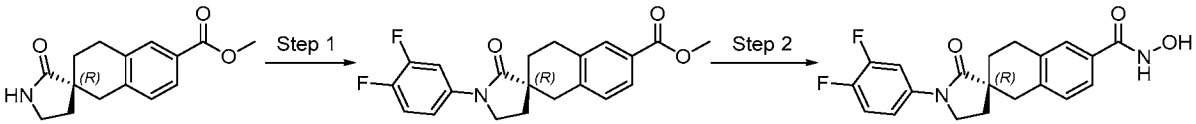
Ex.	**Name**	**Structure**	**Found (ES, *m/z*) $[M+H]^+$**

I-100	(*S*)-1'-(2,4-dimethylphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		365
I-101	(*S*)-*N*-hydroxy-1'-(6-isopropylpyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		380
I-102	(*S*)-*N*-hydroxy-2'-oxo-1'-(quinolin-3-yl)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		388
I-103	(*S*)-*N*-hydroxy-1'-(imidazo[1,2-a]pyridin-6-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		377
I-130	(*S*)-1'-(5-chloropyridin-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		372
I-132	(*S*)-*N*-hydroxy-1'-(2-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-134	(*S*)-*N*-hydroxy-1'-(6-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-138	(*S*)-1'-(5-chloropyridin-3-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		372
I-141	(*S*)-1'-(3-chloropyridin-4-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		372
I-142	(*S*)-*N*-hydroxy-1'-(4-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368
I-146	(*S*)-*N*-hydroxy-1'-(2-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368

I-150	(*S*)-*N*-hydroxy-1'-(2-methoxypyridin-4-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368
I-170	(*S*)-*N*-hydroxy-1'-(1-methyl-1H-pyrazol-4-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		341
I-118	(*S*)-*N*-hydroxy-1'-(6-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368
I-115	*(S)*-N-hydroxy-1'-(2-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		367
I-126	(2*S*)-1'-(2-fluoro-3-methoxyphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-127	(2*S*)-1'-(2-fluoro-4-methoxyphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-129	(2*S*)-1'-(4-fluoro-3-methoxyphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-137	*(S)*-N-hydroxy-1'-(4-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		352
I-144	(2*S*)-*N*-hydroxy-1'-(5-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		368
I-147	(2*S*)-1'-(2-fluoro-5-methoxyphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385
I-148	(2*S*)-1'-(3-fluoro-5-methoxyphenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		385

I-152	(2*S*)-1'-[6-(dimethylamino)pyridin-3-yl]-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		381
I-153	(2*S*)-1'-(5-fluoropyridin-3-yl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		356

Example 28 – Preparation of (R)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-119)



***Step-1*: Methyl (R)-1'-(3,4-difluorophenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00182] A 2-dram vial was charged with (Xantphos)$PdCl_2$ (0.02 M, 0.150 mL, 0.30 μmol) in CH_2Cl_2. The solvent was then evaporated under a stream of N_2. Next 4-bromo-1,2-difluorobenzene in 1,4-dioxane (0.2 M, 0.200 mL, 0.030 mmol) was added followed by Cs_2CO_3 (39 mg, 0.120 mmol). The vial was capped and carried into an inert atmosphere glovebox where a solution of methyl (R)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate in dioxane/Et_3N (98:2, 0.20 M, 0.200 mL, 0.030 mmol) was added. The vial was capped and heated at 100 °C for 16 h. The solvent was removed under a stream of N_2. The residue was diluted with brine (0.50 mL) and extracted with EtOAc (2 x 0.50 mL). The combined organic layers were dried under a stream of N_2.

***Step-2*: (R)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide**

[00183] The residue was dissolved in THF/MeOH (3:1, 0.20 mL). The vial was sealed and shaken at 50 °C for 15 min to dissolve the residue, then cooled to room temperature. NH_2OH (50% v/v solution in water, 0.150 mL) was added, followed by 1N aq NaOH (0.10 mL). The mixture was sealed and then shaken at room temperature for 18 h. The reaction mixture was concentrated under a stream of N_2 at room temperature, then dissolved in 0.50 mL of DMSO and purified by reverse-phase chromatography HPLC Column: Waters Sunfire C18, 5μm, 19x50mm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN/0.1% Formic acid;

Gradient: 15% B to 100% B in 6 min; Flow rate: 23 mL/min; Detector: UV 254 nm, 220 nm. The product-containing fractions were combined and concentrated in a Genevac to afford 3.3mg (28% yield) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.70 (br s, 1H), 7.77 (ddd, *J* = 12, 7.0, 2.7 Hz, 1H), 7.56 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.33-7.29 (m, 1H), 7.20 (d, *J* = 10 Hz, 1H), 7.15 (d, *J* = 10 Hz, 1H), 3.82 (t, *J* = 6.6 Hz, 2H), 3.15 (d, *J* = 17 Hz, 1H), 3.06-2.99 (m, 1H), 2.94-2.85 (m, 1H), 2.75 (d, *J* = 17 Hz, 1H), 2.18-1.94 (m, 3H), 1.88-1.82 (m, 1H). MS: (ES, *m/z*) 373 $[M+H]^+$.

Table-16: The following compounds were prepared according to the parallel synthesis method of Example 28.

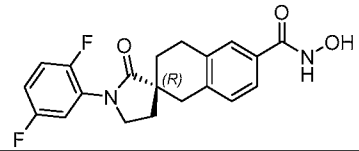
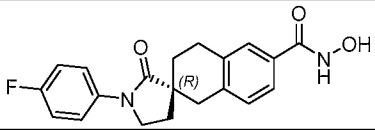
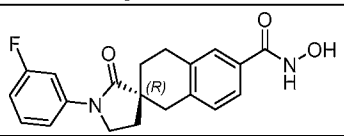
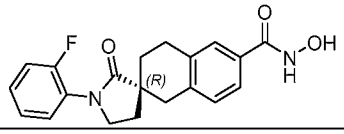
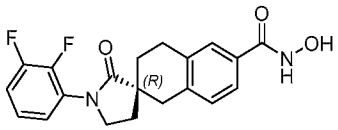
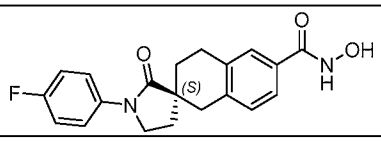
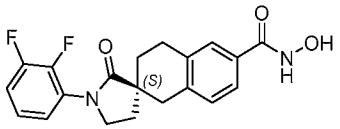
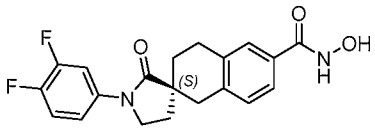
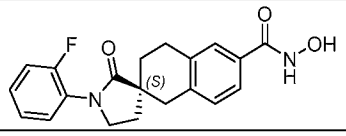
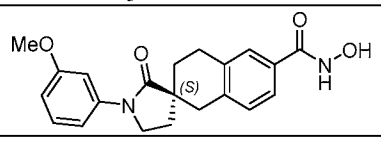
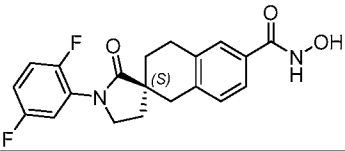
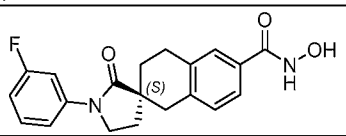
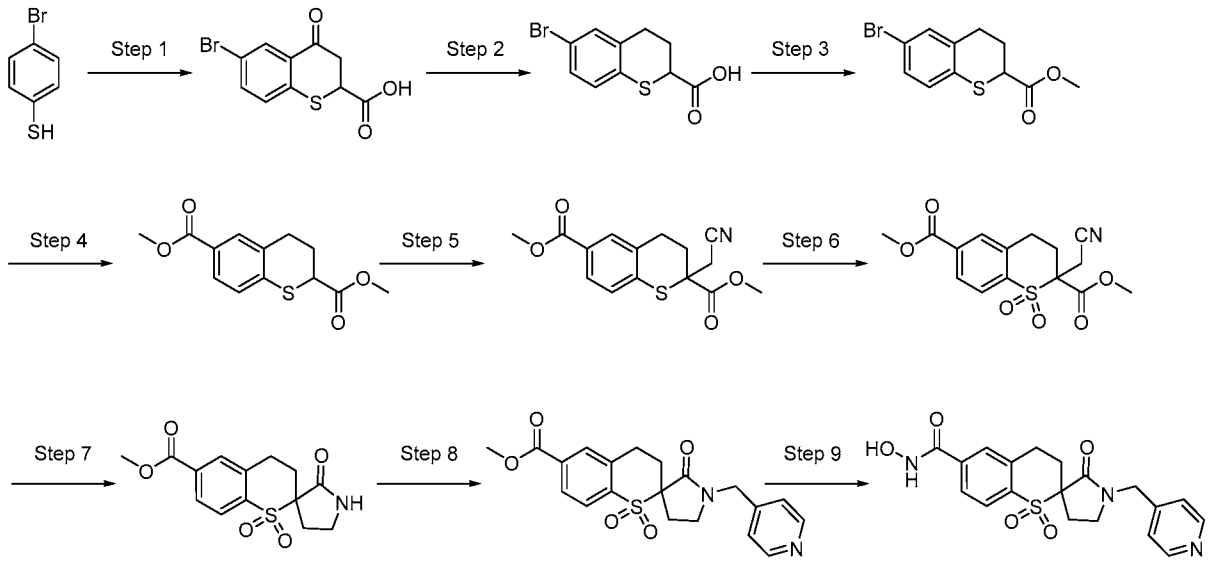
Ex.	Name	Structure	Found (ES, *m/z*) $[M+H]^+$
I-167	(*R*)-1'-(2,5-difluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		373
I-120	(*R*)-1'-(4-fluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		355
I-113	(*R*)-1'-(3-fluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		355
I-121	(*R*)-1'-(2-fluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		355
I-123	(*R*)-1'-(2,3-difluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		373

Table-17: The following compounds were prepared according to the synthesis method of Example 28, using methyl (S)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate in Step 1.

Ex.	Name	Structure	Found (ES, *m/z*) $[M+H]^+$

I-154	(*S*)-1'-(4-fluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		355
I-156	(*S*)-1'-(2,3-difluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		373
I-155	(*S*)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		373
I-157	(*S*)-1'-(2-fluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		355
I-158	(*S*)-*N*-hydroxy-1'-(3-methoxyphenyl)-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		367
I-169	(*S*)-1'-(2,5-difluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		373
I-117	(*S*)-1'-(3-fluorophenyl)-*N*-hydroxy-2'-oxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide		355

Example 29 – Preparation of N-hydroxy-2-oxo-1-(pyridin-4-ylmethyl)spiro[pyrrolidine-3,2'-thiochromane]-6'- carboxamide 1',1'-dioxide (I-242)



***Step-1*: 6-Bromo-4-oxothiochromane-2-carboxylic acid**

[00184] In a 100-mL 3-necked round-bottom flask 4-bromobenzenethiol (20.0 g, 105.78 mmol, 1 equiv) in toluene (25 mL) and 2,5-dihydrofuran-2,5-dione (12.96 g, 132.17 mmol, 1 equiv) were stirred at 50 °C for 1 h. A solution of Et_3N (27.6 mg, 0.28 mmol) in toluene (0.4 mL) was then added, ensuring the reaction temperature did not increase over 60 °C. The reaction was heated at 70 °C for 50 min. The reaction was then concentrated under high vacuum. The residue was dissolved in CH_2Cl_2 (109 mL), cooled to 0 °C in an ice bath and treated with $AlCl_3$ (14.52 g, 108.89 mmol, 1.03 equiv). The reaction was slowly warmed to room temperature. After stirring for 3 h the reaction mixture was then diluted with CH_2Cl_2 (18 mL) and slowly poured into vigorously stirred concentrated HCl (44 mL) and ice (44 g). The reaction was vigorously stirred and diluted with CH_2Cl_2 (500 mL) and isopropanol (72 mL). The CH_2Cl_2 layer was separated, dried over magnesium sulfate, filtered and concentrated in vacuum. The mixture was triturated with Et_2O and then filtered to give 6.64 g (22% yield) of the title compound as a light yellow solid. MS: (ES, *m/z*): 285 $[M+H]^+$.

***Step-2*: 6-Bromothiochromane-2-carboxylic acid**

[00185] Into a 500-mL round-bottom flask was placed a solution of 6-bromo-4-oxothiochromane-2-carboxylic acid (4.0 g, 13.93 mmol, 1 equiv) in TFA (200 mL). This was followed by the addition of triethylsilane (16 g, 137.60 mmol, 10 equiv) at 0 °C. The resulting solution was stirred for 19 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was dissolved in 100 mL of CH_2Cl_2 and washed with 2x40 mL of H_2O, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in 30 mL of H_2O. The pH of the solution was adjusted to 9 with aq. NaOH. The resulting solution was washed with 2x50 mL of CH_2Cl_2 and the aqueous layers combined. 6N aq. HCl was employed to adjust the pH to 4. The resulting solution was extracted with 3x70 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and then concentrated under vacuum to give 1.42 g (37% yield) of the title compound as a light yellow solid. MS: (ES, *m/z*): 271 $[M+H]^+$.

***Step-3*: Methyl 6-bromothiochromane-2-carboxylate**

[00186] Into a 50-mL round-bottom flask was placed a solution of 6-bromothiochromane-2-carboxylic acid (1.42 g, 5.20 mmol, 1 equiv) in MeOH (15 mL) and concentrated sulfuric acid

(2.84 mL). The resulting solution was stirred for 15 h at 70 °C. The resulting mixture was concentrated under vacuum. The residue was dissolved in 100 mL of CH_2Cl_2. The resulting mixture was washed with 2x50 mL of H_2O, washed with 3x50 mL of $NaHCO_3$ and 2x50 mL of brine. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give 1.28 g (86% yield) of the title compound as a yellow solid. MS: (ES, *m/z*): 285 $[M+H]^+$.

***Step-4*: Dimethyl thiochromane-2,6-dicarboxylate**

[00187] Into a 50-mL pressure tank reactor (30 atm), was placed a solution of methyl 6-bromothiochromane-2-carboxylate (1.28 g, 4.47 mmol, 1 equiv) in MeOH (15 mL), Et_3N (1.85 mL), and $Pd(dppf)Cl_2$ (655 mg, 0.90 mmol, 0.20 equiv). CO (g) was introduced into the reactor. The resulting solution was stirred for 2 days at 100 °C. The resulting mixture was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:3). The collected fractions were concentrated to give 811 mg (68% yield) of the title compound as a light brown solid. MS: (ES, *m/z*): 267 $[M+H]^+$.

***Step-5*: Dimethyl 2-(cyanomethyl)thiochromane-2,6-dicarboxylate**

[00188] Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of dimethyl thiochromane-2,6-dicarboxylate (1.55 g, 5.83 mmol, 1 equiv) in THF (20 mL). This was followed by the addition of LDA (7 mL, 1.2 equiv) at -78 °C over 30 min. To this was added 2-bromoacetonitrile (910.6 mg, 7.59 mmol, 1.3 equiv) at -78 °C. The resulting solution was stirred for 1.5 h at the same temperature. The reaction was then quenched by the addition of 35 mL of sat. aq.NH_4Cl. The resulting solution was extracted with 2x100 mL of EtOAc. The organic layers were combined and concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:3). The collected fractions were concentrated to give 1.51 g (85% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 304 $[M-H]^-$.

***Step-6*: Dimethyl 2-(cyanomethyl)thiochromane-2,6-dicarboxylate 1,1-dioxide**

[00189] Into a 250-mL round-bottom flask was placed a solution of dimethyl 2-(cyanomethyl)thiochromane-2,6-dicarboxylate (1.51 g, 4.95 mmol, 1 equiv) in CH_2Cl_2 (150 mL). This was followed by the addition of a solution of m-CPBA (2.57 g, 14.87 mmol, 3 equiv) in CH_2Cl_2 (10 mL) at 0 °C . The resulting mixture was stirred for 14 h at room temperature. Then

K_2CO_3 (1 g) was added and the reaction stirred for 1 h at room temperature. The solids were filtered out. The solid was washed with 100 mL of CH_2Cl_2. The filtrate was concentrated under vacuum to give 1.79 g (crude) of the title compound as a yellow oil. MS: (ES, *m/z*): 336 $[M-H]^-$.

***Step-7*: Methyl 2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide**

[00190] Into a 500-mL round-bottom flask was placed a solution of dimethyl 2-(cyanomethyl)thiochromane-2,6-dicarboxylate 1,1-dioxide (1.79 g, 5.31 mmol, 1 equiv) in MeOH (150 mL), PtO_2 (675 mg, 2.97 mmol, 0.6 equiv), and acetic acid (33.4 mL). Hydrogen (g) was introduced. The resulting solution was stirred for 1 day at room temperature. The solids were filtered out and the filtrate was concentrated under vacuum. The pH of the solution was adjusted to 9 with aq. Na_2CO_3. The resulting solution was extracted with 3x100 mL of CH_2Cl_2, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum to give 1.27 g (78% yield) of the title compound as a gray solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 8.06-8.01 (m, 3H), 6.00 (s, 1H), 3.97 (s, 3H), 3.71-3.55 (m, 2H), 3.49-3.43 (m, 1H), 3.16-3.05 (m, 2H), 2.71-2.63 (m, 2H), 2.31-2.23 (m, 1H). MS: (ES, *m/z*): 310 $[M+H]^+$.

***Step-8*: 2-Oxo-1-(pyridin-4-ylmethyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylic acid 1',1'-dioxide**

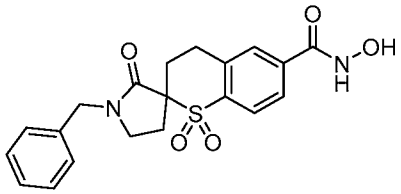
[00191] Into an 8-mL vial, was placed a solution of methyl 2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide (100 mg, 0.32mmol, 1 equiv) in DMF (3 mL). This was followed by the addition of NaH (60% dispersion in oil, 65 mg, 2.71 mmol, 5 equiv) at 0 °C over 10 min. To this was added 4-(bromomethyl) pyridine hydrobromide (163 mg, 0.64 mmol, 2 equiv). The resulting mixture was stirred for 18 h at room temperature. The reaction was then quenched by the addition of NH_4Cl (aq.). The resulting solution was extracted with 2x20 mL of EtOAc and the aqueous layers combined. The pH of the aqueous layers was adjusted to 4 with 1N aq. HCl. The resulting solution was extracted with 3x20 mL of CH_2Cl_2, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give 30 mg (24% yield) of the title compound as a light brown oil which was used in the next step without purification. MS: (ES, *m/z*): 387 $[M+H]^+$.

***Step-9*: N-Hydroxy-2-oxo-1-(pyridin-4-ylmethyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide**

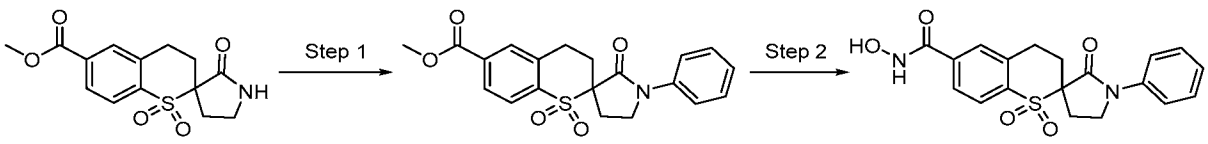
[00192] Into an 8-mL vial, was placed a solution of 2-oxo-1-(pyridin-4-ylmethyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylic acid 1',1'-dioxide (55 mg, 0.14

mmol, 1 equiv) in DMA (1.5 mL). This was followed by the dropwise addition of isopropyl chloroformate (90 mg, 0.71 mmol, 5 equiv) with stirring at 0 °C over 15 min. NMM (72 mg, 0.71 mmol, 5 equiv) was added dropwise with stirring at 0 °C. The mixture was stirred for 15 min at 0 °C. A solution of NH_2OH•HCl (50 mg, 0.71 mmol, 5 equiv) in DMA (0.5 mL) was added to the stirring mixture. The resulting solution was stirred for 19 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Sunfire Prep C18, 5 μm, 19x100mm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 25 ml/min; Gradient: 4% B to 58% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 8 mg (11% yield) of the title compound as a brown solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.41 (br s, 1H), 8.66 (s, 2H), 7.90-7.88 (m, 1H), 7.80-7.74 (m, 2H), 7.48 (s, 2H), 4.74-4.70 (m, 1H), 4.52-4.44 (m, 1H), 3.42-3.33 (m, 2H), 3.16-3.04 (m, 2H), 2.75-2.67 (m, 3H), 2.37-2.29 (m, 1H). MS: (ES, *m/z*): 402 $[M+H]^+$.

Table-18: The following compound was prepared according to the method of Example 29.

Ex.	**Structure**	**^{1}H-NMR δ (ppm)**	**Found (ES, *m/z*) $[M+H]^+$**
I-239		(400 MHz , DMSO-d6): 11.41 (br s, 1H), 7.89-7.87 (d, *J* = 8.0 Hz, 1H), 7.79-7.74 (m, 2H), 7.37-7.24 (m, 5H), 4.58-4.55 (d, *J* = 12.0 Hz, 1H), 4.35-4.31 (d, *J* = 16.0 Hz, 1H), 3.41-3.29 (m, 3H), 3.10-3.02 (m, 1H), 2.70-2.61 (m, 2H), 2.48-2.43 (m, 1H), 2.28-2.21 (m, 1H)	401

Example 30 – Preparation of N-hydroxy-2-oxo-1-phenylspiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-238)



***Step-1*: Methyl 2-oxo-1-phenylspiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide**

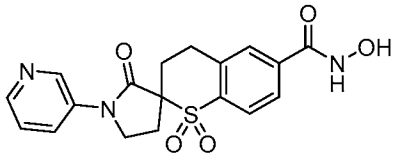
[00193] Into a 25-mL vial purged and maintained with an inert atmosphere of nitrogen, were placed methyl 2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide (100 mg, 0.32 mmol, 1 equiv), Cs_2CO_3 (211 mg, 0.65 mmol, 2 equiv) in 1,4-dioxane (6 mL), XantPhos (41 mg, 0.07 mmol, 0.22 equiv), iodobenzene (79 mg, 0.39 mmol, 1.2 equiv), and $Pd(OAc)_2$ (7.3 mg, 0.03 mmol, 0.1 equiv). The resulting mixture was stirred for 17 h at 100 °C and then concentrated under vacuum. The residue was dissolved in 30 mL of EtOAc and washed with 3x20 mL of H_2O. The organics were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (5:6). The collected fractions were concentrated to give 60.5 mg (49% yield) of the title compound as a light brown oil. MS: (ES, *m/z*): 386 $[M+H]^+$.

***Step-2*: N-Hydroxy-2-oxo-1-phenylspiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide**

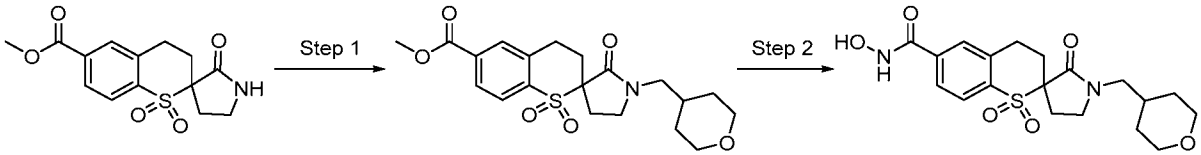
[00194] Into an 8-mL vial, was placed a solution of methyl 2-oxo-1-phenylspiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide (60.5 mg, 0.16 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), NH_2OH (50% in H_2O, 0.31 mL, 30 equiv) and 1N aq. NaOH (0.31 mL, 2 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Xbridge C18, 5 μm, 19x100mm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 25 mL/min; Gradient: 5% B to 57% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 45.9 mg (76% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.42 (br s, 1H), 7.90-7.87 (d, *J* = 12.0 Hz, 1H), 7.80-7.76 (m, 2H), 7.66-7.64 (d, *J* = 8.0 Hz, 2H), 7.43-7.38 (m, 2H), 7.26-7.18 (m, 1H), 4.09-3.89 (m, 2H), 3.40-3.30 (m, 1H), 3.19-3.05 (m, 1H), 2.84-2.75 (m, 2H), 2.57-2.55 (m, 1H), 2.44-2.39 (m, 1H). MS: (ES, *m/z*): 387 $[M+H]^+$.

Table-19: The following compound was prepared according to the method of Example 30.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$

I-240		(400 MHz , DMSO-d6): 11.43 (br s, 1H), 8.95-8.94 (d, *J* = 4.0 Hz, 1H), 8.46-8.45 (d, *J* = 4 Hz, 1H), 8.20-8.17 (d, *J* = 12 Hz, 1H), 7.91-7.88(d, *J* = 12 Hz, 1H), 7.81-7.77 (m, 2H), 7.57-7.52 (m, 1H), 4.06-4.01 (m, 2H), 3.40-3.29 (m, 1H), 3.16-3.06 (m, 1H), 2.89-2.77 (m 2H), 2.59-2.56 (m, 1H), 2.46-2.39 (m, 1H)	388

Example 31 – Preparation of N-hydroxy-2-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)spiro[pyrrolidine-3,2'- thiochromane]-6'-carboxamide 1',1'-dioxide (I-241)



***Step-1*: Methyl 2-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)spiro[pyrrolidine-3,2'-thiochromane]-6'- carboxylate 1',1'-dioxide**

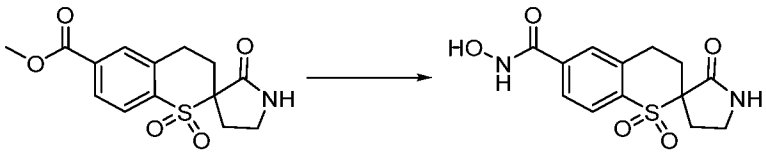
[00195] Into a 25-mL vial, was placed a solution of methyl 2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide (150 mg, 0.48 mmol, 1 equiv) in DMF (4 mL). This was followed by the addition of NaH (60% dispersion in oil, 39 mg, 1.62 mmol, 2 equiv) at 0 °C over 10 min. 4-(Bromomethyl)oxane (261 mg, 1.46 mmol, 3 equiv) was then added. The resulting solution was stirred for 4 h at room temperature. The reaction was quenched with a solution of aq. NH_4Cl. The resulting solution was extracted with 3x20 mL of EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give 144.8 mg (73% yield) of the title compound as a light yellow oil. MS: (ES, *m/z*): 408 $[M+H]^+$.

***Step-2*: N-Hydroxy-2-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide**

[00196] Into an 8-mL vial, was placed a solution of methyl 2-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide (100 mg, 0.25 mmol, 1 equiv) in THF/MeOH (4:1, 3 mL), NH_2OH (50% in H_2O, 0.48 mL, 30 equiv), and aq. NaOH (1N, 0.49 mL, 2 equiv). The resulting solution was stirred for 5 h at room temperature. The crude

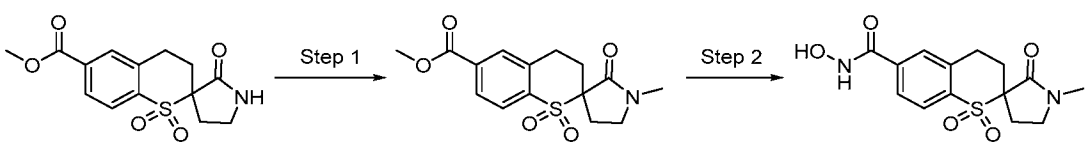
product was purified by Prep-HPLC with the following conditions: Column: Xbridge C18, 19x150mm, 5 μm; Mobile Phase A: Water/0.05% TFA, CH_3CN/0.05% TFA; Flow rate: 25 mL/min; Gradient: 5% B to 57% B in 6 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 15 mg (15% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.40 (br s, 1H), 7.85-7.83 (d, *J* = 8.0 Hz, 1H), 7.77-7.71 (m, 2H), 3.83-3.80 (m, 2H), 3.50-3.44 (m, 3H), 3.35-3.24 (m, 3H), 3.05-2.98 (m, 2H), 2.67-2.63 (m, 2H), 2.42-2.40 (m, 1H), 2.24-2.22 (m, 1H), 1.89-1.79 (m, 1H), 1.56-1.48 (m, 2H), 1.14-1.05 (m, 2H). MS: (ES, *m/z*): 409 $[M+H]^+$.

Example 32 – Preparation of N-hydroxy-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-243)



[00197] Into an 8-mL vial, was placed a solution of methyl 2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide (50 mg, 0.16 mmol, 1 equiv) in THF/MeOH (4:1, 1 mL), NH_2OH (50% in H_2O, 0.48 mL, 30 equiv), and 1N aq. NaOH (0.32 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Xbridge C18, 19x150mm, 5 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 25 mL/min; Gradient: 5% B to 57% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 4.6 mg (9% yield) of the title compound as a brown oil. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.39 (br s, 1H), 9.21 (br s, 1H), 8.35 (s, 1H), 7.86-7.84 (d, *J* = 8.0 Hz, 1H), 7.77-7.75 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 3.33-3.27 (m, 3H), 3.05-2.98 (m, 1H), 2.71- 2.60 (m, 2H), 2.43-2.32 (m, 1H), 2.27-2.20 (m, 1H). MS: (ES, *m/z*): 311 $[M+H]^+$.

Example 33 – Preparation of N-hydroxy-1-methyl-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-244)



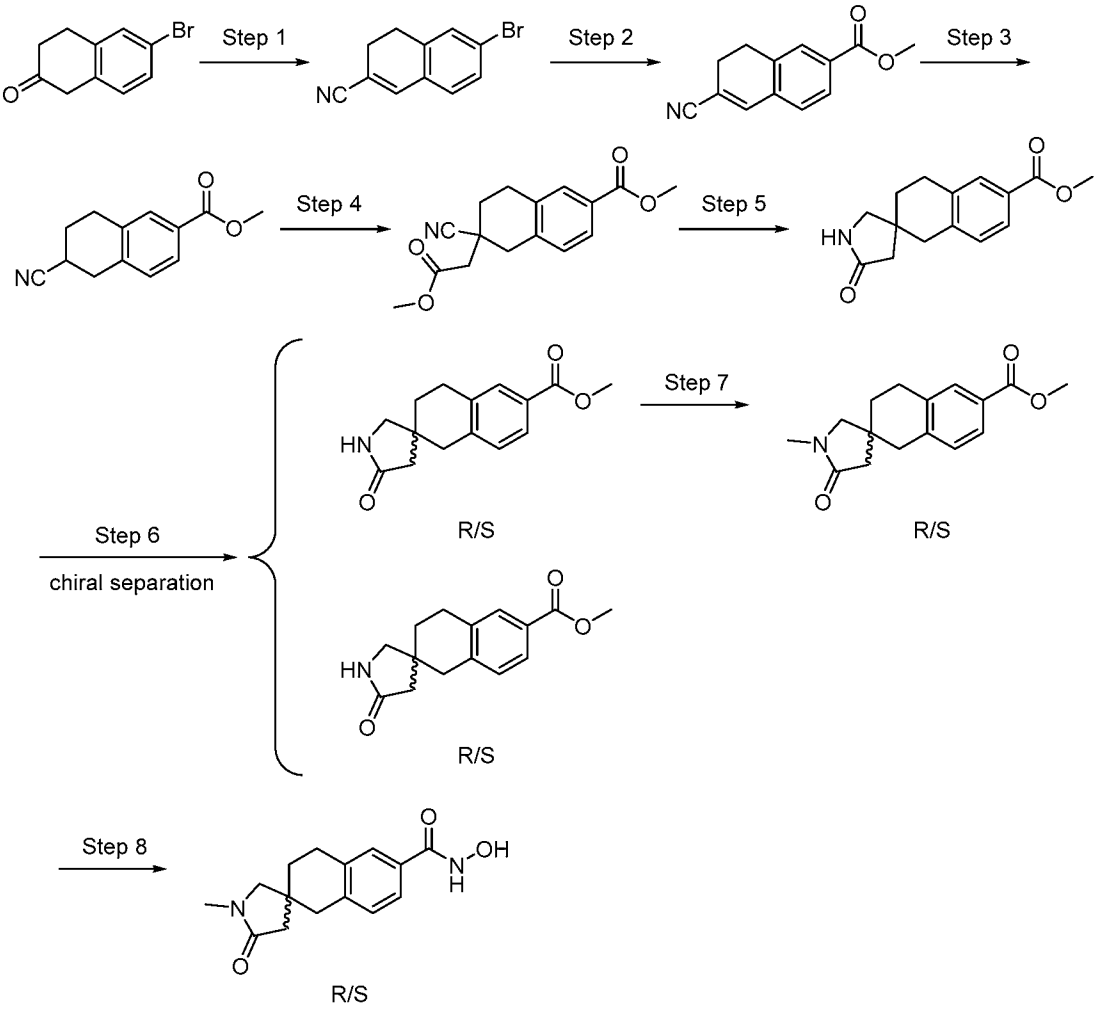
***Step-1*: Methyl 1-methyl-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide**

[00198] Into an 8-mL vial, was placed a solution of methyl 2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide (80 mg, 0.26 mmol, 1 equiv) in DMF (3 mL) and Cs_2CO_3 (104 mg, 0.75 mmol, 3 equiv). This was followed by the dropwise addition of CH_3I (74 mg, 0.52 mmol, 2 equiv) with stirring at 0 °C. The resulting mixture was stirred for 14 h at room temperature. The reaction was diluted with 20 mL of water and extracted with 2x20 mL of CH_2Cl_2. The organic layers were combined and washed with 3x10 mL of H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with CH_2Cl_2/MeOH (25:1) to give 46.4 mg (55% yield) of the title compound as a light yellow oil. MS: (ES, *m/z*): 324 $[M+H]^+$.

***Step-2*: N-Hydroxy-1-methyl-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide**

[00199] Into an 8-mL vial, was placed a solution of methyl 1-methyl-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxylate 1',1'-dioxide (46.4 mg, 0.14 mmol, 1 equiv) in THF/MeOH (4:1, 1.5 mL), NH_2OH (50% in H_2O, 0.28 mL, 30 equiv), and 1N aq. NaOH (0.29 mL, 2 equiv). The resulting solution was stirred for 3 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Xbridge C18, 19x150mm, 5 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 25 mL/min; Gradient: 4% B to 56% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 14.4 mg (23% yield) of the title compound as a brown oil. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.40 (br s, 1H), 9.21 (br s, 1H), 7.85-7.71 (m, 3H), 3.45-3.41 (m, 3H), 3.05-2.98 (m, 1H), 2.78 (s, 3H), 2.66-2.59 (m, 2H), 2.49-2.41 (m, 1H), 2.20-2.19 (m, 1H). MS: (ES, *m/z*): 325 $[M+H]^+$.

Example 34 – Preparation of (R)-N-hydroxy-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-201)



***Step-1*: 6-Bromo-3,4-dihydronaphthalene-2-carbonitrile**

[00200] Into a 500-mL round-bottom flask, was placed a solution of 6-bromo-3,4-dihydronaphthalen-2(1H)-one (15.00 g, 66.64 mmol, 1 equiv) in toluene (150 mL), TMSCN (7.29 g, 1 equiv), and ZnI_2 (513 mg, 0.02 equiv). The resulting solution was stirred overnight at 25 °C. Then pyrazine (100 mL) and $POCl_3$ (30 mL) were added to the solution and allowed to react with stirring for 4 h at 110 °C. The reaction was then quenched by the addition of 1000 mL of 10% HCl aqueous solution at 0 °C. The resulting solution was extracted with 3x500 mL of EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel

with EtOAc/petroleum ether (1:10). The collected fractions were concentrated under vacuum to give 6 g (38% yield) of the title compound as a yellow solid. MS: (ES, *m/z*): 234 $[M+H]^+$.

***Step-2*: Methyl 6-cyano-7,8-dihydronaphthalene-2-carboxylate**

[00201] Into a 100-mL pressure tank reactor (60 atm), was placed a solution of 6-bromo-3,4-dihydronaphthalene-2-carbonitrile (6.00 g, 25.63 mmol, 1 equiv) in MeOH (40 mL), $Pd(dppf)Cl_2$ (1.88 g, 2.57 mmol, 0.10 equiv) and Et_3N (7.80 g, 77.08 mmol, 3 equiv). CO (g) was introduced to the flask. The resulting solution was stirred overnight at 130 °C. The resulting mixture was concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with EtOAc/petroleum ether (1:3). The collected fractions were concentrated under vacuum to give 4.0 g (73% yield) of the title compound as a yellow solid. MS: (ES, *m/z*): 214 $[M+H]^+$.

***Step-3*: Methyl 6-cyano-5,6,7,8-tetrahydronaphthalene-2-carboxylate**

[00202] Into a 500-mL round-bottom flask, was placed a solution of methyl 6-cyano-7,8-dihydronaphthalene-2-carboxylate (3.00 g, 14.07 mmol, 1 equiv) in MeOH (200 mL). Then magnesium (3.38 g, 139.07 mmol, 10 equiv) was added at 0 °C. The resulting solution was stirred for 30 min at 0 °C. The resulting mixture was the poured into 100 mL of water and MeOH was evaporated under vacuum. The pH of the solution was adjusted to 3 with 2N HCl at 0 °C. The resulting solution was extracted with 3x100 mL of CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with EtOAc/petroleum ether (1:10). The collected fractions were concentrated under vacuum to give 1.9 g (63% yield) of the title compound as a white solid. MS: (ES, *m/z*): 216 $[M+H]^+$.

***Step-4*: Methyl 6-cyano-6-(2-methoxy-2-oxoethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate**

[00203] Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl 6-cyano-5,6,7,8-tetrahydronaphthalene-2-carboxylate (1.50 g, 6.97 mmol, 1 equiv) in THF (90 mL). LDA (2M in THF, 13.95 mL, 2 equiv) was added dropwise into the solution at -78 °C. The resulting solution was stirred for 1 h at -78 °C. 2-Bromoacetate (2.12 g, 1 equiv) was the added dropwise into the solution at -78 °C. The resulting solution was allowed to react with stirring for 3 h at 25 °C. The reaction was then

quenched by the addition of 150 mL of aq. NH_4Cl solution, then extracted with 3x100 mL of EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with EtOAc/petroleum ether (1:5). The collected fractions were concentrated under vacuum to give 450 mg (22% yield) of the title compound as a yellow solid. MS: (ES, *m/z*): 288 $[M+H]^+$.

***Step-5*: Methyl 5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00204] Into a 100-mL round-bottom flask, was placed a solution of methyl 6-cyano-6-(2-methoxy-2-oxoethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (550 mg, 1.91 mmol, 1 equiv) in MeOH (25 mL), PtO_2 (225 mg, 0.99 mmol), and AcOH (5 mL, 87.26 mmol). Hydrogen gas was introduced into the flask and the resulting solution was stirred for 1 h at 25 °C. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was dissolved in 7M NH_3 in MeOH (25 mL) and allowed to react with stirring for 1 h at 25 °C. The resulting mixture was concentrated under vacuum and the residue was purified by normal phase column chromatography on silica gel with CH_2Cl_2/MeOH (100:1). The collected fractions were concentrated under vacuum to give 250 mg (50% yield) of the title compound as a white solid. MS: (ES, *m/z*): 260 $[M+H]^+$.

***Step-6*: Chiral separation of methyl (R)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate and methyl (S)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00205] 250 mg of the racemate methyl 5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate was separated by Chiral-Prep-HPLC with the following conditions: Column: Phenomenex Lux 5u Cellulose-4AXIA Packed, 250x21.2mm, 5 μm; Mobile Phase A: Hexanes, Mobile Phase B: EtOH; Gradient: hold 30% B in 25 min; Detector: UV 254 nm, 220 nm. The first eluting isomer (Rt 3.626 min) was collected and concentrated under vacuum to give 105 mg (42% yield) of a white solid which was assigned as the R isomer of methyl 5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate. MS: (ES, *m/z*): 260 $[M+H]^+$. The second eluting isomer (Rt 4.410 min) was collected and concentrated under vacuum to give 100 mg (40% yield) of a white solid which was assigned as the S isomer of methyl 5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as a white solid. MS: (ES, *m/z*): 260 $[M+H]^+$.

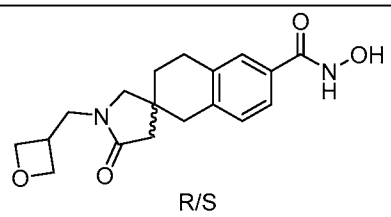
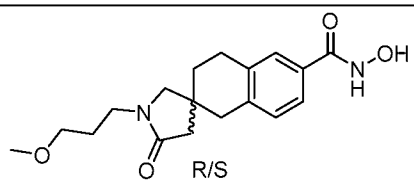
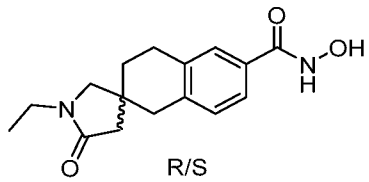
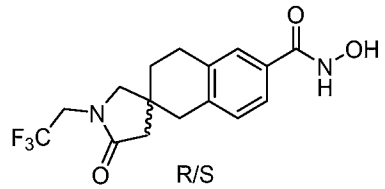
***Step-7*: Methyl (R)-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00206] Into a 10-mL round-bottom flask, was placed a solution of the first eluted isomer from Step 6, which was assigned as methyl (R)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (50 mg, 0.19 mmol, 1 equiv) in DMF (2 mL). NaH (60% dispersion in oil, 9 mg, 2 equiv) was added into the solution at 0 °C. The resulting mixture was stirred for 1 h at 25 °C. Iodomethane (55 mg, 0.39 mmol, 2 equiv) was added into the solution and the resulting solution was allowed to react with stirring for 1 h at 25 °C. The reaction was then quenched by the addition of 15 mL of water, extracted with 3x15 mL of EtOAc. The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 50 mg (90% yield) of the title compound as a yellow solid. MS: (ES, *m/z*): 274 $[M+H]^+$.

***Step-8*: (R)-N-Hydroxy-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00207] Into a 10-mL round-bottom flask, was placed a solution of the product from Step 7, which was assigned as methyl (R)-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (50 mg, 0.18 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), NH_2OH (50% in water, 725 mg, 14.20 mmol, 120 equiv), and 1N aq. NaOH (14.4 mg, 0.36 mmol, 2 equiv). The resulting solution was stirred for 2 h at 25 °C. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 19x150mm 5 μm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN; Gradient: 5% B to 30% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 17.9 mg (36% yield) of the title compound as a light pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.08 (s, 1H), 8.95 (s, 1H), 7.51 (s, 1H), 7.47-7.45 (d, J = 8.0 Hz, 1H), 7.13-7.11 (d, J = 8.0 Hz, 1H), 3.24-3.22 (d, J = 9.6 Hz, 1H), 3.08-3.05 (d, J = 9.6 Hz, 1H), 2.86-2.82 (m, 2H), 2.78-2.76 (d, J = 8.4 Hz, 2H), 2.71 (s, 3H), 2.27-2.23 (d, J = 16.4 Hz, 1H), 2.03-1.99 (d, J = 16.4 Hz, 1H), 1.80-1.76 (m, 2H). MS: (ES, *m/z*): 275 $[M+H]^+$.

Table-20: The following compounds were prepared according to the method of Example 34, with the following modifications: (1) In Step 7, the first eluted product from Step 6 was used; (2) in Step 7, the halide can be an iodide, a chloride, or a bromide.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-215		(300 MHz, DMSO-d6): 7.51 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 4.64-4.59 (m, 2H), 4.31-4.26 (m, 2H), 3.49 (d, *J* = 7.5 Hz, 2H), 3.21-3.11 (m, 2H), 3.05 (d, *J* = 9.6 Hz, 1H), 2.86-2.82 (m, 2H), 2.75 (s, 2H), 2.27 (d, *J* = 16.5 Hz, 1H), 2.04 (d, *J* = 16.5 Hz, 1H), 1.79-1.75 (m, 2H)	331
I-219		(300 MHz, DMSO-d6+D_2O): 7.51 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 3.29-3.18 (m, 8H), 3.08 (d, *J* = 9.6 Hz, 1H), 2.87-2.83 (m, 2H), 2.77-2.76 (m, 2H), 2.27 (d, *J* = 16.2 Hz, 1H), 2.04 (d, *J* = 16.5 Hz, 1H), 1.81-1.77 (m, 2H), 1.70-1.61 (m, 2H)	333
I-206		(300 MHz, DMSO-d6): 10.95 (s, 1H), 8.95 (s, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 3.32-3.17 (m, 3H), 3.08 (d, *J* = 9.9 Hz, 1H), 2.87-2.76 (m, 4H), 2.26 (d, *J* = 16.2 Hz, 1H), 2.03 (d, *J* = 16.5 Hz, 1H), 1.81-1.79 (m, 2H), 1.03-1.00 (m, 3H)	289
I-220		(300 MHz, DMSO-d6): 10.80 (s, 1H), 9.00 (s, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 4.11-4.02 (m, 2H), 3.38-3.35 (m, 1H), 3.25-3.22 (m, 1H), 2.87-2.83 (m, 2H), 2.80-1.73 (m, 2H), 2.37 (d, *J* = 16.8 Hz, 1H), 2.15 (d, *J* = 16.8 Hz, 1H), 1.81-1.79 (m, 2H)	343

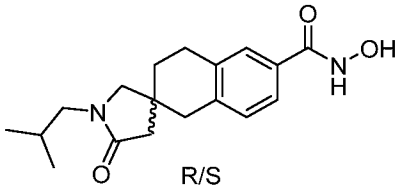
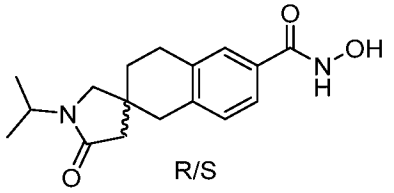
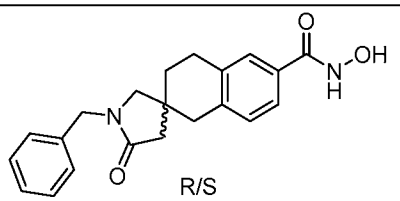
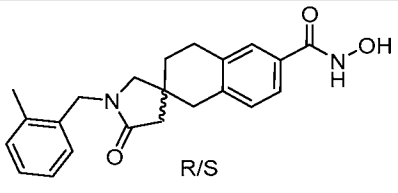
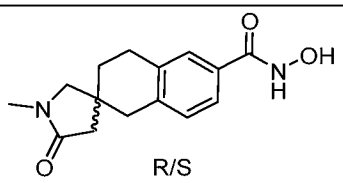
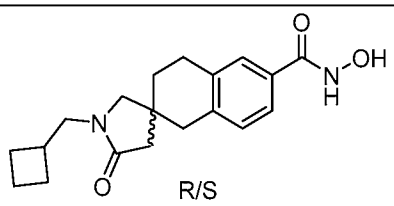
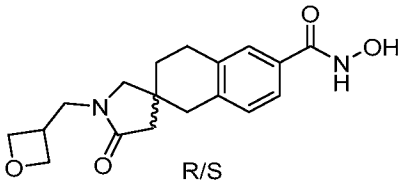
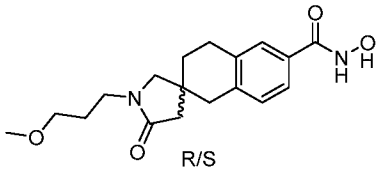
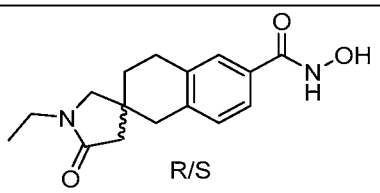
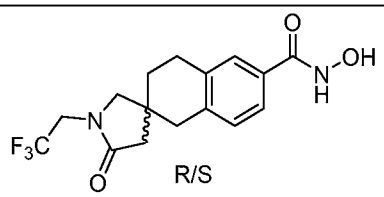
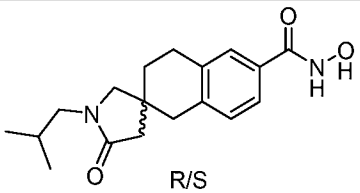
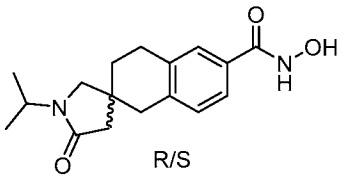
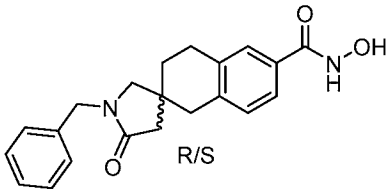
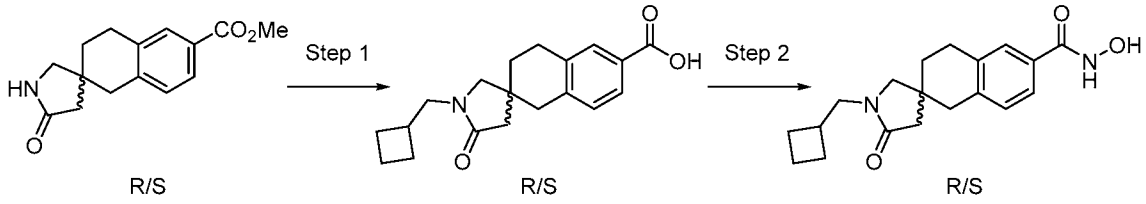
I-207		(400 MHz, DMSO-d6): 11.11 (s, 1H), 8.98 (s, 1H), 7.53-7.47 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 3.24 (d, *J* = 9.6 Hz, 1H), 3.09 (d, *J* = 9.6 Hz, 1H), 2.99 (d, *J* = 7.6 Hz, 2H), 2.88-2.78 (m, 4H), 2.30 (d, *J* = 16.4 Hz, 1H), 2.07 (d, *J* = 16.4 Hz, 1H), 1.85-1.79 (m, 3H), 0.85-0.83 (m, 6H)	317
I-208		(400 MHz, DMSO-d6): 11.11 (s, 1H), 8.96 (s, 1H), 7.52-7.46 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 4.19-4.15 (m, 1H), 3.15 (d, *J* = 10.0 Hz, 1H), 3.03 (d, *J* = 9.6 Hz, 1H), 2.87-2.74 (m, 4H), 2.25 (d, *J* = 16.4 Hz, 1H), 2.03 (d, *J* = 16.4 Hz, 1H), 1.80-1.76 (m, 2H), 1.05-1.02 (m, 6H)	303
I-216		(400 MHz, DMSO-d6): 11.05 (s, 1H), 8.96 (s, 1H), 7.47 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.38-7.21 (m, 5H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 2H), 3.11 (d, *J* = 9.6 Hz, 1H), 2.96 (d, *J* = 9.6 Hz, 1H), 2.87-2.71 (m, 4H), 2.35 (d, *J* = 16.8 Hz, 1H), 2.13 (d, *J* = 16.8 Hz, 1H), 1.75 (s, 2H)	351
I-225		(400 MHz, DMSO-d6): 11.04 (br s, 1H), 8.96 (br s, 1H), 7.48-7.43 (m, 2H), 7.18-7.14 (m, 4H), 7.09 (d, *J* = 8 Hz, 1H), 4.39 (s, 2H), 3.05 (d, *J* = 10 Hz, 1H), 2.92 (d, *J* = 9.6 Hz, 1H), 2.87-2.71 (m, 4H), 2.37 (d, *J* = 16.4 Hz, 1H), 2.24 (s, 3H), 2.14 (d, *J* = 16.4 Hz, 1H), 1.79-1.74 (m, 2H)	365

Table-21: The following compounds were prepared according to the method of Example 34, with the following modifications: (1) In Step 7, the second eluted product from Step 6 was used; (2) In Step 7, the halide can be an iodide, a chloride, or a bromide.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-202		(300 MHz, DMSO-d6): 11.01 (s, 1H), 8.94 (s, 1H), 7.51 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 3.23 (d, *J* = 9.9 Hz, 1H), 3.07 (d, *J* = 9.9 Hz, 1H), 2.84 (m, 2H), 2.77-2.76 (m, 2H), 2.71 (s, 3H), 2.25 (d, *J* = 16.5 Hz, 1H), 2.02 (d, *J* = 16.5 Hz, 1H), 1.80-1.76 (m, 2H)	275
I-210		(300 MHz, DMSO-d6): 11.08 (br s, 1H), 8.95 (br s, 1H), 7.51-7.45 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 1H), 3.21-3.17 (m, 3H), 3.04 (d, *J* = 9.9 Hz, 1H), 2.85-2.81 (m, 2H), 2.75-2.65 (m, 2H), 2.50-2.41 (m, 1H), 2.25 (d, *J* = 16.5 Hz, 1H), 2.05-1.84 (m, 3H), 1.82-1.75 (m, 4H), 1.73-1.58 (m, 2H)	329
I-217		(300 MHz, DMSO-d6): 7.50-7.45 (m, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 4.63-4.58 (m, 2H), 4.30-4.25 (m, 2H), 3.49 (d, *J* = 7.5 Hz, 2H), 3.20-3.02 (m, 3H), 2.84-2.80 (m, 2H), 2.72 (s, 2H), 2.28-2.23 (m, 1H), 2.03 (d, *J* = 16.5 Hz, 1H), 1.77-1.73 (m, 2H)	331
I-222		(400 MHz, DMSO-d6): 7.50-7.45 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 3.74-3.20 (m, 8H), 3.10 (d, *J* = 9.6 Hz, 1H), 2.87-2.83 (m, 2H), 2.78 (d, *J* = 7.2 Hz, 2H), 2.29 (d, *J* = 16.4 Hz, 1H), 2.06 (d, *J* = 16.4 Hz, 1H), 1.80-1.78 (m, 2H), 1.70-1.63 (m, 2H)	333
I-211		(300 MHz, DMSO-d6): 11.09 (br s, 1H), 8.95 (br s, 1H), 7.51-7.45 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 1H), 3.25-3.16 (m, 3H), 3.08 (d, *J* = 9.6 Hz, 1H), 2.87-2.82 (m, 2H), 2.77-2.76 (m, 2H), 2.26 (d, *J* =	289

		16.2 Hz, 1H), 2.02 (d, *J* = 16.5 Hz, 1H), 1.81-1.76 (m, 2H), 1.02-0.97 (m, 3H)	
I-223		(300 MHz, DMSO-d6): 11.01 (br s, 1H), 9.04 (br s, 1H), 7.52-7.34 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 4.11-4.01 (m, 2H), 3.38 (s, 1H), 3.24 (d, *J* = 9.3 Hz, 1H), 2.85-2.78 (m, 4H), 2.37 (d, *J* = 16.5 Hz, 1H), 2.14 (d, *J* = 16.8 Hz, 1H), 1.83-1.79 (m, 2H)	343
I-212		(300 MHz, DMSO-d6): 11.10 (br s, 1H), 8.95 (br s, 1H), 7.51-7.45 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 1H), 3.22 (d, *J* = 9.9 Hz, 1H), 3.07 (d, *J* = 9.6 Hz, 1H), 2.98-2.91 (m, 2H), 2.87-2.83 (m, 2H), 2.77 (s, 2H), 2.29 (d, *J* = 16.5 Hz, 1H), 2.06 (d, *J* = 16.2 Hz, 1H), 1.88-1.69 (m, 3H), 0.83-0.80 (m, 6H)	317
I-213		(400 MHz, DMSO-d6): 11.10 (s, 1H), 8.95 (s, 1H), 7.52-7.46 (m, 2H), 7.13 (d, *J* = 8 Hz, 1H), 4.19-4.15 (m, 1H), 3.15 (d, *J* = 10 Hz, 1H), 3.03 (d, *J* = 9.6 Hz, 1H), 2.87-2.83 (m, 2H), 2.76-2.74 (m, 2H), 2.25 (d, *J* = 16.4 Hz, 1H), 2.03 (d, *J* = 16.4 Hz, 2H), 1.80-1.76 (m, 2H), 1.05-1.02 (m, 6H)	303
I-218		(300 MHz, DMSO-d6): 11.07 (br s, 1H), 8.97 (br s, 1H), 7.47-7.42 (m, 2H), 7.36-7.21 (m, 5H), 7.08 (d, *J* = 8.1 Hz, 1H), 4.37 (s, 2H), 3.11 (d, *J* = 9.9 Hz, 1H), 2.96 (d, *J* = 9.9 Hz, 1H), 2.89-2.74 (m, 4H), 2.36 (d, *J* = 16.5 Hz, 1H), 2.13 (d, *J* = 16.5 Hz, 1H), 1.78-1.73 (m, 2H)	351

Example 35 – Preparation of (R)-1'-(cyclobutylmethyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-205)



***Step-1*: (R)-1'-(Cyclobutylmethyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylic acid**

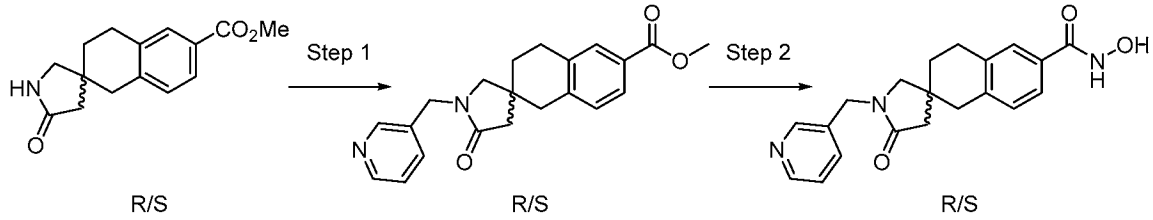
[00208] Into a 10-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of the first eluted isomer from Example 34, Step 6, which was assigned as methyl (R)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (50 mg, 0.19 mmol, 1 equiv) in DMF (2 mL). This was followed by the portionwise addition of NaH (60% dispersion in oil, 30 mg, 0.75 mmol, 3.89 equiv) at 0 °C. The mixture was stirred for 30 min at 25 °C. To this was added (bromomethyl)cyclobutane (115 mg, 0.77 mmol, 4 equiv). The resulting solution was stirred for 2 h at 25 °C. The reaction was then poured into 10 mL of ice/water. The resulting solution was extracted with 10 mL of EtOAc. The pH of the aqueous layer was adjusted to 3 with 6N HCl. The resulting solution was extracted with 3x50 mL of CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel column with CH_2Cl_2/MeOH (10:1). The collected fractions were concentrated under vacuum to give 67 mg (crude) of the title compound as a yellow oil. MS: (ES, *m/z*): 314 $[M+H]^+$.

***Step-2*: (R)-1'-(Cyclobutylmethyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide**

[00209] Into a 25-mL round-bottom flask was placed a solution of the product from Step 1, which was assigned as (R)-1'-(cyclobutylmethyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylic acid as described above, (67 mg, 0.21 mmol, 1 equiv) in DMA (3 mL). This was followed by the dropwise addition of isopropyl chloroformate (135 mg, 1.10 mmol, 5.15 equiv) with stirring at 0 °C. NMM (128 mg, 1.27 mmol, 5.92 equiv) was added to the solution dropwise with stirring at 0 °C. The mixture was stirred for 30 min at 0 °C. Next, a solution of NH_2OH•HCl (75 mg, 1.08 mmol, 5.05 equiv) in DMA (2 mL) was added dropwise with stirring at 0 °C. The resulting solution was stirred overnight at room temperature. The solids

were filtered out and the crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 19x150mm 5 μm; Mobile Phase A: Water/0.1% Formic Acid, Mobile Phase B: CH_3CN/0.1% Formic Acid; Gradient: 25% B up to 55% B in 7 min; Detector: UV 254, 220nm. The collected fractions were lyophilized to give 10.5 mg (15% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.17 (br s, 1H), 8.97 (br s, 1H), 7.46-7.44 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 3.19-3.16 (m, 3H), 3.03 (d, *J* = 9.6 Hz, 1H), 2.84-2.80 (m, 2H), 2.78-2.72 (m, 2H), 2.48-2.41 (m, 1H), 2.24 (d, *J* = 16.4 Hz, 1H), 2.03-1.91 (m, 3H), 1.83-1.74(m, 4H), 1.68-1.60 (m, 2H). MS: (ES, *m/z*): 329 $[M+H]^+$.

Example 36 – Preparation of (R)-N-hydroxy-5'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-226)



R/S R/S R/S

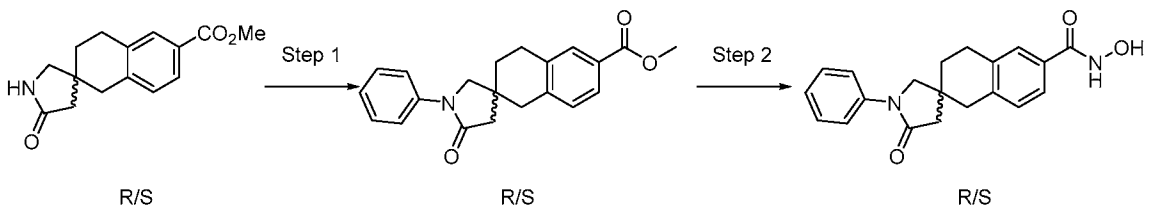
***Step-1*: Methyl (R)-5'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00210] Into a 10-mL vial was placed a solution of the first eluted isomer from Example 34, Step 6, which was assigned as methyl (R)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (60 mg, 0.23 mmol, 1 equiv) in DMF (5 mL). This was followed by the portionwise addition of NaH (60% in oil, 56 mg, 1.40 mmol, 6 equiv) at 0 °C. The resulting solution was stirred for 30 min at room temperature. Next, a solution of Et_3N (93 mg, 0.92 mmol, 4 equiv) and 3-(bromomethyl)pyridine hydrobromide (232 mg, 0.92 mmol, 4 equiv) in DMF (1 mL) were added dropwise at 0 °C. The resulting solution was stirred for 2 h at 25 °C. The reaction mixture was poured into 20 mL of water/ice. The resulting solution was extracted with 3x20 mL of EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give 47 mg (58% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 351 $[M+H]^+$.

***Step-2*: (R)-N-Hydroxy-5'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide**

[00211] Into a 25-mL round-bottom flask was placed a solution of the product from Step 1, which was assigned as methyl (R)-5'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (47 mg, 0.13 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), and NH_2OH (50% in water, 531 mg, 8.04 mmol, 60 equiv). This was followed by the dropwise addition of 1N aq. NaOH (0.3 mL, 0.27 mmol, 2 equiv). The resulting solution was stirred for 2 h at 25 °C. The solids were filtered and the crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 19x150mm 5 μm; Mobile Phase A: Water/0.01% NH_4HCO_3, Mobile Phase B: CH_3CN/0.01% NH_4HCO_3; Gradient: 5% B up to 20% B in 6 min; Detector: UV 254, 220 nm. The collected fractions were lyophilized to give 13.7 mg (29% yield) of the title compound as a brown solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 10.90 (br s, 1H), 9.07 (br s, 1H), 8.50-8.47 (m, 2H), 7.65 (d, *J* = 8 Hz, 1H), 7.49-7.44 (m, 2H), 7.40-7.36 (m, 1H), 7.08 (d, *J* = 8 Hz, 1H), 4.42 (s, 2H), 3.15 (d, *J* = 10 Hz, 1H), 3.00 (d, *J* = 10 Hz, 1H), 2.90-2.74 (m, 4H), 2.37 (d, *J* = 16.4 Hz, 1H), 2.14 (d, *J* = 16.8 Hz, 1H), 1.81-1.76 (m, 2H). MS: (ES, *m/z*): 352 $[M+H]^+$.

Example 37 – Preparation of (R)-N-hydroxy-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-203).



R/S R/S R/S

***Step-1*: Methyl (R)-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

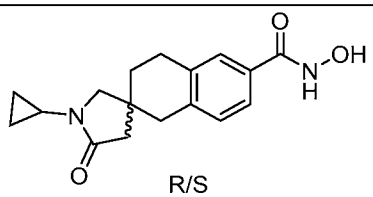
[00212] Into a 50-mL round-bottom flask, was placed a solution of the first eluted isomer from Example 34, Step 6, which was assigned as methyl (R)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (50 mg, 0.19 mmol, 1 equiv) in CH_2Cl_2 (15 mL), Et_3N (58 mg, 0.57 mmol, 3 equiv), phenylboronic acid (48 mg, 0.39 mmol, 2 equiv), $Cu(OAc)_2$ (38 mg, 0.21 mmol, 1 equiv), and 4Å molecular sieves (100 mg). O_2 was introduced into the flask and the resulting solution was stirred overnight at 25 °C. The reaction was then quenched by the addition of 20 mL of water and diluted with 20 mL of

CH_2Cl_2. The solids were filtered out and the filtrate was extracted with 2x20 mL of CH_2Cl_2. The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase column chromatography on silica gel with EtOAc/petroleum ether (1:3). The collected fractions were concentrated under vacuum to give 60 mg (92% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 336 $[M+H]^+$.

***Step-2*: (R)-N-Hydroxy-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00213] Into a 10-mL round-bottom flask, was placed a solution of the product from Step 1, which was assigned as methyl (R)-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (60 mg, 0.18 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), NH_2OH (50% in water, 709 mg, 120 equiv), and 1N aq. NaOH (14.4 mg, 0.36 mmol, 2 equiv) . The resulting solution was stirred for 2 h at 25 °C. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD, 19x150mm 5 μm; Mobile Phase A: Water/0.1% Formic acid, Mobile Phase B: CH_3CN; Gradient: 20% B to 45% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 23.9 mg (40% yield) of the title compound as a white solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.06 (s, 1H), 8.94 (s, 1H), 7.63-7.61 (m, 2H), 7.52 (s, 1H), 7.47-7.44 (m, 1H), 7.35-7.31 (m, 2H), 7.14-7.08 (m, 2H), 3.77-3.74 (d, *J* = 9.6 Hz, 1H), 3.57-3.55 (d, *J* = 9.6 Hz, 1), 2.96-2.80 (m, 4H), 2.58-2.54 (d, *J* = 16.8 Hz, 1H), 2.33-2.28 (d, *J* = 16.8 Hz, 1H), 1.89-1.85 (m, 2H) .MS: (ES, *m/z*): 337 $[M+H]^+$.

Table-22: The following compounds were prepared according to the method of Example 37 with the first eluted product from Example 34, Step 6.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-209	 R/S	(400 MHz, DMSO-d6): 11.08 (s, 1H), 8.93 (s, 1H), 7.49-7.44 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 3.13 (d, *J* = 9.6 Hz, 1H), 2.96 (d, *J* = 9.6 Hz, 1H), 2.83-2.60 (m, 5H), 2.25 (d, *J* = 16.4 Hz, 1H), 2.01 (d, *J* = 16.8 Hz, 1H), 1.75-1.72 (m, 2H), 0.64-0.52 (m, 4H)	301

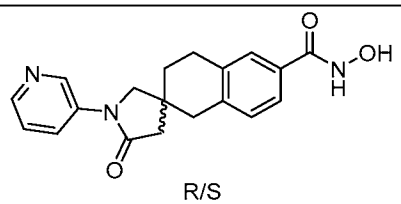
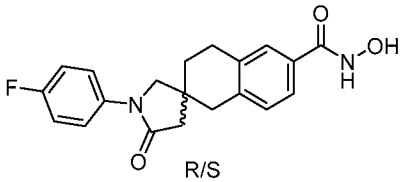
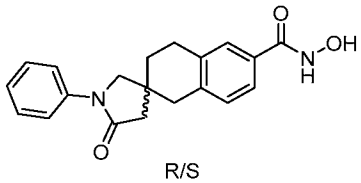
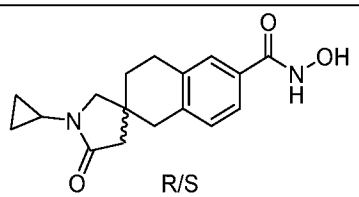
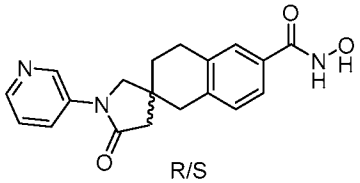
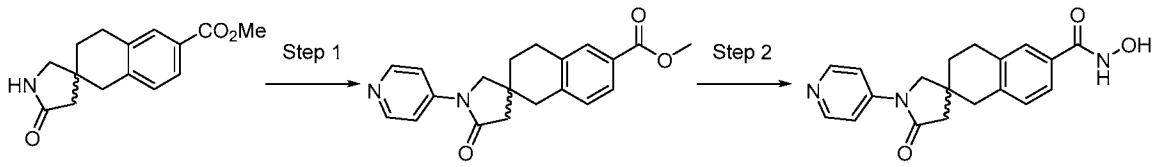
I-221	 R/S	(300 MHz, DMSO-d6): 11.16 (s, 1H), 8.96 (s, 1H), 8.87 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 3.3 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.54 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.39 (m, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 3.82 (d, *J* = 9.9 Hz, 1H), 3.63 (d, *J* = 9.9 Hz, 1H), 2.90-2.88 (m, 4H), 2.60 (d, *J* = 16.5 Hz, 1H), 2.35 (d, *J* = 16.5 Hz, 1H), 1.89 (s, 2H)	338
I-227	 R/S	(400 MHz, DMSO-d6): 11.11 (br s, 1H), 8.99 (br s, 1H), 7.70-7.64 (m, 2H), 7.54 (s, 1H), 7.49-7.41 (m, 1H), 7.23-7.08 (m, 3H), 3.77 (d, *J* = 10 Hz, 1H), 3.57 (d, *J* = 9.6 Hz, 1H), 3.98-2.86 (m, 4H), 2.8 (d, *J* = 16.8 Hz, 1H), 2.32 (d, *J* = 16.4 Hz, 1H), 1.90-1.87 (m, 2H)	355

Table-23: The following compounds were prepared according to the method of Example 37, with the following modification: In Step 1, the second eluted product from Example 34, Step 6 was used.

Ex.	**Structure**	**^{1}H-NMR δ (ppm)**	**Found (ES, *m/z*) $[M+H]^+$**
I-204	 R/S	(300 MHz, DMSO-d6): 11.09 (s, 1H), 9.00 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.54 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.37-7.32 (m, 2H), 7.16-7.09 (m, 2H), 3.78 (d, *J* = 9.9 Hz, 1H), 3.58 (d, *J* = 9.9 Hz, 1H), 2.94-2.86 (m, 4H), 2.58 (d, *J* = 16.8 Hz, 1H), 2.32 (d, *J* = 16.8 Hz, 1H), 1.91-1.86 (m, 2H)	337
I-214	 R/S	(300 MHz, DMSO-d6): 11.06 (br s, 1H), 8.94 (s, 1H), 7.50-7.45 (m, 2H), 7.12 (d, *J* = 7.8 Hz, 1H), 3.14 (d, *J* = 9.6 Hz, 1H), 2.97 (d, *J* = 9.6 Hz, 1H), 2.85-2.80 (m, 2H), 2.73-2.72 (m, 1H), 2.66-2.61 (m, 2H), 2.26 (d, *J* = 16.2 Hz,	301

		1H), 2.02 (d, *J* = 16.5 Hz, 1H), 1.77-1.73 (m, 2H), 0.66-0.56 (m, 4H)	
I-224	 R/S	(300 MHz, DMSO-d6): 11.12 (br s, 1H), 9.01 (br s, 1H), 8.88 (d, *J* = 1.8 Hz, 2H), 8.33 (d, *J* = 4.2 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.55 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.42-7.37 (m, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 3.82 (d, *J* = 9.9Hz, 1H), 3.63 (d, *J* = 9.9 Hz, 1H), 2.99-2.89 (m, 4H), 2.61 (d, *J* = 16.8 Hz, 1H), 2.35 (d, *J* = 16.8 Hz, 1H), 1.92-1.88(m, 2H)	338

Example 38 – Preparation of (R)-N-hydroxy-5'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxamide (I-228)



R/S R/S R/S

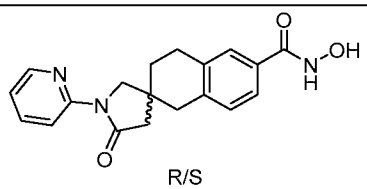
***Step-1*: Methyl (R)-5'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate**

[00214] Into a 10-mL sealed tube purged and maintained with an inert atmosphere of nitrogen was placed the first eluted isomer from Example 34, Step 6, which was assigned as methyl (R)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate as described above, (50 mg, 0.19 mmol, 1 equiv), toluene (4 mL), 4-bromopyridine (60.6 mg, 0.38 mmol, 2 equiv), RuPhos Pd G2 (15 mg, 0.02 mmol, 0.1 equiv), RuPhos (18 mg, 0.04 mmol, 0.20 equiv), and Cs_2CO_3 (189 mg, 0.58 mmol, 3 equiv). The resulting solution was stirred for 16 h at 100 °C in an oil bath. The reaction mixture was cooled to room temperature. The resulting solution was poured into 20 mL of water, extracted with 2x10 mL of EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by preparative TLC with CH_2Cl_2/MeOH (20:1). The collected band was dissolved in CH_2Cl_2/MeOH (20:1), filtered and was concentrated under vacuum to give 60 mg (93% yield) of the title compound as a yellow oil. MS: (ES, *m/z*): 337 $[M+H]^+$.

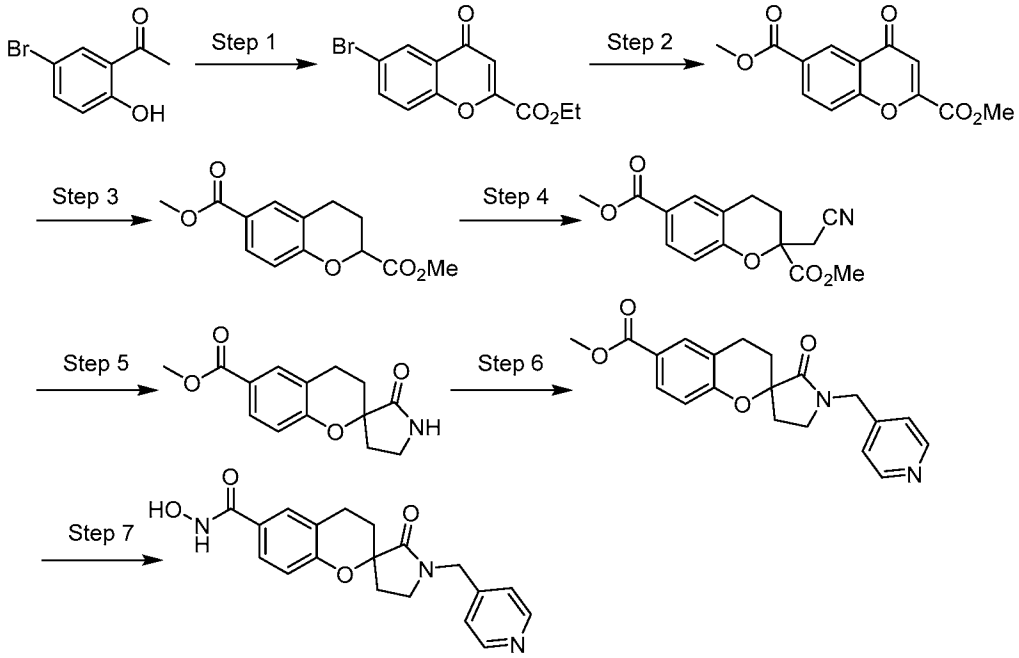
***Step-2*: (R)-N-Hydroxy-5'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00215] Into a 8-mL vial was placed a solution of the product from Step 1, which was assigned as methyl (R)-5'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6- carboxylate as described above, (60 mg, 0.18 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), NH_2OH (50% in water, 1.4 g, 21.43 mmol, 120 equiv) and 1N aq. NaOH (0.35 mL, 0.35 mmol, 2 equiv). The resulting solution was stirred for 3 h at room temperature. The solids were filtered out and the crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD, 5 μm, 19x150mm; Mobile Phase A: Water/0.1% Formic Acid, Mobile Phase B: CH_3CN/0.1% Formic Acid; Gradient: 3% B up to 23% B in 5 min; Detector: UV 220, 254nm. The collected fractions were lyophilized with 1M HCl (1 mL) to give 23.4 mg (39% yield) of the title compound as the HCl salt as a pink solid. ^{1}H-NMR (300 MHz, DMSO-d6) δ (ppm):11.14 (br s, 1H), 8.96 (br s, 1H), 8.67 (d, *J* = 6.3 Hz, 2H), 8.04 (d, *J* = 6 Hz, 2H), 7.56-7.47 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 1H), 3.86 (d, *J* = 10.2 Hz, 1H), 3.71 (d, *J* = 10.2 Hz, 1H), 2.99-2.82 (m, 4H), 2.74 (d, *J* = 17.1 Hz, 1H), 2.49 (d, *J* = 16.8 Hz, 1H), 1.92-1.87 (m, 2H). MS: (ES, *m/z*): 338 $[M+H]^+$.

Table-24: The following compound was prepared according to the method of Example 38.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-229	 R/S	(300 MHz, DMSO-d6): 11.10 (br s, 1H), 8.99 (br s, 1H), 8.33-8.30 (m, 2H), 7.84-7.78 (m, 1H), 7.54-7.41 (m, 2H), 7.14-7.10 (m, 2H), 3.87 (s, 1H), 2.92-2.85 (m, 4H), 2.68 (d, *J* = 16.8 Hz, 1H), 2.41 (d, *J* = 17.1 Hz, 1H), 1.91-1.87 (m, 2H)	338

Example 39 – Preparation of N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)spiro[chromane-2,3'-pyrrolidine]-6- carboxamide (I-230)



***Step-1*: Ethyl 6-bromo-4-oxo-4H-chromene-2-carboxylate**

[00216] Into a 250-mL 3-necked round-bottom flask was placed NaH (28 g, 3 equiv) in THF (800 mL) at 0 °C. Then 1-(5-bromo-2-hydroxyphenyl)ethan-1-one (50 g, 232.51 mmol, 1 equiv) and diethyl oxalate (65 mL, 2 equiv) were added at 0 °C. The resulting mixture was stirred overnight at 25 °C. The reaction was then quenched by the addition of NH_4Cl. The resulting solution was extracted with 3x500 mL of EtOAc. The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was taken up in toluene (800 mL) and PTSA (1.5 g, 0.05 equiv) was added. The resulting mixture was allowed to react with stirring, using a Dean-Stark Separator, for an additional overnight while the temperature was maintained at 120 °C in an oil bath. The solution was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:20). The collected fractions were concentrated to give 38 g (55% yield) of the title compound as a yellow solid. MS: (ES, *m/z*): 297 $[M+H]^+$.

***Step-2*: Dimethyl 4-oxo-4H-chromene-2,6-dicarboxylate**

[00217] Into a 150-mL pressure tank reactor, was placed ethyl 6-bromo-4-oxo-4H-chromene-2-carboxylate (20 g, 67.32 mmol, 1 equiv) in MeOH (150 mL), Et_3N (28.3 mL, 3 equiv) and

$Pd(dppf)Cl_2•CH_2Cl_2$ (2.8 g, 0.05 equiv). The resulting mixture was stirred for 4 days at 80 °C under CO (g) (20 atm). The reaction mixture was cooled to room temperature. The solids were filtered out and the resulting mixture was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:10). The collected fractions were concentrated to give 4 g (23% yield) of the title compound as a white solid. MS: (ES, *m/z*): 263 $[M+H]^+$.

***Step-3*: Dimethyl chromane-2,6-dicarboxylate**

[00218] Into a 250-mL pressure tank reactor, was placed dimethyl 4-oxo-4H-chromene-2,6-dicarboxylate (15 g, 57.20 mmol, 1 equiv), palladium on carbon (3 g, 0.2 equiv), MeOH (150 mL) and AcOH (15 mL, 10 equiv). The resulting mixture was stirred for 2 days at 80 °C under H_2 (g). The reaction mixture was cooled to room temperature. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:10). The collected fractions were concentrated to give 10 g (70% yield) of the title compound as a white solid. MS: (ES, *m/z*): 251 $[M+H]^+$.

***Step-4*: Dimethyl 2-(cyanomethyl)chromane-2,6-dicarboxylate**

[00219] Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, were placed a solution of dimethyl chroman-2,6-dicarboxylate (2 g, 7.99 mmol, 1 equiv) in THF (20 mL). This was followed by the dropwise addition of LDA (10.4 mL, 1.30 equiv) with stirring at -78 °C. The resulting solution was stirred for 1 h at -78 °C. 2-Bromoacetonitrile (0.84 mL, 1.5 equiv) was added dropwise with stirring at -78 °C. The reaction was stirred for 1 h at -60 °C. The reaction was then quenched by the addition of 20 mL of sat aq. NH_4Cl. The resulting solution was extracted with 3x50 mL of EtOAc. The organics were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:3). The collected fractions were concentrated to give 0.7 g (30% yield) of the title compound as a white solid. MS: (ES, *m/z*): 290 $[M+H]^+$.

***Step-5*: Methyl 2'-oxospiro[chroman-2,3'-pyrrolidine]-6-carboxylate**

[00220] Into a 50-mL round-bottom flask were placed dimethyl 2-(cyanomethyl)chroman-2,6-dicarboxylate (700 mg, 2.42 mmol, 1 equiv) in MeOH (15 mL), 7M NH_3 in MeOH (1 mL) and

PtO_2 (160 mg, 0.70 mmol, 0.13 equiv). H_2 (g) was introduced to the flask. The resulting mixture was stirred overnight at room temperature. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:1). The collected fractions were concentrated to give 0.22 g (35% yield) of the title compound as a white solid. MS: (ES, *m/z*): 262 $[M+H]^+$.

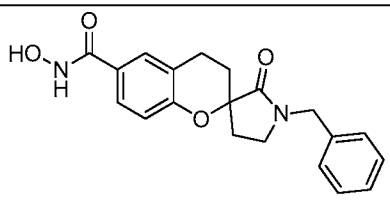
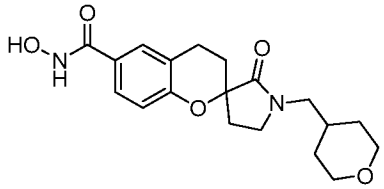
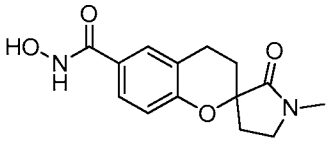
***Step-6*: Methyl 2'-oxo-1'-(pyridin-4-ylmethyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxylate**

[00221] Into a 25-mL round-bottom flask was placed methyl 2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxylate (50 mg, 0.19 mmol, 1 equiv) in DMF (5 mL), NaH (23 mg, 0.96 mmol, 3 equiv) and 4-(bromomethyl)pyridine (73 mg, 0.43 mmol, 1.5 equiv). The resulting mixture was stirred for 4 h at room temperature. The reaction was then quenched by the addition of NH_4Cl. The resulting solution was extracted with 3x30 mL of EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with CH_3Cl/MeOH (50:1). The collected fractions were concentrated to give 30 mg (45% yield) of the title compound as a light yellow solid. MS: (ES, *m/z*): 353 $[M+H]^+$.

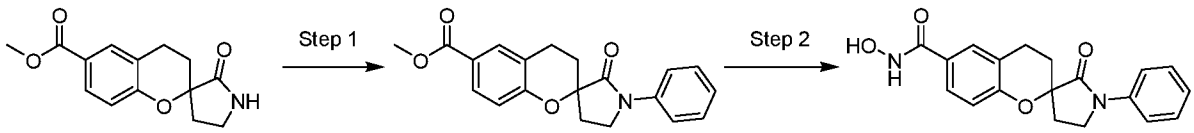
***Step-7*: N-Hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide**

[00222] Into a 25-mL round-bottom flask was placed a solution of methyl 2'-oxo-1'-(pyridin-4-ylmethyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxylate (30 mg, 0.09 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), NH_2OH (50% in water, 168 mg, 30 equiv) and 1N aq. NaOH (1.7 mL, 2 equiv). The resulting solution was stirred for 5 h at 25 °C. The pH of the solution was adjusted to 6 with 3N aq. HCl. The crude product was purified by Prep-HPLC with the following conditions: Column: Waters HSS C18, 2.1x50 mm, 1.8 μm; Mobile Phase A:Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2.0 min, hold 0.6 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 1.3 mg (3% yield) of the title compound as a white solid. ^{1}H-NMR (300 MHz, DMSO-d6) δ (ppm): 11.04 (s, 1H), 8.63-8.65 (d, 2H), 7.50-7.56 (t, 2H), 7.37-7.39 (d, 2H), 6.82-6.84 (d, 1H), 4.54-4.55 (d, 2H), 2.96 (s, 2H), 2.73-2.83 (d, 2H), 2.21-2.27 (m, 2H), 1.98-2.13 (m, 2H). MS: (ES, *m/z*): 354 $[M+H]^+$.

Table-25: The following compounds were prepared according to the method of Example 39, with the following modification: In Step 6, the halide can be an iodide, a chloride, or a bromide.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-232		(300 MHz, DMSO-d6): 11.01 (s, 1H), 7.55 (s, 1H), 7.49-7.52 (d, 1H), 7.23-7.38 (m, 4H), 6.79-6.82 (d, 1H), 4.43-4.44 (d, 2H), 3.21-3.35 (m, 2H), 2.95-3.05 (m, 1H), 2.72-2.83 (m, 1H), 2.04-2.27 (m, 3H), 1.92-1.94 (d, 1H)	353
I-234		(300 MHz, DMSO-d6): 11.00 (s, 1H), 7.47-7.54 (m, 2H), 6.76-6.79 (d, 1H), 3.81-3.86 (m, 2H), 3.38-3.50 (m, 2H), 3.23-3.35 (m, 2H), 3.10-3.13 (m, 2H), 2.90 (s, 1H), 2.80 (s, 1H), 2.02-2.20 (m, 3H), 1.85-1.93 (m, 2H), 1.49-1.53 (t, 2H), 1.13-1.17 (m, 2H)	361
I-237		(400 MHz, DMSO-d6): 10.99 (br s, 1H), 8.85 (br s, 1H), 7.53 (s, 1H), 7.50-7.45 (m, 1H), 6.78-6.73 (m, 1H), 3.43-3.38 (m, 2H), 3.01-2.89 (m, 1H), 2.85-2.75 (m, 1H), 2.79 (s, 3H), 2.23-1.97 (m, 3H), 1.96-1.80 (m, 1H)	277

Example 40 – Preparation of N-hydroxy-2'-oxo-1'-phenylspiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-231)



***Step-1*: Methyl 2'-oxo-1'-phenylspiro[chromane-2,3'-pyrrolidine]-6-carboxylate**

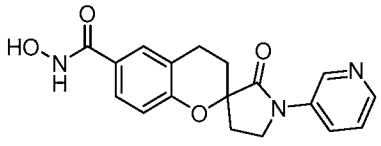
[00223] Into a 50-mL 3-necked round-bottom flask was placed a solution of methyl 2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxylate (80 mg, 0.31 mmol, 1 equiv) in 1,4-dioxane (10 mL), iodobenzene (76 mg, 0.37 mmol, 1.2 equiv), $Pd(OAc)_2$ (6.8 mg, 0.1 equiv), XantPhos (39.2 mg, 0.07 mmol, 0.2 equiv) and Cs_2CO_3 (200 mg, 0.61 mmol, 2 equiv). The resulting

mixture was stirred for 3 h at 100 °C under N_2. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:2). The collected fractions were concentrated to give 40 mg (39% yield) of the title compound as a brown solid. MS: (ES, *m/z*): 338 $[M+H]^+$.

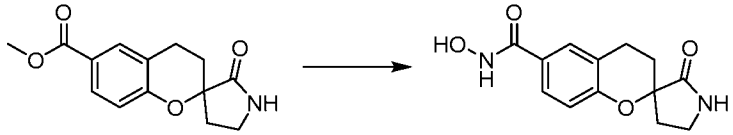
***Step-2*: N-Hydroxy-2'-oxo-1'-phenylspiro[chromane-2,3'-pyrrolidine]-6-carboxamide**

[00224] Into a 25-mL round-bottom flask was placed a solution of methyl 2'-oxo-1'-phenylspiro[chromane-2,3'-pyrrolidine]-6-carboxylate (40 mg, 0.12 mmol, 1 equiv) in THF/MeOH (4:1, 2 mL), NH_2OH (50% in water, 235 mg, 30 equiv), and 1N aq. NaOH (0.238 mL, 2 equiv). The resulting solution was stirred for 1 h at 25 °C. The crude product was purified by Prep-HPLC with the following conditions: Column: Waters HSS C18, 2.1x50 mm, 1.8 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2.0 min, hold 0.6 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 26.1 mg (65% yield) of the title compound as an off-white solid. ^{1}H-NMR (300 MHz, DMSO-d6) δ (ppm): 11.02 (s, 1H), 7.70-7.23 (d, 2H), 7.50-7.57 (m, 2H), 7.39-7.44 (t, 2H), 7.17-7.22 (t, 1H), 6.83-6.86 (d, 1H), 3.87-3.92 (m, 2H), 2.83-2.93 (m, 2H), 2.29-2.39 (m, 2H), 2.17-2.22 (t, 1H), 2.00-2.05 (t, 1H). MS: (ES, *m/z*): 339 $[M+H]^+$.

Table-26: The following compound was prepared according to the method of Example 40.

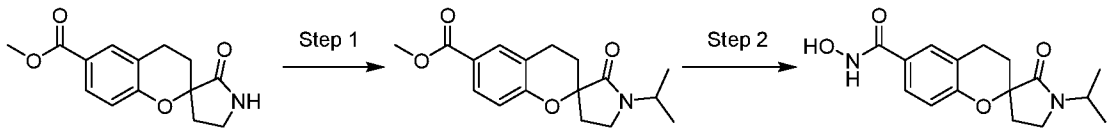
Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
I-233		(300 MHz, DMSO-d6): 11.05 (s, 1H), 8.93 (s, 1H), 8.39-8.43 (m, 1H), 8.13-8.17 (m, 1H), 7.44-7.58 (m, 3H), 6.83-6.86 (d, 1H), 3.92-3.97 (m, 2H), 2.73-2.92 (m, 2H), 2.34-2.43 (m, 2H), 2.19-2.29 (m, 1H), 2.04-2.07 (d, 1H)	340

Example 41 – Preparation of N-hydroxy-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-236)



[00225] Into an 8-mL vial, was placed a solution of methyl 2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxylate (70 mg, 0.27 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL), NH_2OH (in 50% water, 0.53 mL, 30 equiv), and 1N aq. NaOH (0.54 mL, 2 equiv). The resulting solution was stirred for 2 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Sunfire C18, 19x150 mm, 5 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Gradient: 5% B to 65% B in 8 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 22.8 mg (32% yield) as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 10.99 (s, 1H), 8.88 (m, 1H), 8.06 (s, 1H), 7.52-7.46 (m, 2H), 6.79-6.77 (d, *J* = 8.0 Hz, 1H), 3.31-3.28 (m, 2H),2.97-2.93 (m, 1H), 2.79-2.73 (m, 1H), 2.21-2.19 (m, 2H), 2.17-2.00 (m, 1H), 1.89-1.83 (m, 1H). MS: (ES, *m/z*): 263 $[M+H]^+$.

Example 42 – Preparation of N-hydroxy-1'-isopropyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-235)



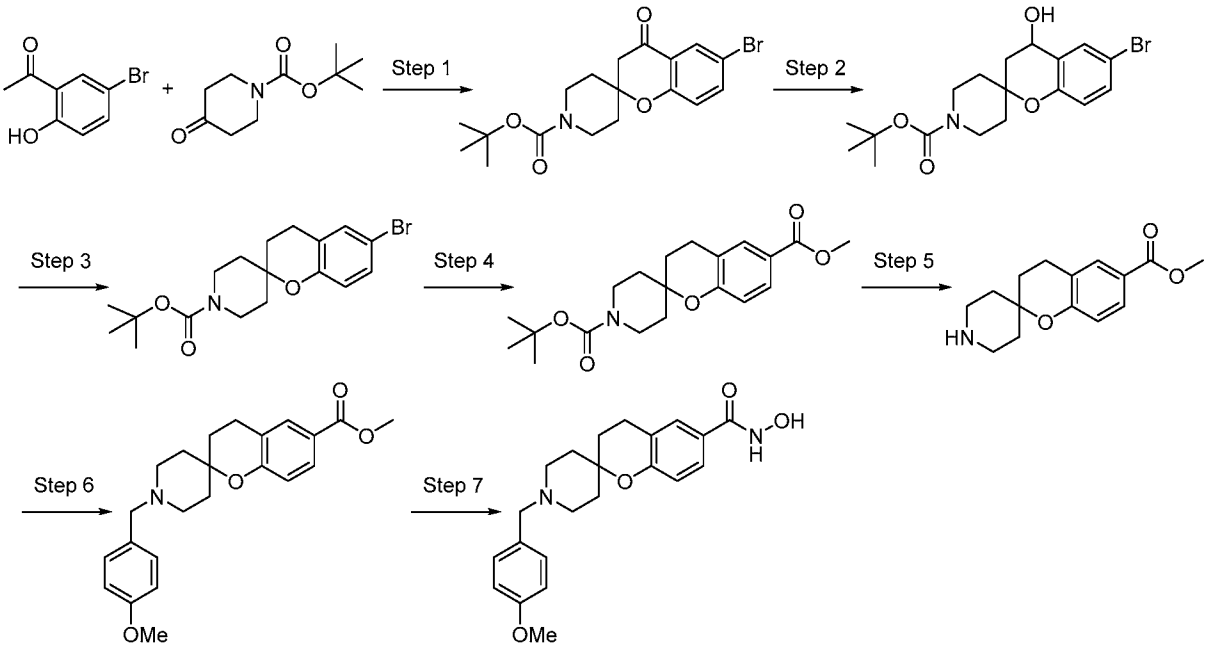
***Step-1*: Methyl 1'-isopropyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxylate**

[00226] Into a 25-mL round-bottom flask was placed a solution of methyl 2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxylate (100 mg, 0.38 mmol, 1 equiv) in CH_3CN (6 mL), 2-iodopropane (326 mg, 1.92 mmol, 5 equiv), Cs_2CO_3 (375 mg, 1.15 mmol, 3 equiv). The resulting solution was stirred for 18 h at 70 °C. The resulting mixture was concentrated under vacuum. The residue was dissolved in 20 mL of EtOAc. The resulting mixture was washed with 2x15 mL of H_2O. The organics were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by normal phase chromatography on silica gel with EtOAc/petroleum ether (1:1). The collected fractions were concentrated to give 44.2 mg (38% yield) of the title compound as a solid. MS: (ES, *m/z*): 304 $[M+H]^+$.

***Step-2*: N-Hydroxy-1'-isopropyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide**

[00227] Into an 8-mL vial, was placed a solution of methyl 1'-isopropyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxylate (44.2 mg, 0.15 mmol, 1 equiv) in THF/MeOH (4:1, 1 mL), NH_2OH (50% in water, 0.29 mL, 30 equiv) , and 1N aq. NaOH (0.29 mL, 2 equiv). The resulting solution was stirred for 2.5 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Xbridge C18, 19x150mm, 5 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 25 mL/min; Gradient: 5% B to 57% B in 7 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to give 15.8 mg (36% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 11.00 (br s, 1H), 8.87 (s, 1H), 7.53-7.47 (s, 2H), 6.79-6.76 (d, J = 12 Hz, 1H), 4.11 (m, 1H), 3.36-3.35 (m, 1H), 3.30-3.28 (m, 1H), 2.98-2.88 (m, 1H), 2.79-2.73 (m, 1H), 2.18-1.99 (m, 3H), 1.88-1.83 (m, 1H), 1.13-1.08 (m, 6H). MS: (ES, *m/z*): 305 $[M+H]^+$.

Example 43 – Preparation of N-hydroxy-1'-(4-methoxybenzyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-1)



***Step-1*: tert-Butyl 6-bromo-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate**

[00228] 1-(5-Bromo-2-hydroxyphenyl)ethan-1-one (10.0 g, 45.5 mmol), tert-butyl 4-oxopiperidine-1-carboxylate (9.27 g, 46.5 mmol) and pyrrolidine (1.91 mL, 23.3 mmol) were combined in 75 mL of MeOH and refluxed for 12 h. After cooling down to room temperature the reaction mixture was concentrated to dryness and purified by normal phase chromatography on

silica gel (EtOAc/hexanes gradient). After purification 17.1 g (92% yield) of the title compound was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.96 (d, J = 2.5 Hz, 1H), 7.55 (dd, J_1 = 8.8 Hz, J_2 = 2.5 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 3.86 (br s, 2H), 3.20-3.10 (m, 2H), 2.71 (s, 2H), 2.05-1.90 (m, 2H), 1.70-1.55 (m, 2H), 1.45 (s, 9H). MS: (ES, *m/z*): 296/298 $[M\text{-}Boc]^+$.

***Step-2*: tert-Butyl 6-bromo-4-hydroxyspiro[chromane-2,4'-piperidine]-1'-carboxylate**

[00229] Sodium borohydride (0.120 g, 3.15 mmol, 1 equiv)was added to a suspension of tert-butyl 6-bromo-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (1.25 g, 3.15 mmol, 1 equiv) in EtOH (25 mL). The reaction was stirred at room temperature for 16 h. The reaction was concentrated under vacuum to afford 1g (crude) of the title compound and was used without further purification.

***Step-3*: 1'-(tert-Butyl) 6-methyl spiro[chromane-2,4'-piperidine]-1',6-dicarboxylate**

[00230] To a solution of tert-butyl 6-bromo-4-hydroxyspiro[chromane-2,4'-piperidine]-1'-carboxylate (1 g, 2.51 mmol, 1 equiv) in CH_2Cl_2 (14.5 ml) was added TFA (6.38 ml, 83 mmol, 33.07 equiv) and triethylsilane (3.21 ml, 20.09 mmol, 8 equiv). The reaction was concentrated to afford 882 mg of the title compound, which was used without further purification.

***Step-4*: 1'-(tert-Butyl) 6-methyl spiro[chromane-2,4'-piperidine]-1',6-dicarboxylate**

[00231] To a solution of tert-butyl 6-bromospiro[chromane-2,4'-piperidine]-1'-carboxylate (249 mg, 0.651 mmol, 1 equiv) in THF (5 mL) cooled to -78 °C (dry ice/acetone bath), was added *n*-Butyl lithium (1.6M, 0.602 mL, 0.964 mmol, 1.48 equiv). The resulting mixture was stirred at -78 °C for 45 min when methyl chloroformate (1.0 mL, 13.02 mmol, 20 equiv) was added. The resulting mixture was stirred and slowly warmed to room temperature and then stirred for 1 h. The reaction was concentrated under reduced pressure. The light pink residue was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The organic layers were combined and dried over Na_2SO_4, concentrated and purified by normal phase chromatography on silica gel (10-50% EtOAc/hexanes) to provide 243 mg of the title compound. MS: (ES, *m/z*): 362 $[M+H]^+$.

***Step-5*: Methyl spiro[chromane-2,4'-piperidine]-6-carboxylate**

[00232] To a solution of 1'-(tert-butyl) 6-methyl spiro[chromane-2,4'-piperidine]-1',6-dicarboxylate (243 mg, 0.672 mmol, 1 equiv) in CH_2Cl_2 (0.5 mL) was added TFA (0.259 mL, 3.36 mmol, 5 equiv). The reaction mixture was stirred at room temperature for 40 min. The

reaction mixture was then concentrated under vacuum and azeotroped with toluene 3 times. The crude mixture was used in the next step without further purification. MS: (ES, *m/z*): 262 $[M+H]^+$.

***Step-6*: Methyl 1'-(4-methoxybenzyl)spiro[chromane-2,4'-piperidine]-6-carboxylate**

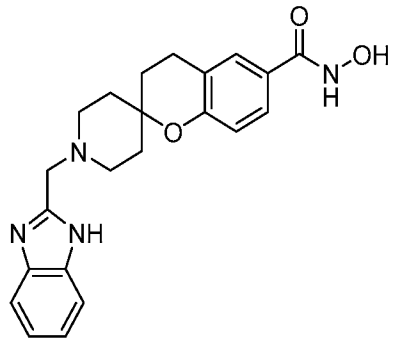
[00233] Methyl spiro[chromane-2,4'-piperidine]-6-carboxylate (126.3 mg, 0.336 mmol, 1 equiv) was combined with Et_3N (0.094 mL, 0.671 mmol, 2 equiv) and 4-methoxybenzaldehyde (0.041 mL, 0.336 mmol, 1 equiv) in DCE (2.0 mL). The reaction was stirred at room temperature for 1.5 h. Then $NaBH(OAc)_3$ (92 mg, 0.436 mmol, 1.3 equiv) was added and the reaction was allowed to stir at room temperature for 16 h. The reaction mixture was directly purified by normal phase chromatography on silica gel (10%-60% EtOAc/hexanes) to afford 37 mg (28% yield) of the title compound. MS: (ES *m/z*) 382 $[M+H]^+$.

***Step-7*: N-hydroxy-1'-(4-methoxybenzyl)spiro[chromane-2,4'-piperidine]-6-carboxamide**

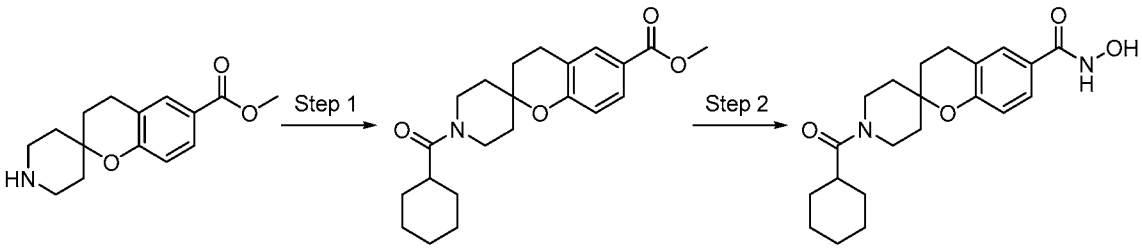
[00234] Methyl 1'-(4-methoxybenzyl)spiro[chromane-2,4'-piperidine]-6-carboxylate (36 mg, 0.095 mmol, 1 equiv) was dissolved in a solution of THF/MeOH (4:1, 1.25 mL). NH_2OH (50% in water, 0.263 mL, 8.59 mmol, 90 equiv) was added followed by 2N aq. NaOH (0.095 mL, 2 equiv). The reaction was allowed to stir at room temperature for 18 h and was purified directly by reverse-phase chromatography using the following conditions: Column: XTerra Prep MS C18 OBD, 5 μm, 19x100 mm; Mobile Phase A:Water/0.05% Formic Acid, Mobile Phase B: CH_3CN/0.05% Formic Acid; Flow rate: 20 mL/min; Gradient: 15% B to 85% B in 10 min; Detector: UV 254 nm, 220 nm. Combined fractions were lyophilized to afford 30 mg (83% yield) of the title compound. ^1H NMR (300 MHz, CD_3OD) δ (PPM): 8.26-8.58 (m, 1H), 7.39-7.67 (m, 4H), 6.87-7.15 (m, 3H), 4.30 (br s, 2H), 3.82 (s, 3H), 3.27-3.44 (m, 6H), 2.82-3.02 (m, 2H), 1.87-2.20 (m, 6H). MS: (ES *m/z*) 383 $[M+H]^+$.

Table-27: The following compound was prepared according to the method of Example 43.

Ex.	Structure	^1H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$

II-2		(300 MHz, CD_3OD): 8.08-8.22 (m, 2H), 7.40-7.71 (m, 4H), 7.29 (br dd, J = 5.9, 2.9 Hz, 2H), 6.67-6.97 (m, 1H), 4.12 (s, 2H), 3.32 (dt, J = 3.2, 1.6 Hz, 6H), 2.75-3.01 (m, 4H), 1.80-1.96 (m, 4H)	393

Example 44 – Preparation of 1'-(cyclohexanecarbonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-3)



***Step-1*: Methyl 1'-(cyclohexanecarbonyl)spiro[chromane-2,4'-piperidine]-6-carboxylate**

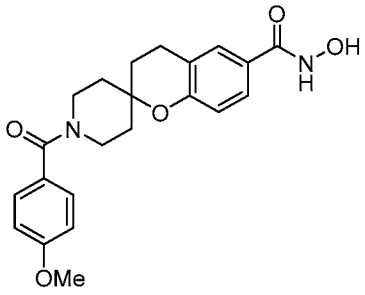
[00235] To a solution of methyl spiro[chromane-2,4'-piperidine]-6-carboxylate (78 mg, 0.196 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added cyclohexane carboxylic acid (26 mg, 0.206 mmol, 1.05 equiv), DIEA (0.137 mL, 0.589 mmol, 3 equiv) and HBTU (86 mg, 0.226 mmol, 1.50 equiv). The reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated and purified by normal phase chromatography on silica gel (10%-50% EtOAc/hexanes) to afford 57 mg (78% yield) of the title compound. MS: (ES, *m/z*): 372 $[M+H]^+$.

***Step-2*: 1'-(Cyclohexanecarbonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide**

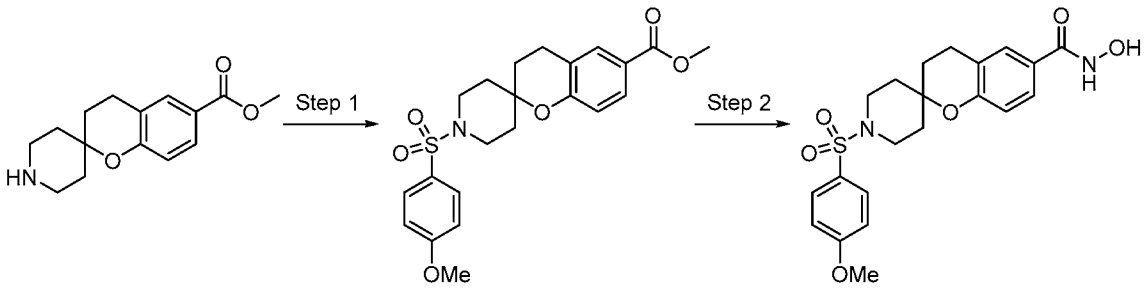
[00236] Methyl 1'-(cyclohexanecarbonyl)spiro[chromane-2,4'-piperidine]-6-carboxylate (57 mg, 0.154 mmol, 1 equiv) was dissolved in a solution of THF/MeOH (4:1, 1.25 mL). NH_2OH (50% in water, 0.801 mL, 13.07 mmol, 85 equiv) was added, followed by 2N aq. NaOH (0.154 mL, 2 equiv). The reaction was stirred at room temperature for 18 h and was purified directly by reverse-phase chromatography using the following conditions: Column: XTerra Prep MS C18 OBD 5 μm, 19x100 mm; Mobile Phase A: Water/0.05% Formic Acid, Mobile Phase B: CH_3CN/0.05% Formic Acid; Flow rate: 20 mL/min; Gradient: 15% B to 85% B in 10 min;

Detector: UV 254 nm, 220 nm. Combined fractions were lyophilized to afford 18 mg (31% yield) of the title compound. ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 10.92 (br s, 1H), 8.81 (s, 1H), 7.17-7.52 (m, 2H), 6.59-6.85 (m, 1H), 4.02 (br d, J = 13.2 Hz, 1H), 3.67 (br d, J = 14.1 Hz, 1H), 2.93 (br t, J = 11.6 Hz, 2H), 2.60-2.78 (m, 2H), 1.67-1.85 (m, 3H), 1.49-1.67 (m, 7H), 0.97-1.33 (m, 6H). MS: (ES, *m/z*): 373 $[M+H]^+$.

Table-28: The following compound was prepared according to the method of Example 44.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$
II-4			397

Example 45 – Preparation of N-hydroxy-1'-((4-methoxyphenyl)sulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-5)



***Step-1*: Methyl 1'-((4-methoxyphenyl)sulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxylate**

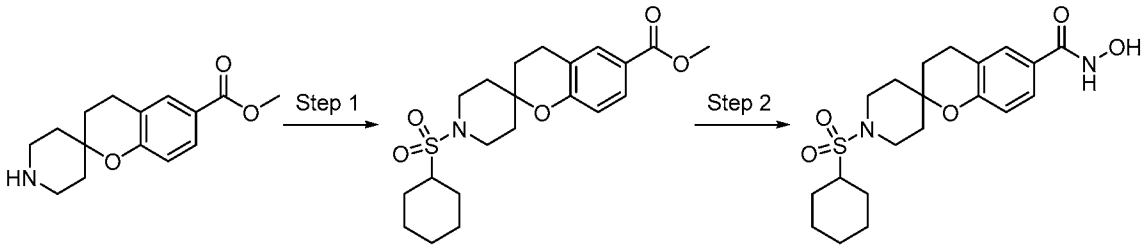
[00237] Methyl spiro[chromane-2,4'-piperidine]-6-carboxylate (75.8 mg, 0.189 mmol, 1 equiv) was combined with DIEA (0.115 mL, 0.660 mmol, 3.5 equiv) in THF (2.0 ml). After several min, 4-methoxybenzene-1-sulfonyl chloride (47 mg, 0.226 mmol, 1.20 equiv) was added and the resulting mixture was left to stir at room temperature for 16 h. The reaction mixture was partitioned between sat. aq. $NaHCO_3$ and EtOAc. Water was added to dissolve salts. The organic

phase was separated and the aqueous layer was extracted with several portions of EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by normal phase chromatography on silica gel to afford 68 mg (84% yield) of the title compound. MS: (ES, *m/z*) 431 $[M+H]^+$.

***Step-2*: N-Hydroxy-1'-((4-methoxyphenyl)sulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxamide**

[00238] Methyl 1'-((4-methoxyphenyl)sulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxylate (63 mg, 0.147 mmol, 1 equiv) was dissolved in a solution of THF/MeOH (4:1, 1.25 mL). NH_2OH (50% in water, 0.76 mL, 12.47 mmol, 85 equiv) was added, followed by 1N aq. NaOH (0.015 mL, 2 equiv). The reaction was allowed to stir at room temperature for 2 h and was directly purified by reverse-phase chromatography using the following conditions: Column: XTerra Prep MS C18 OBD, 5 μm, 19x100 mm; Mobile Phase A: Water/0.05% Formic Acid, Mobile Phase B: CH_3CN/0.05% Formic Acid; Flow rate: 20 mL/min; Gradient: 15% B to 85% B in 10 min; Detector: UV 254 nm, 220 nm. Combined fractions were lyophilized to afford 14 mg (22% yield) of the title compound. ^1H NMR (300 MHz, DMSO-d6) δ (ppm): 10.90 (br s, 1H), 8.80 (s, 1H), 7.59-7.67 (m, 2H), 7.41-7.59 (m, 1H), 7.35 (dd, J = 8.4, 2.2 Hz, 1H), 6.99-7.15 (m, 2H), 6.51 (d, J = 8.5 Hz, 1H), 3.81 (s, 3H), 3.32-3.40 (m, 2H), 2.65 (br t, J = 6.3 Hz, 2H), 2.51 (br t, J = 10.8 Hz, 2H), 1.38-1.76 (m, 6H). MS: (ES, *m/z*) 432 $[M+H]^+$.

Example 46 – Preparation of 1'-(cyclohexylsulfonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-6)



***Step-1*: Methyl 1'-(cyclohexylsulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxylate**

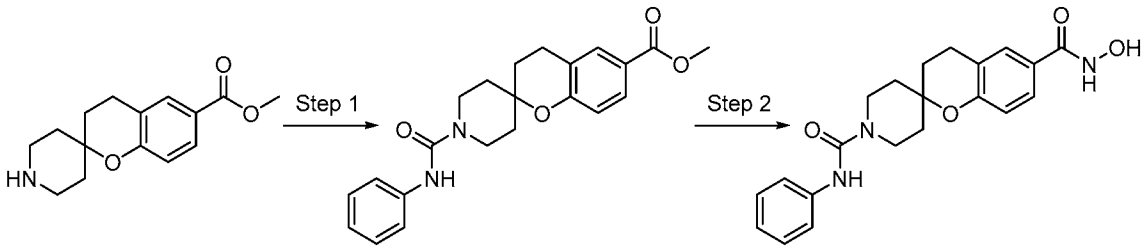
[00239] Into a 50-mL round-bottom flask, was placed a solution of methyl 3,4-dihydrospiro[1-benzopyran-2,4'-piperidine]-6-carboxylate (70 mg, 0.24 mmol, 1 equiv) in CH_2Cl_2 (2 mL). This was followed by the addition of Et_3N (95 mg, 0.94 mmol, 4 equiv) dropwise with stirring at 0 °C. To this was added cyclohexanesulfonyl chloride (74 mg, 0.41 mmol, 1.73 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred overnight at

room temperature. The residue was purified by preparative TLC with EtOAc/petroleum ether (1:2). The collected fractions were combined and concentrated under vacuum to afford 60 mg (63% yield) of the title compound as a yellow solid. MS: (ES, *m/z*) 408 $[M+H]^+$.

***Step-2*: 1'-(Cyclohexylsulfonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide**

[00240] Into a 25-mL round-bottom flask, was placed a solution of methyl 1'-(cyclohexylsulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxylate (60 mg, 0.15 mmol, 1 equiv) in THF/MeOH (1.5 mL), NH_2OH (35.12 mmol, 234 equiv), and aq. 1N NaOH (0.29 mL, 2 equiv). The resulting solution was stirred for 7 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Shield RP18 OBD 5 μm, 19x150mm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Gradient: 10% B to 80% B in 7 min; Detector: UV 254 nm, 220 nm. The product fractions were dried by lyophilization to afford 4.9 mg (6% yield) of the title compound as a orange solid. ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 11.00 (br s, 1H), 8.90 (br s, 1H), 7.55 (s, 1H), 7.51 (m, 2H), 6.85 (d, *J* = 8 Hz, 1H), 3.50 (m, 2H), 3.24-3.10 (m, 3H), 2.78 (t, *J* = 6.8 Hz, 2H), 2.02 (m, 2H), 1.86-1.62 (m, 9H), 1.42-1.11 (m, 5H) 11.00 (br s, 1H), 8.90 (br s, 1H), 7.55 (s, 1H), 7.51 (m,2H), 6.85 (d, *J* = 8 Hz, 1H), 3.50 (m, 2H), 3.24-3.10 (m, 3H), 2.78 (t, *J* = 6.8 Hz, 2H), 2.02 (m, 2H), 1.86-1.62 (m, 9H), 1.42-1.11 (m, 5H). MS: (ES, *m/z*): 409 $[M+H]^+$.

Example 47 – Preparation of N6-hydroxy-N1'-phenylspiro[chromane-2,4'-piperidine]-1',6-dicarboxamidedicarboxamide (II-7)



***Step-1*: Methyl 1'-(phenylcarbamoyl)spiro[chromane-2,4'-piperidine]-6-carboxylate**

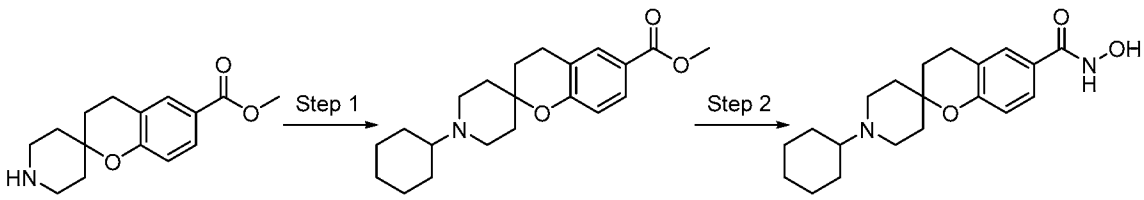
[00241] Into a 100-mL round-bottom flask was placed a solution of methyl spiro[chromane-2,4'-piperidine]-6-carboxylate (70 mg, 0.24 mmol, 1 equiv) in CH_2Cl_2 (10 mL), This was followed by the addition of Et_3N (81.26 mg, 0.80 mmol, 3 equiv) and isocyanatobenzene (40 mg, 0.34 mmol, 1.5 equiv). The resulting solution was stirred for 2 h at 0 °C. The resulting mixture was concentrated under vacuum and the residue was purified by normal phase chromatography

on silica gel with EtOAc/petroleum ether (1:3). The collected fractions were concentrated to give 72 mg (81% yield) of the title compound as a light yellow solid. MS: (ES, *m/z*): 381 $[M+H]^+$.

***Step-2*: N6-Hydroxy-N1'-phenylspiro[chromane-2,4'-piperidine]-1',6-dicarboxamidedicarboxamide**

[00242] Into a 100-mL round-bottom flask was placed a solution of methyl 1'-(phenylcarbamoyl)spiro[chromane-2,4'-piperidine]-6-carboxylate (72 mg, 0.19 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL), NH_2OH (50% in water ,0.5 mL, 60 equiv), and 1N aq. NaOH (0.25 mL, 2 equiv). The resulting solution was stirred for 6 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Waters HSS C18, 2.1x50 mm, 1.8 μm; Mobile Phase, A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 22.1 mg (31% yield) of the title compound as a pink solid. ^{1}H-NMR (400 MHz, DMSO-d6) δ (ppm): 10.99 (br s, 1H), 8.54 (s, 1H), 7.45-7.56 (m, 4H), 7.21-7.25 (d, *J* = 8 Hz, 2H), 6.83-6.90 (m, 2H), 3.90-3.86 (m, 2H), 3.28-3.22 (t, *J* = 11.2 Hz, 2H), 2.80-2.77 (t, *J* = 6.4 Hz, 2H), 1.86-1.83 (t, *J* = 6.8Hz, 2H), 1.75-1.59 (m, 4H) MS: (ES, *m/z*): 382 $[M+H]^+$.

Example 48 – Preparation of 1'-cyclohexyl-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-8)



***Step-1*: Methyl 1'-cyclohexylspiro[chromane-2,4'-piperidine]-6-carboxylate**

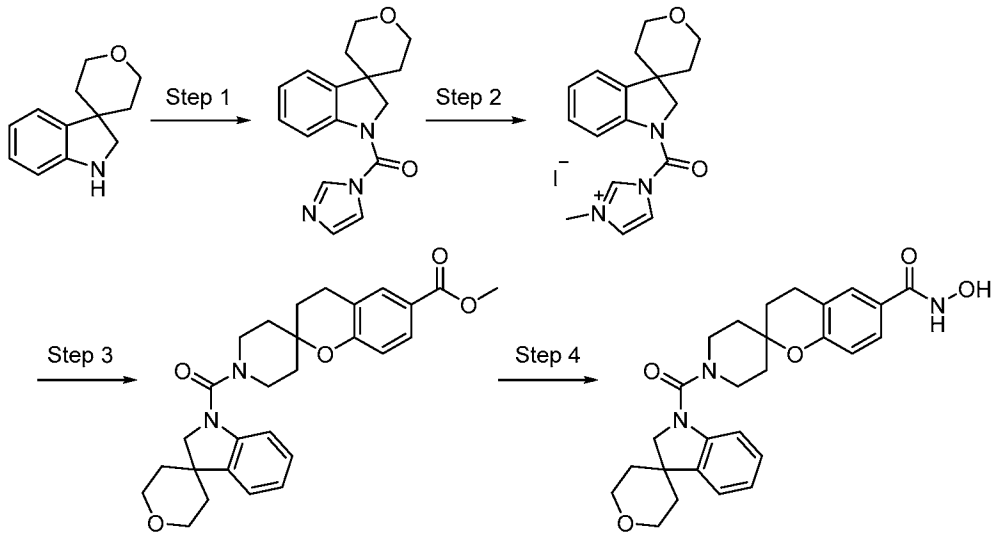
[00243] Into a 100-mL round-bottom flask was placed a solution of methyl spiro[chromane-2,4'-piperidine]-6-carboxylate (50 mg, 0.17 mmol, 1 equiv) in CH_2Cl_2 (5 mL). This was followed by the addition of cyclohexanone (18.77 mg, 0.19 mmol, 1 equiv) and $NaBH(OAc)_3$ (60.9 mg, 0.29 mmol, 1.5 equiv). The resulting solution was stirred for 3 days at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse-phase chromatography using the following conditions: C18 column; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/ 0.05% TFA; Gradient: 3% B to 50% B in 30 min. The collected

fractions were concentrated to give 35 mg (61% yield) of the title compound as a light yellow oil. MS: (ES, *m/z*): 344 $[M+H]^+$.

***Step-2*: 1'-Cyclohexyl-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide**

[00244] Into a 100-mL round-bottom flask was placed a solution of methyl 1'-cyclohexylspiro[chromane-2,4'-piperidine]-6-carboxylate (35 mg, 0.10 mmol, 1 equiv) in THF/MeOH (4:1, 2.5 mL), NH_2OH (50% in water, 0.7 mL, 60 equiv), and 1N aq. NaOH (0.3 ml, 7.50 mmol, 2 equiv). The resulting solution was stirred for 8 h at room temperature. The crude product was purified by Prep-HPLC with the following conditions: Column: Waters HSS C18, 2.1x50 mm, 1.8 μm; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: CH_3CN/0.05% TFA; Flow rate: 0.7 mL/min; Gradient: 5% B to 95% B in 2 min, hold 0.6 min; Detector: UV 254 nm. The collected fractions were lyophilized to give 10.9 mg (22% yield) of the title compound as a pink solid. ^{1}H-NMR (300 MHz, DMSO-d6) δ (ppm): 11.02 (br s, 1H), 9.25 (br s, 1H), 8.90 (br s, 1H), 7.58-7.52 (m, 2H), 6.90-6.80 (m, 1H), 3.41-3.22 (m, 3H), 3.14-3.10 (m, 3H), 2.82-2.78 (t, J = 6.6 Hz, 2H), 2.27-2.05 (m, 3H), 1.97-1.82 (m, 7H), 1.65-1.61 (m, 1H), 1.49-1.22 (m, 4H), 1.17-1.09 (m, 1H). MS: (ES, *m/z*): 345 $[M+H]^+$.

Example 49 – Preparation of N-hydroxy-1'-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carbonyl)spiro [chromane-2,4'-piperidine]-6-carboxamide (II-9)



***Step-1*: (1H-Imidazol-1-yl)(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-yl)methanone**

[00245] In a 20-mL scintillation vial, 1,1′-carbonyldiimidazole (236 mg, 1.453 mmol, 1.09 equiv) was taken up in THF (10 mL) and 2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran] (250 mg,

1.321 mmol, 1 equiv) was added. The resulting solution was heated at 50 °C with agitation for 3 h. The reaction was cooled to ambient temperature, and then concentrated to dryness. The residue was dissolved in 20 mL of CH_2Cl_2 and washed with 20 mL of brine. The organic layer was passed through an Isolute© phase separator, and then concentrated to dryness to afford the title compound as a white solid which was used without further purification. MS: (ES, *m/z*): 284 $[M+H]^+$.

***Step-2*: 3-Methyl-1-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carbonyl)-1H-imidazol-3-ium iodide**

[00246] In a 20-mL scintillation vial (1H-imidazol-1-yl)(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-yl)methanone (400 mg, 1.412 mmol, 1 equiv) was taken up in CH_3CN (10 mL). CH_3I (0.53 mL, 8.47 mmol, 5.96 equiv) was added and the reaction was stirred at ambient temperature for 24 h. The reaction was concentrated to dryness to afford the title compound as a yellow solid which was used without further purification. MS: (ES, *m/z*): 299 $[M-I+H]^+$.

***Step-3*: Methyl 1'-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carbonyl)spiro[chromane-2,4'- piperidine]-6-carboxylate**

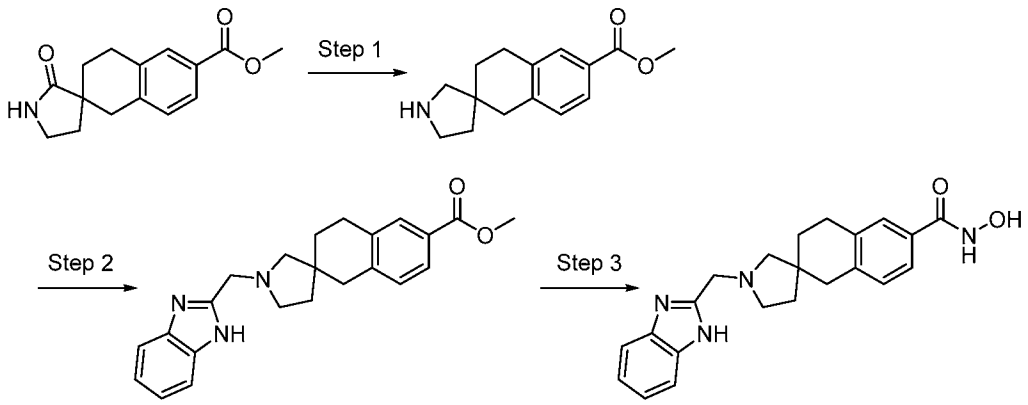
[00247] In a 20-mL scintillation vial 3-methyl-1-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carbonyl)-1H-imidazol-3-ium iodide (30 mg, 0.071 mmol, 1 equiv) and methyl spiro[chromane-2,4'-piperidine]-6-carboxylate (18 mg, 0.071 mmol, 1 equiv) were taken up in CH_3Cl (2 mL). Et_3N (0.029 ml, 0.212 mmol, 3 equiv) was added. The resulting solution was stirred at ambient temperature for 18 h. The reaction was diluted with 10 mL of CH_2Cl_2 and washed with 20 mL of brine. The organic layer was passed through an Isolute© phase separator, and then concentrated to dryness to afford the title compound as an orange oil which was used without further purification. MS: (ES, *m/z*): 477 $[M+H]^+$.

***Step-4*: N-Hydroxy-1'-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carbonyl)spiro [chromane-2,4'-piperidine]-6-carboxamide**

[00248] Into a 20-mL scintillation vial was placed a solution of methyl 2-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-ylcarbonyl)-5-thia-2-azaspiro[3.4]octane-7-carboxylate 5,5-dioxide (30 mg, 0.069 mmol, 1 equiv) in THF/MeOH (1:1, 2 mL), NH_2OH (50% in water, 0.5 mL, 7.57 mmol, 110 equiv), and 1N aq. NaOH (0.5 mL, 0.5 mmol, 7.24 equiv). The resulting solution was stirred for 2 h at ambient temperature and concentrated to dryness. The crude product was purified by Prep-HPLC using the following conditions: Column: XBridge Prep C18

OBD 5 μm, 19x50mm; Mobile Phase A: Water/0.05% Formic acid, Mobile Phase B: CH_3CN/0.05% Formic Acid; Flow Rate: 23 mL/min; Gradient: 15% B to 65% B in 8 min; Detector: UV 254 nm, 220 nm. The collected fractions were lyophilized to obtain 5 mg (16% yield) of the title compound as an off- white solid. ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 11.00 (s, 1H), 8.89 (s, 1H), 8.36 (s, 1H), 7.39-7.63 (m, 2H), 7.12-7.30 (m, 2H), 7.03 (d, *J*=8.21 Hz, 1H), 6.78-6.97 (m, 2H), 3.83 (s, 4H), 3.44-3.58 (m, 4H), 2.75 (br d, *J* = 15.24 Hz, 4H), 1.73-1.89 (m, 6H), 1.54 (s, 2H). MS: (ES, *m/z*): 478 $[M+H]^+$.

Example 50 – Preparation of 1'-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-1)



***Step-1*: Methyl 3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate**

[00249] A solution of methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (0.100 g, 0.386 mmol, 1 equiv) in 3 mL of THF was cooled to -10 °C (ice/acetone) when borane-THF complex (1M in THF; 0.58 mL, 0.58 mmol, 1.5 equiv) was added drop wise over 5 min. The mixture was stirred at -10 °C for 5 min, then heated up to 52 °C for about 7 days and an additional 0.5 eq borane-THF complex was added after 24 and 48 h; THF was added as needed to maintain volume. The resulting mixture was cooled to room temperature and quenched with 0.3 mL 2 N HCl, heated to 52 °C for 1 h, then concentrated. The residue was loaded onto a 10 g (70 mL) SCX-2 cartridge with MeOH (with some CH_2Cl_2), flushed with MeOH (with some CH_2Cl_2), and eluted with 2 M NH_3 in MeOH (with some CH_2Cl_2). The fractions from the NH_3 elution were combined and concentrated. Purification by silica gel chromatography with CH_2Cl_2/MeOH/NH_4OH (90/20/1) afforded 134 mg (50% yield) of the title compound. ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 7.73-7.63 (m, 2H), 7.23-7.14 (m, 1H), 3.82 (s, 3H), 3.12-3.05 (dd, 2H), 2.90-2.62 (m, 6H), 2.50 (br s, 1H), 1.78-1.45 (m, 4H). MS: (APCI, *m/z*): 246 $[M+H]^+$.

***Step-2*: Methyl 1'-((1H-benzo[d]imidazol-2-yl)methyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'- pyrrolidine]-6-carboxylate**

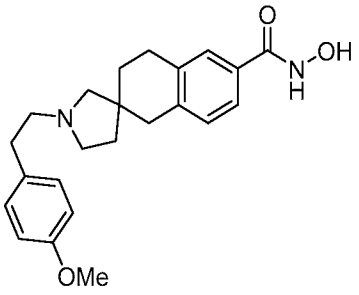
[00250] To a 20 mL vial was added methyl 3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (0.045 g, 0.183 mmol, 1 equiv), K_2CO_3 (0.051 g, 0.367 mmol, 2 equiv) and DMF (1 mL). Next, 2-(chloromethyl)-1H-benzo[d]imidazole (0.035 g, 0.211 mmol, 1.15 equiv) was added and the mixture was stirred at 50 °C overnight. Water was added to the reaction mixture and extracted with two portions of EtOAc. The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by column chromatography on silica gel (0-5% MeOH/ CH_2Cl_2) afforded 39 mg (57% yield) of the title compound as a colourless glassy solid. MS: (ES, *m/z*): 376 [M+H]+.

***Step-3*: 1'-((1H-Benzo[d]imidazol-2-yl)methyl)-N-hydroxy-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

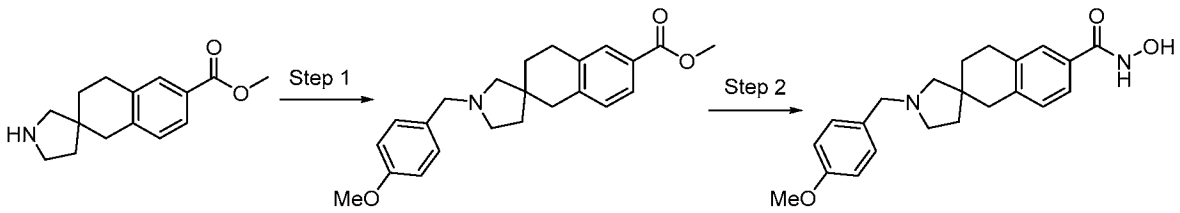
[00251] Methyl 1'-((1H-benzo[d]imidazol-2-yl)methyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (0.039 g, 0.104 mmol, 1 equiv) was dissolved in a solution of THF/MeOH (4:1, 1.38 mL). Hydroxylamine (50% in water, 0.58 mL, 9.4 mmol, 90 equiv) was added followed by 1N aq. NaOH (0.157 mL, 3 equiv). The reaction was stirred at room temperature for 1 h and was purified directly by reverse-phase chromatography using the following conditions: Column: XTerra Prep MS C18 OBD 5 μm, 19x100 mm; Mobile Phase A: Water/0.05% Formic Acid, Mobile Phase B: CH_3CN/0.05% Formic Acid; Flow rate: 20 mL/min; Gradient:15% B to 85% B in 10 min; Detector: UV 254 nm, 220 nm. Combined fractions were lyohpilized to afford 0.016 g (41% yield) of the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 8.29 (s, 2H), 7.58 (br dd, J = 5.9, 3.2 Hz, 3H), 7.39-7.49 (m, 2H), 7.21-7.34 (m, 2H), 7.04-7.18 (m, 1H), 4.28 (br s, 2H), 3.29-3.35 (m, 4H), 2.77-3.02 (m, 8H), 1.81-1.99 (m, 4H). MS: (ES, *m/z*): 377 $[M+H]^+$.

Table-29: The following compound was prepared according to the method of Example 50.

Ex.	Structure	^{1}H-NMR δ (ppm)	Found (ES, *m/z*) $[M+H]^+$

I-2		(300 MHz, CD_3OD): 8.47 (s, 1H), 7.34-7.69 (m, 3H), 7.11-7.29 (m, 3H), 6.88 (d, J=8.5 Hz, 2H), 3.76 (s, 3H), 3.46-3.64 (m, 2H), 3.16-3.46 (m, 6H), 2.87-3.14 (m, 4H), 1.83-2.11 (m, 4H)	381

Example 51 – Preparation of N-hydroxy-1'-(4-methoxybenzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-3)



***Step-1*: Methyl 1'-(4-methoxybenzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-7-carboxylate**

[00252] Methyl 3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate (0.043 g, 0.177 mmol, 1 equiv) was combined with Et_3N (0.025 mL, 0.179 mmol, 1 equiv) and 4-methoxybenzaldehyde (0.024 mL, 0.195 mmol, 1.1 equiv) in DCE (2.0 mL). The reaction was stirred at room temperature for 1 hour. Then $NaBH(OAc)_3$ (0.049 g, 0.23 mmol, 1.3 equiv) was added and the reaction was stirred at room temperature for 16 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and the organic layer was separated and directly purified by normal phase chromatography on silica gel (30% to 100% EtOAc/hexanes) to afford 0.045 g (70% yield) of the title compound as a colorless, glassy solid. MS: (ES, *m/z*): 366 $[M+H]^+$.

***Step-2*: N-Hydroxy-1'-(4-methoxybenzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide**

[00253] Methyl 1'-(4-methoxybenzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-7-carboxylate (0.045 g, 0.123 mmol, 1 equiv) was dissolved in a solution of THF/MeOH (4:1, 1.25 mL). Hydroxylamine (50% in water, 0.68 mL, 11.1 mmol, 90 equiv) was added followed by 2N aq. NaOH (0.185 mL, 3 equiv). The reaction was stirred at room temperature for 48 h and was purified directly by reverse-phase chromatography using the following conditions: Column: XTerra Prep MS C18 OBD 5 μm, 19x100 mm; Mobile Phase A: Water/0.05% Formic Acid,

Mobile Phase B: CH_3CN/0.05% Formic Acid; Flow rate: 20 mL/min; Gradient:15%B to 85%B in 10 min; Detector: UV 254 nm, 220 nm. Combined fractions were lyohpilized to afford 27 mg (61% yield) of the title compound. ^1H NMR (300 MHz, CD_3OD) δ (ppm): 8.44 (s, 2H), 7.37-7.56 (m, 4H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.84-7.09 (m, 2H), 4.32 (s, 2H), 3.79 (s, 3H), 3.10-3.61 (m, 8H), 2.84-3.08 (m, 4H), 1.86-2.11 (m, 4H). MS: (ES, *m/z*): 367 $[M+H]^+$.

Example 52 – Small Molecule X-ray Crystallography Experiment for methyl (R)-1'-[(4-methanesulfonylphenyl)methyl]-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate

[00254] Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å). All structures were solved by direct methods and were refined against F^2 on all data by full-matrix least squares. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). All atoms shown are depicted with 50% thermal contours. The hydrogen atoms are shown as arbitrary spheres. Carbon atoms C11 and C34 both have R stereochemistry (Figure 1).

Table-30: Crystal data and structure refinement for methyl (R)-1'-[(4-methanesulfonylphenyl)methyl]-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxylate.

Empirical formula	$C_{23}H_{25}NO_5S$	
Formula weight	427.50	
Temperature	93(2) K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	*P* 2_1	
Unit cell dimensions	a = 19.8815(6) Å	α = 90°
	b = 5.6009(2) Å	β = 113.941(8)°
	c = 20.4656(14) Å	γ = 90°
Volume	2082.9(2) $Å^3$	
Z	4	
Density (calculated)	1.363 Mg/m^3	
Absorption coefficient	1.680 mm^{-1}	
F(000)	904	

Crystal size	0.140 x 0.040 x 0.010 mm^3	
Crystal color and habit	Colorless Plate	
Diffractometer	Rigaku Saturn 944+ CCD	
Θ range for data collection	2.362 to 68.068°.	
Index ranges	$-21 \leq h \leq 22$, $-6 \leq k \leq 6$, $-24 \leq l \leq 23$	
Reflections collected	34368	
Independent reflections	7110 [R(int) = 0.1679]	
Observed reflections (I > 2σ (I))	3779	
Completeness to θ = 67.687°	97.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.983 and 0.775	
Solution method	SHELXL-2014/7 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	7110 / 1 / 545	
Goodness-of-fit on F^2	0.933	
Final R indices [I>2σ(I)]	R1 = 0.0633, wR2 = 0.1111	
R indices (all data)	R1 = 0.1253, wR2 = 0.1362	
Absolute structure parameter	0.05(3)	
Largest diff. peak and hole	0.381 and -0.629 e.$Å^{-3}$	

Example 53 – *In vitro* Histone Deacetylase Assay

[00255] The enzymatic HDAC6 assay was performed using electrophoretic mobility shift assay. Full length human recombinant HDAC6 protein was expressed in baculoviral system and purified by affinity chromatography. The enzymatic reactions were assembled in 384 well plates in a total volume of 25 µL in a reaction buffer composing: 100 mM HEPES, pH7.5, 25 mM KCl, 0.1% bovine serum albumin, 0.01% Triton X-100, 1% DMSO (from compounds) 2 µM of the fluorescently labeled peptide substrate and enzyme. The enzyme was added at a final concentration of 1 nM. The peptide substrate RHKK(Ac)-NH2 was used. The compounds were tested at 12 concentrations spaced by 3x dilution intervals. Negative control samples (0%-inhibition in the absence of inhibitor) and positive control samples (100%-inhibition) were assembled in replicates of four in each assay plate. The reactions were incubated at 25 °C and quenched by the addition of 45 µL of termination buffer (100 mM HEPES, pH 7.5, 0.01% Triton X-100, 0.05% SDS).

[00256] The terminated assay plates were analyzed on LabChip® 3000 microfluidic electrophoresis instrument (Perkin Elmer/Caliper Life Sciences). The fluorescence intensity of

the electrophoretically separated de-acetylated product and substrate peptide was measured. Activity in each sample was determined as the product to sum ratio (PSR): P/(S+P), where P is the peak height of the product peptide and S is the peak height of the substrate peptide. Percent inhibition (Pinh) is determined using the following equation:

[00257] Pinh = (PSR0% - PSRinh)/(PSR0% - PSR100%)*100 , where PSRinh is the product sum ratio in the presence of inhibitor, PSR0% is the average product sum ration in the absence of inhibitor and PSR100% is the average product sum ratio in 100%-inhibition control samples. The IC50 values of inhibitors were determined by fitting the %-inhibition curves with 4 parameter dose-response model using XLfit 4 software.

[00258] As set forth in Table-31, below, IC_{50} values are defined as follows: IC50 $\leq$ 0.1 μM (+++); IC50 > 0.1 μM and $\leq$ 0.5 μM (++); IC50 > 0.5 μM (+).

Table-31: Inhibitory Concentration (IC50) Values for Representative Compounds against HDAC6

ChemDraw Name	**Number**	**HDAC6 activity range**
1'-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-1)	+++
N-hydroxy-1'-(4-methoxyphenethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-2)	++
N-hydroxy-1'-(4-methoxybenzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-3)	++
N-hydroxy-1'-(4-methoxyphenethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-4)	+++
1'-(1H-benzo[d]imidazol-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-5)	+++
1'-(3,4-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-6)	+++
1'-(cyclohexylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-7)	++
N-hydroxy-1'-(4-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-8)	++
1'-(3-(dimethylamino)propyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-9)	++
(R)-N-hydroxy-2'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-10)	+++
(S)-N-hydroxy-2'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-11)	+++

(R)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-12)	++
(S)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-13)	+++
(R)-N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-14)	+
(S)-N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-15)	+++
(R)-N-hydroxy-2'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-16)	++
(S)-N-hydroxy-2'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-17)	+++
(R)-N-hydroxy-2'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-18)	+++
(S)-N-hydroxy-2'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-19)	+++
(R)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-20)	+++
(S)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-21)	+++
(R)-N-hydroxy-1'-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-22)	+++
(S)-N-hydroxy-1'-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-23)	+++
(R)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-24)	+++
(S)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-25)	+++
(R)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-26)	+++
(R)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-27)	+++
(S)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-28)	+++
(S)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-29)	+++
(R)-1'-((2-chlorothiazol-5-yl)methyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-30)	+++
(R)-N-hydroxy-1'-((2-hydroxythiazol-5-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-31)	+++
(R)-N-hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-32)	+++

(R)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-33)	+++
(R)-N-hydroxy-1'-isopentyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-34)	+++
(R)-1'-(but-2-yn-1-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-35)	+++
(R)-N-hydroxy-1'-(2-methoxyethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-36)	+++
(R)-1'-cinnamyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-37)	+++
(R)-N-hydroxy-1'-(2-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-38)	+++
(R)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-39)	+++
(R)-1'-(2-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-40)	+++
(R)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-41)	+++
(R)-1'-(benzo[c][1,2,5]oxadiazol-5-ylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-42)	+++
(R)-N-hydroxy-1'-(2-morpholino-2-oxoethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-43)	+++
(R)-N-hydroxy-1'-(2-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-44)	+++
(R)-N-hydroxy-1'-((1-isopropyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-45)	+++
(R)-N-hydroxy-1'-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-46)	+++
(R)-N-hydroxy-1'-(2-methylallyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-47)	+++
(R)-1'-(2,5-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-48)	+++
(R)-1'-(2,6-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-49)	+++
(R)-1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-50)	+++
(R)-N-hydroxy-1'-(3-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-51)	+++
(R)-N-hydroxy-2'-oxo-1'-(pyridin-2-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-52)	+++
(R)-1'-(3-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-53)	+++

(R)-1'-(3-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-54)	+++
(R)-1'-(4-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-55)	+++
(R)-N-hydroxy-1'-(4-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-56)	+++
(R)-1'-(2-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-57)	+++
(R)-N-hydroxy-1'-(naphthalen-2-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-58)	+++
(R)-1'-(2-(difluoromethoxy)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-59)	+++
(S)-N-hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-60)	++
(S)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-61)	++
(S)-N-hydroxy-1'-isopentyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-62)	++
(S)-1'-(but-2-yn-1-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-63)	+++
(S)-N-hydroxy-1'-(2-methoxyethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-64)	++
(S)-1'-cinnamyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-65)	+++
(S)-N-hydroxy-1'-(2-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-66)	+++
(S)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-67)	++
(S)-1'-(2-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-68)	++
(S)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-69)	++
(S)-1'-(benzo[c][1,2,5]oxadiazol-5-ylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-70)	+++
(S)-N-hydroxy-1'-(2-morpholino-2-oxoethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-71)	++
(S)-N-hydroxy-1'-(2-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-72)	+++
(S)-N-hydroxy-1'-((1-isopropyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-73)	+++
(S)-1'-(2,5-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-74)	++
(S)-1'-(2,6-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-75)	++

(S)-1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-76)	+++
(S)-N-hydroxy-1'-(3-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-77)	+++
(S)-N-hydroxy-2'-oxo-1'-(pyridin-2-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-78)	+++
(S)-1'-(3-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-79)	+++
(S)-N-hydroxy-2'-oxo-1'-(4-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-80)	++
(S)-1'-(3-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-81)	+++
(S)-1'-(4-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-82)	+++
(S)-N-hydroxy-1'-(4-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-83)	+++
(S)-1'-(2-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-84)	+++
(S)-1'-(4-(tert-butyl)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-85)	++
(S)-N-hydroxy-1'-(naphthalen-2-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-86)	+++
(S)-1'-(2-(difluoromethoxy)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-87)	+++
(R)-N-hydroxy-1'-(4-(methylsulfonyl)benzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-88)	+++
(R)-N-hydroxy-1'-(naphthalen-1-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-89)	+++
(R)-1'-(3-fluoro-4-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-90)	+++
(R)-1'-(benzo[d][1,3]dioxol-5-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-91)	+++
(R)-N-hydroxy-1'-(3-(methylthio)phenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-92)	+++
(R)-1'-(4-(dimethylamino)phenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-93)	+++
(R)-N-hydroxy-1'-(6-isopropylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-94)	+++
(R)-N-hydroxy-2'-oxo-1'-(quinolin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-95)	+++
(R)-1'-(2,3-dihydrobenzofuran-7-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-96)	+++
(R)-1'-(6-(tert-butylamino)pyrimidin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-97)	+++
(R)-1'-(1,3-dimethyl-1H-pyrazol-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-98)	+++

(R)-N-hydroxy-1'-(imidazo[1,2-a]pyridin-6-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-99)	+++
(S)-1'-(2,4-dimethylphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-100)	+++
(S)-N-hydroxy-1'-(6-isopropylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-101)	+++
(S)-N-hydroxy-2'-oxo-1'-(quinolin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-102)	+++
(S)-N-hydroxy-1'-(imidazo[1,2-a]pyridin-6-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-103)	+++
(R)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-104)	+++
(S)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-105)	+++
(R)-N-hydroxy-2'-oxo-1'-(4-((trifluoromethyl)sulfonyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-106)	+++
(S)-N-hydroxy-2'-oxo-1'-(4-((trifluoromethyl)sulfonyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-107)	++
(R)-N-hydroxy-1'-(3-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-108)	+++
(R)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-109)	+++
(R)-1'-(5-fluoropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-110)	+++
(R)-N-hydroxy-1'-(2-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-111)	+++
(R)-1'-(3-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-112)	+++
(R)-1'-(3-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-113)	+++
(R)-N-hydroxy-1'-(6-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-114)	+++
(S)-N-hydroxy-1'-(2-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-115)	+++
(S)-1'-(3-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-116)	+++
(S)-1'-(3-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-117)	+++
(S)-N-hydroxy-1'-(6-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-118)	+++
(R)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-119)	+++
(R)-1'-(4-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-120)	+++

(R)-1'-(2-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-121)	
(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-122)	++
(R)-1'-(2,3-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-123)	+++
(R)-N-hydroxy-1'-(4-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-124)	+++
(R)-1'-(2-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-125)	+++
(S)-1'-(2-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-126)	+++
(S)-1'-(2-fluoro-4-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-127)	+++
(R)-1'-(4-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-128)	+++
(S)-1'-(4-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-129)	+++
(S)-1'-(5-chloropyridin-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-130)	+++
(R)-N-hydroxy-1'-(2-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-131)	+++
(S)-N-hydroxy-1'-(2-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-132)	+++
(R)-N-hydroxy-1'-(6-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-133)	+++
(S)-N-hydroxy-1'-(6-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-134)	+++
(R)-N-hydroxy-1'-(5-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-135)	+++
(R)-N-hydroxy-1'-(4-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-136)	+++
(S)-N-hydroxy-1'-(4-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-137)	+++
(R)-1'-(5-chloropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-138)	+++
(S)-1'-(5-chloropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-139)	+++
(R)-1'-(3-chloropyridin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-140)	+++
(S)-1'-(3-chloropyridin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-141)	+++
(S)-N-hydroxy-1'-(4-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-142)	+++
(R)-N-hydroxy-1'-(5-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-143)	+++

(S)-N-hydroxy-1'-(5-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-144)	+++
(R)-N-hydroxy-1'-(2-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-145)	+++
(S)-N-hydroxy-1'-(2-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-146)	+++
(S)-1'-(2-fluoro-5-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-147)	+++
(S)-1'-(3-fluoro-5-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-148)	+++
(R)-N-hydroxy-1'-(2-methoxypyridin-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-149)	+++
(S)-N-hydroxy-1'-(2-methoxypyridin-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-150)	+++
(R)-1'-(6-(dimethylamino)pyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-151)	+++
(S)-1'-(6-(dimethylamino)pyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-152)	++
(S)-1'-(5-fluoropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-153)	+++
(S)-1'-(4-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-154)	+++
(S)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-155)	+++
(S)-1'-(2,3-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-156)	+++
(S)-1'-(2-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-157)	+++
(S)-N-hydroxy-1'-(3-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-158)	+++
(R)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-159)	+++
(S)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-160)	++
(R)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-161)	+++
(S)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-162)	+++
(R)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-163)	+++
(S)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-164)	++
(R)-N-hydroxy-2'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-165)	+++
(S)-N-hydroxy-2'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-166)	++

(R)-1'-(2,5-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-167)	+++
(R)-N-hydroxy-1'-(1-methyl-1H-pyrazol-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-168)	+++
(S)-1'-(2,5-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-169)	+++
(S)-N-hydroxy-1'-(1-methyl-1H-pyrazol-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-170)	+++
(R)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-171)	+++
(S)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-172)	+++
(S)-1'-(4-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-173)	+++
(S)-1'-(2-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-174)	+++
(R)-1'-(2-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-175)	+++
1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-176)	+++
N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-177)	+++
N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-178)	+++
(R)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-179)	+++
(S)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-180)	+++
(R)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-181)	+++
(S)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-182)	+++
(S)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-183)	+++
(S)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-184)	+++
(R)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-185)	+++
(S)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-186)	+++
(R)-N-hydroxy-1'-(3-methoxypropyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-187)	+++
(S)-N-hydroxy-1'-(3-methoxypropyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-188)	+++
(R)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-189)	+++

(S)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-190)	+++
(R)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-191)	+++
(S)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-192)	+++
(R)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-193)	+++
(R)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-194)	+++
(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-195)	+++
(R)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-196)	+++
(R)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-197)	+++
(S)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-198)	+++
(R)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-199)	+++
(S)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide	(I-200)	+++
(R)-N-hydroxy-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-201)	+++
(S)-N-hydroxy-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-202)	+++
(R)-N-hydroxy-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-203)	+++
(S)-N-hydroxy-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-204)	+++
(R)-1'-(cyclobutylmethyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-205)	+++
(R)-1'-ethyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-206)	+++
(R)-N-hydroxy-1'-isobutyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-207)	+++
(R)-N-hydroxy-1'-isopropyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-208)	+++
(R)-1'-cyclopropyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-209)	+++
(S)-1'-(cyclobutylmethyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-210)	+++
(S)-1'-ethyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-211)	+++
(S)-N-hydroxy-1'-isobutyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-212)	+++

(S)-N-hydroxy-1'-isopropyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-213)	+++
(S)-1'-cyclopropyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-214)	+++
(R)-N-hydroxy-1'-(oxetan-3-ylmethyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-215)	+++
(R)-1'-benzyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-216)	+++
(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-217)	++
(S)-1'-benzyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-218)	+++
(R)-N-hydroxy-1'-(3-methoxypropyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-219)	+++
(R)-N-hydroxy-5'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-220)	+++
(R)-N-hydroxy-5'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-221)	+++
(S)-N-hydroxy-1'-(3-methoxypropyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-222)	+++
(S)-N-hydroxy-5'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-223)	+++
(S)-N-hydroxy-5'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-224)	+++
(R)-N-hydroxy-1'-(2-methylbenzyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-225)	+++
(R)-N-hydroxy-5'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-226)	+++
(R)-1'-(4-fluorophenyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-227)	+++
(R)-N-hydroxy-5'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-228)	+++
(R)-N-hydroxy-5'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide	(I-229)	+++
N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide	(I-230)	+
N-hydroxy-2'-oxo-1'-phenylspiro[chromane-2,3'-pyrrolidine]-6-carboxamide	(I-231)	++
1'-benzyl-N-hydroxy-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide	(I-232)	++
N-hydroxy-2'-oxo-1'-(pyridin-3-yl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide	(I-233)	++
N-hydroxy-2'-oxo-1'-((tetrahydro-2H-pyran-4-yl)methyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide	(I-234)	+
N-hydroxy-1'-isopropyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide	(I-235)	+

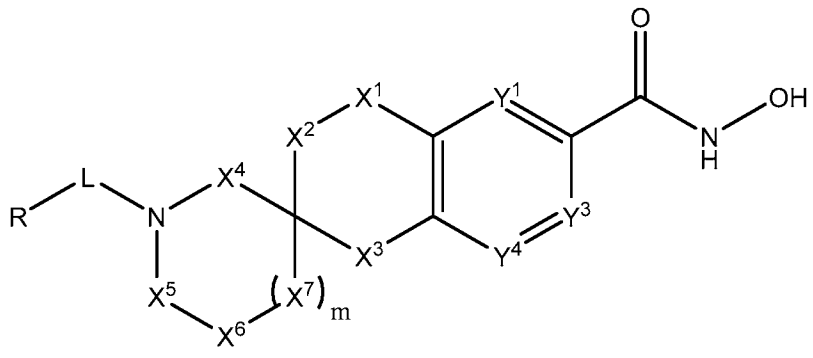
N-hydroxy-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide	(I-236)	++
N-hydroxy-1'-methyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide	(I-237)	++
N-hydroxy-2-oxo-1-phenylspiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide	(I-238)	++
1-benzyl-N-hydroxy-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide	(I-239)	++
N-hydroxy-2-oxo-1-(pyridin-3-yl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide	(I-240)	++
N-hydroxy-2-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide	(I-241)	+
N-hydroxy-2-oxo-1-(pyridin-4-ylmethyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide	(I-242)	+
N-hydroxy-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide	(I-243)	+
N-hydroxy-1-methyl-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide	(I-244)	+
N-hydroxy-1'-(4-methoxybenzyl)spiro[chromane-2,4'-piperidine]-6-carboxamide	(II-1)	+
1'-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide	(II-2)	+
1'-(cyclohexanecarbonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide	(II-3)	+
N-hydroxy-1'-(4-methoxybenzoyl)spiro[chromane-2,4'-piperidine]-6-carboxamide	(II-4)	+
N-hydroxy-1'-((4-methoxyphenyl)sulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxamide	(II-5)	+
1'-(cyclohexylsulfonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide	(II-6)	++
N6-hydroxy-N1'-phenylspiro[chromane-2,4'-piperidine]-1',6-dicarboxamide	(II-7)	++
1'-cyclohexyl-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide	(II-8)	+
N-hydroxy-1'-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carbonyl)spiro[chromane-2,4'-piperidine]-6-carboxamide	(II-9)	+

Equivalents

[00259] While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

Claims:

1. A compound of the Formula I:



(I)

or a pharmaceutically acceptable salt, prodrug , solvate, hydrate, tautomer, or isomer or thereof, wherein:

X^1, X^2, X^3, X^6, and X^7 are each independently $–CR^1R^2–$, $–NR^3–$, $–O–$, $–C(O)–$, $–SO_2–$, $–S(O)–$, or $–S–$;

X^4 and X^5 are each independently $–CR^1R^2–$, $–C(O)–$, $–SO_2–$, $–S(O)–$, or $–S–$;

Y^1, Y^3 and Y^4 are each independently N or CR^1;

L is a bond, $–(CR^1R^2)_n–$, $–C(O)NR^3–$, $–S(O)_2–$, $–S(O)_2NR^3–$, $–S(O)–$, $–S(O)NR^3–$, $–C(O)(CR^1R^2)_nO–$, or $–C(O)(CR^1R^2)_n–$;

R is independently –H, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, $–C_5$-C_{12}spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, or O, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, oxo, $–NO_2$, –CN, $–R^1$, $–R^2$, $–SR^3$, $–OR^3$, $–NHR^3$, $–NR^3R^4$, $–S(O)_2NR^3R^4$, $–S(O)_2R^1$, $–C(O)R^1$, $–CO_2R^1$, $–NR^3S(O)_2R^1$, $–S(O)R^1$, $–S(O)NR^3R^4$, $–NR^3S(O)R^1$, heterocycle, aryl, or heteroaryl;

R^1 and R^2 are independently, at each occurrence, –H, $–R^3$, $–R^4$, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P and O, –OH, halogen, $–NO_2$, –CN, $–NHC_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)_2$, $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–N(C_1$-C_6alkyl$)S(O)_2R^5$, $–S(O)_2(C_1$-C_6alkyl), $–(C_1$-C_6alkyl$)S(O)_2R^5$, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)S(O)_2C_1$-C_6alkyl, or $(CHR^5)_nNR^3R^4$, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl,

cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, $–NO_2$, oxo, –CN, $–R^5$, $–OR^3$, $–NHR^3$, NR^3R^4, $–S(O)_2N(R^3)_2–$, $–S(O)_2R^5$, $–C(O)R^5$, $–CO_2R^5$, $–NR^3S(O)_2R^5$, $–S(O)R^5$, $–S(O)NR^3R^4$, $–NR^3S(O)R^5$, heterocycle, aryl, or heteroaryl;

or R^1 and R^2 can combine with the carbon atom to which they are both attached to form a cycloalkyl, heterocycle, spirocycle, spiroheterocycle, or spirocycloalkenyl;

or R^1 and R^2, when on adjacent or non-adjacent atoms, can combine to form a heterocycle, cycloalkyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P and O, or cycloalkenyl;

R^3 and R^4 are independently, at each occurrence, –H, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from N, S, P, and O, $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2(C_1$-C_6alkyl), $–(C_1$-C_6alkyl$)S(O)_2R^5$, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, or $–(CHR^5)_nN(C_1$-C_6alkyl$)_2$, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more substituents selected from –OH, halogen, $–NO_2$, oxo, –CN, $–R^5$, $–O(C_1$-$C_6)$alkyl, $–NH(C_1$-$C_6)$alkyl, $–N(C_1$-C_6alkly$)_2$, $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2NHC_1$-C_6alkyl, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)S(O)_2C_1$-C_6alkyl, $–S(O)R^5$, $–S(O)N(C_1$-C_6alkyl$)_2$, $–N(C_1$-C_6alkyl$)S(O)R^5$, heterocycle, aryl, or heteroaryl;

R^5 is independently, at each occurrence, –H, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from N, S, P and O, –OH, halogen, $–NO_2$, –CN, $–NHC_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)_2$, $–S(O)_2NH(C_1$-C_6alkyl), $–S(O)_2N(C_1$-C_6alkyl$)_2$, $–S(O)_2C_1$-C_6alkyl, $–C(O)C_1$-C_6alkyl, $–CO_2C_1$-C_6alkyl, $–N(C_1$-C_6alkyl$)SO_2C_1$-C_6alkyl, $–S(O)(C_1$-C_6alkyl), $–S(O)N(C_1$-C_6alkyl$)_2$, $–N(C_1$-C_6alkyl$)S(O)(C_1$-C_6alkyl) or $–(CH_2)_nN(C_1$-C_6alkyl$)_2$;

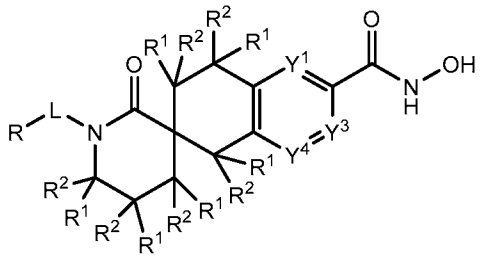
n is an integer from 0 to 6; and

m is 0, 1, 2 or 3.

2. The compound of claim 1, wherein X^4 is $–C(O)–$.

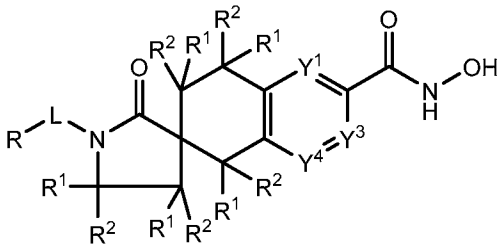
3. The compound of claim 1, wherein m is 0 or 1.

4. The compound of claim 1, wherein the compound is of the Formula I-a:



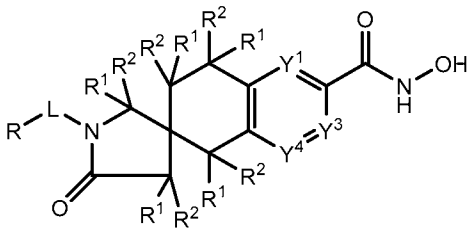
(I-a).

5. The compound of claim 1, wherein the compound is of the Formula I-b:



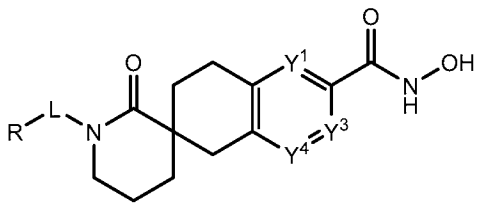
(I-b).

6. The compound of claim 1, wherein the compound is of the Formula I-c:



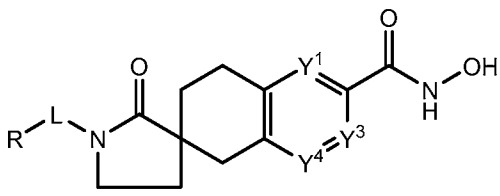
(I-c).

7. The compound of claim 1, wherein the compound is of the Formula I-d:



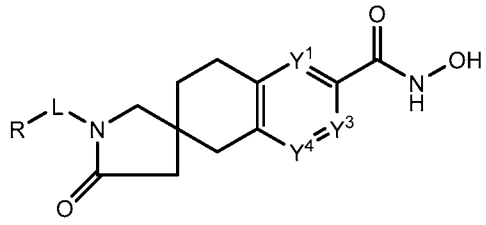
(I-d).

8. The compound of claim 1, wherein the compound is of the Formula I-e:



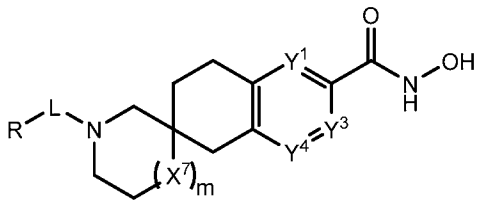
(I-e).

9. The compound of claim 1, wherein the compound is of the Formula I-f:



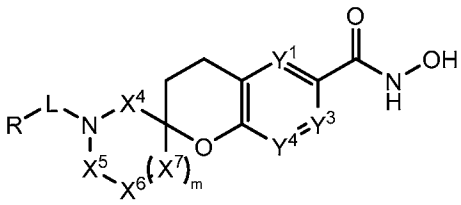
(I-f).

10. The compound of claim 1, wherein the compound is of the Formula I-g:



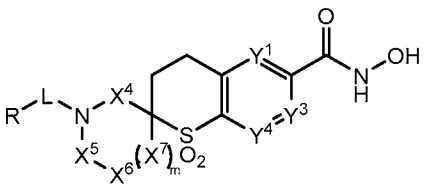
(I-g).

11. The compound of claim 1, wherein the compound is of the Formula I-h:



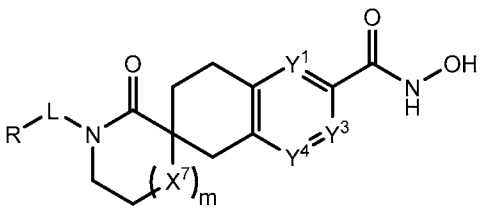
(I-h).

12. The compound of claim 1, wherein the compound is of the Formula I-j:



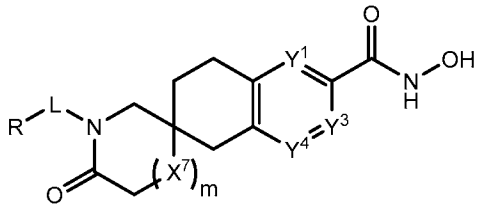
(I-j).

13. The compound of claim 1, wherein the compound is of the Formula I-k:



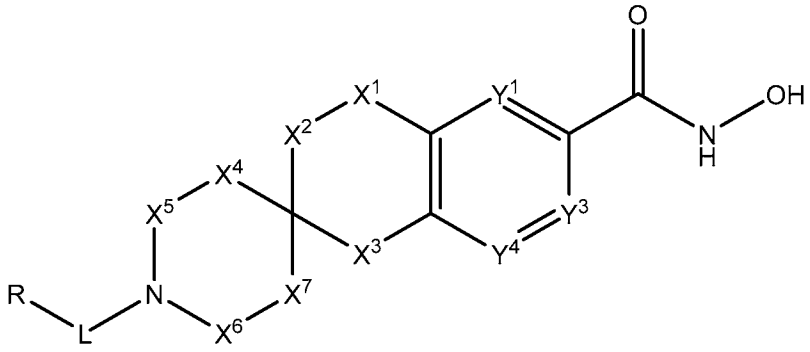
(I-k).

14. The compound of claim 1, wherein the compound is of the Formula I-m:



(I-m).

15. A compound of the Formula II:



(II)

or a pharmaceutically acceptable salt, prodrug , solvate, hydrate, tautomer, or isomer or thereof, wherein:

X^1 is independently $-CR^1R^2-$, $-NR^3-$, $-O-$, $-SO_2-$, $-S(O)-$, or $-S-$;

X^2, X^3, X^4, and X^7 are each independently $-CR^1R^2-$, $-NR^3-$, $-O-$, $-C(O)-$, $-SO_2-$, $-S(O)-$, or $-S-$;

X^5 and X^6 are each independently $-CR^1R^2-$, $-C(O)-$, $-SO_2-$, $-S(O)-$, or $-S-$;

Y^1, Y^3 and Y^4 are each independently N or CR^1;

L is a bond, $-(CR^1R^2)_n-$, $-C(O)NR^3-$, $-S(O)_2-$, $-S(O)_2NR^3-$, $-S(O)-$, $-S(O)NR^3-$, $-C(O)(CR^1R^2)_nO-$, or $-C(O)(CR^1R^2)_n-$;

R is independently –H, $-C_1$-C_6alkyl, $-C_2$-C_6alkenyl, $-C_4$-C_8cycloalkenyl, $-C_2$-C_6alkynyl, $-C_3$-C_8cycloalkyl, $-C_5$-C_{12}spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, or O, wherein each –alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, spirocycle, heterocyclyl, spiroheterocyclyl, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, oxo, $-NO_2$, –CN, $-R^1$, $-R^2$, $-SR^3$, $-OR^3$, $-NHR^3$, $-NR^3R^4$, $-S(O)_2NR^3R^4$, $-S(O)_2R^1$, $-C(O)R^1$, $-CO_2R^1$, $-NR^3S(O)_2R^1$, $-S(O)R^1$, $-S(O)NR^3R^4$, $-NR^3S(O)R^1$, heterocycle, aryl, or heteroaryl;

R^1 and R^2 are independently, and at each occurrence, –H, –R^3, –R^4, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, or O, –OH, halogen, –NO_2, –CN, –NHC_1-C_6alkyl, –$N(C_1$-C_6alkyl$)_2$, –$S(O)_2N(C_1$-C_6alkyl$)_2$, –$N(C_1$-C_6alkyl$)S(O)_2R^5$, –$S(O)_2(C_1$-C_6alkyl), –$(C_1$-C_6alkyl$)S(O)_2R^5$, –$C(O)C_1$-C_6alkyl, –CO_2C_1-C_6alkyl, –$N(C_1$-C_6alkyl$)S(O)_2C_1$-C_6alkyl, or $(CHR^5)_nNR^3R^4$, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from –OH, halogen, –NO_2, oxo, –CN, –R^5, –OR^3, –NHR^3, NR^3R^4, –$S(O)_2N(R^3)_2$–, –$S(O)_2R^5$, –$C(O)R^5$, –CO_2R^5, –$NR^3S(O)_2R^5$, –$S(O)R^5$, –$S(O)NR^3R^4$, –$NR^3S(O)R^5$, heterocycle, aryl, or heteroaryl;

or R^1 and R^2 can combine with the carbon atom to which they are both attached to form a cycloalkyl, heterocycle, spirocycle, spiroheterocycle, or spirocycloalkenyl;

or R^1 and R^2, when on adjacent or non-adjacent atoms, can combine to form a heterocycle, cycloalkyl, aryl, heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P and O, or cycloalkenyl;

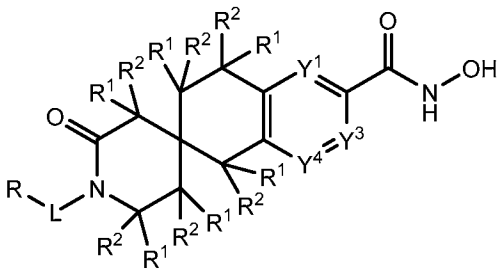
R^3 and R^4 are independently, at each occurrence, –H, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from N, S, P and O, –$S(O)_2N(C_1$-C_6alkyl$)_2$, –$S(O)_2(C_1$-C_6alkyl), –$(C_1$-C_6alkyl$)S(O)_2R^5$, –$C(O)C_1$-C_6alkyl, –CO_2C_1-C_6alkyl, or –$(CHR^5)_nN(C_1$-C_6alkyl$)_2$, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more substituents selected from –OH, halogen, –NO_2, oxo, –CN, –R^5, –$O(C_1$-$C_6)$alkyl, –$NH(C_1$-$C_6)$alkyl, –$N(C_1$-C_6alkly$)_2$, –$S(O)_2N(C_1$-C_6alkyl$)_2$, –$S(O)_2NHC_1$-C_6alkyl, –$C(O)C_1$-C_6alkyl, –CO_2C_1-C_6alkyl, –$N(C_1$-C_6alkyl$)S(O)_2C_1$-C_6alkyl, –$S(O)R^5$, –$S(O)N(C_1$-C_6alkyl$)_2$, –$N(C_1$-C_6alkyl$)S(O)R^5$, heterocycle, aryl, or heteroaryl;

each R^5 is independently –H, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, heterocyclyl, aryl, heteroaryl containing 1-5 heteroatoms selected from N, S, O and P, –OH, halogen, –NO_2, –CN, –NHC_1-C_6alkyl, –$N(C_1$-C_6alkyl$)_2$, –$S(O)_2NH(C_1$-C_6alkyl), –$S(O)_2N(C_1$-C_6alkyl$)_2$, –$S(O)_2C_1$-C_6alkyl, –$C(O)C_1$-C_6alkyl, –CO_2C_1-C_6alkyl, –$N(C_1$-C_6alkyl$)SO_2C_1$-C_6alkyl, –$S(O)(C_1$-C_6alkyl), –$S(O)N(C_1$-C_6alkyl$)_2$, –$N(C_1$-C_6alkyl$)S(O)(C_1$-C_6alkyl) or –$(CH_2)_nN(C_1$-C_6alkyl$)_2$; and

n is an integer from 0 to 6.

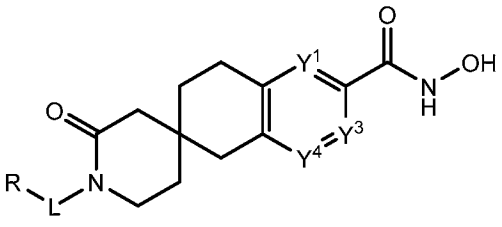
16. The compound of claim 15, wherein X^5 is C(O).

17. The compound of claim 15 wherein the compound is of the Formula II-a:



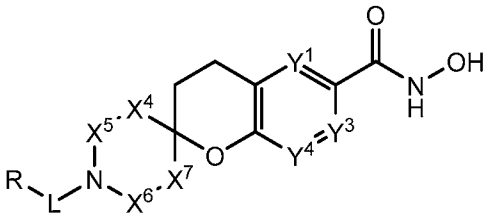
(II-a).

18. The compound of claim 15, wherein the compound is of the Formula II-b:



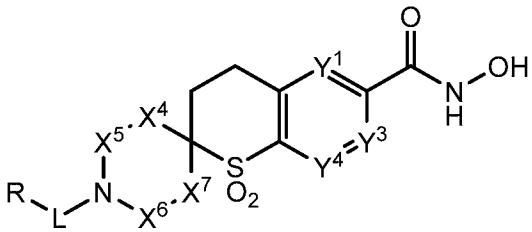
(II-b).

19. The compound of claim 15, wherein the compound is of the Formula II-c:



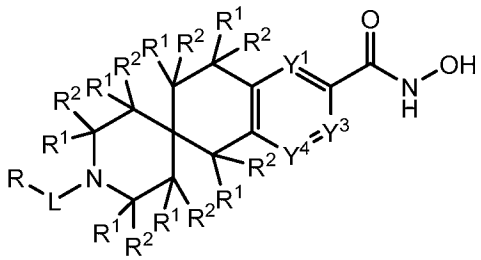
(II-c).

20. The compound of claim 15, wherein the compound is of the Formula II-d:



(II-d).

21. The compound of claim 15, wherein the compound is of the Formula II-e:



(II-e).

22. A compound of claim 1 selected from the group consisting of:

1'-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxy-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-1);

N-hydroxy-1'-(4-methoxyphenethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-2);

N-hydroxy-1'-(4-methoxybenzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-3);

N-hydroxy-1'-(4-methoxyphenethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-4);

1'-(1H-benzo[d]imidazol-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-5);

1'-(3,4-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-6);

1'-(cyclohexylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-7);

N-hydroxy-1'-(4-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-8);

1'-(3-(dimethylamino)propyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-9);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-10);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-11);

(R)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-12);

(S)-N-hydroxy-1'-(1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-13);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-14);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-15);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-16);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-17);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-18);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-19);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-20);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-21);

(R)-N-hydroxy-1'-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-22);

(S)-N-hydroxy-1'-((1-(2-methoxyethyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-23);

(R)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-24);

(S)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-25);

(R)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-26);

(R)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-27);

(S)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-28);

(S)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-29);

(R)-1'-((2-chlorothiazol-5-yl)methyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-30);

(R)-N-hydroxy-1'-((2-hydroxythiazol-5-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-31);

(R)-N-hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-32);

(R)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-33);

(R)-N-hydroxy-1'-isopentyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-34);

(R)-1'-(but-2-yn-1-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-35);

(R)-N-hydroxy-1'-(2-methoxyethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-36);

(R)-1'-cinnamyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-37);

(R)-N-hydroxy-1'-(2-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-38);

(R)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-39);

(R)-1'-(2-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-40);

(R)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-41);

(R)-1'-(benzo[c][1,2,5]oxadiazol-5-ylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-42);

(R)-N-hydroxy-1'-(2-morpholino-2-oxoethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-43);

(R)-N-hydroxy-1'-(2-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-44);

(R)-N-hydroxy-1'-((1-isopropyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-45);

(R)-N-hydroxy-1'-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-46);

(R)-N-hydroxy-1'-(2-methylallyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-47);

(R)-1'-(2,5-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-48);

(R)-1'-(2,6-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-49);

(R)-1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-50);

(R)-N-hydroxy-1'-(3-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-51);

(R)-N-hydroxy-2'-oxo-1'-(pyridin-2-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-52);

(R)-1'-(3-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-53);

(R)-1'-(3-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-54);

(R)-1'-(4-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-55);

(R)-N-hydroxy-1'-(4-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-56);

(R)-1'-(2-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-57);

(R)-N-hydroxy-1'-(naphthalen-2-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-58);

(R)-1'-(2-(difluoromethoxy)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-59);

(S)-N-hydroxy-2'-oxo-1'-propyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-60);

(S)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-61);

(S)-N-hydroxy-1'-isopentyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-62);

(S)-1'-(but-2-yn-1-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-63);

(S)-N-hydroxy-1'-(2-methoxyethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-64);

(S)-1'-cinnamyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-65);

(S)-N-hydroxy-1'-(2-methylbenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-66);

(S)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-67);

(S)-1'-(2-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-68);

(S)-N-hydroxy-2'-oxo-1'-(2-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-69);

(S)-1'-(benzo[c][1,2,5]oxadiazol-5-ylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-70);

(S)-N-hydroxy-1'-(2-morpholino-2-oxoethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-71);

(S)-N-hydroxy-1'-(2-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-72);

(S)-N-hydroxy-1'-((1-isopropyl-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-73);

(S)-1'-(2,5-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-74);

(S)-1'-(2,6-dichlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-75);

(S)-1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-76);

(S)-N-hydroxy-1'-(3-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-77);

(S)-N-hydroxy-2'-oxo-1'-(pyridin-2-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-78);

(S)-1'-(3-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-79);

(S)-N-hydroxy-2'-oxo-1'-(4-(trifluoromethoxy)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-80);

(S)-1'-(3-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-81);

(S)-1'-(4-chlorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-82);

(S)-N-hydroxy-1'-(4-methoxybenzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-83);

(S)-1'-(2-fluorobenzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-84);

(S)-1'-(4-(tert-butyl)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-85);

(S)-N-hydroxy-1'-(naphthalen-2-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-86);

(S)-1'-(2-(difluoromethoxy)benzyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-87);

(R)-N-hydroxy-1'-(4-(methylsulfonyl)benzyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-88);

(R)-N-hydroxy-1'-(naphthalen-1-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-89);

(R)-1'-(3-fluoro-4-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-90);

(R)-1'-(benzo[d][1,3]dioxol-5-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-91);

(R)-N-hydroxy-1'-(3-(methylthio)phenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-92);

(R)-1'-(4-(dimethylamino)phenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-93);

(R)-N-hydroxy-1'-(6-isopropylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-94);

(R)-N-hydroxy-2'-oxo-1'-(quinolin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-95);

(R)-1'-(2,3-dihydrobenzofuran-7-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-96);

(R)-1'-(6-(tert-butylamino)pyrimidin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-97);

(R)-1'-(1,3-dimethyl-1H-pyrazol-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-98);

(R)-N-hydroxy-1'-(imidazo[1,2-a]pyridin-6-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-99);

(S)-1'-(2,4-dimethylphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-100);

(S)-N-hydroxy-1'-(6-isopropylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-101);

(S)-N-hydroxy-2'-oxo-1'-(quinolin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-102);

(S)-N-hydroxy-1'-(imidazo[1,2-a]pyridin-6-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-103);

(R)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-104);

(S)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-105);

(R)-N-hydroxy-2'-oxo-1'-(4-((trifluoromethyl)sulfonyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-106);

(S)-N-hydroxy-2'-oxo-1'-(4-((trifluoromethyl)sulfonyl)benzyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-107);

(R)-N-hydroxy-1'-(3-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-108);

(R)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-109);

(R)-1'-(5-fluoropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-110);

(R)-N-hydroxy-1'-(2-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-111);

(R)-1'-(3-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-112);

(R)-1'-(3-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-113);

(R)-N-hydroxy-1'-(6-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-114);

(S)-N-hydroxy-1'-(2-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-115);

(S)-1'-(3-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-116);

(S)-1'-(3-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-117);

(S)-N-hydroxy-1'-(6-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-118);

(R)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-119);

(R)-1'-(4-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-120);

(R)-1'-(2-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-121);

(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-122);

(R)-1'-(2,3-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-123);

(R)-N-hydroxy-1'-(4-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-124);

(R)-1'-(2-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-125);

(S)-1'-(2-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-126);

(S)-1'-(2-fluoro-4-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-127);

(R)-1'-(4-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-128);

(S)-1'-(4-fluoro-3-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-129);

(S)-1'-(5-chloropyridin-2-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-130);

(R)-N-hydroxy-1'-(2-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-131);

(S)-N-hydroxy-1'-(2-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-132);

(R)-N-hydroxy-1'-(6-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-133);

(S)-N-hydroxy-1'-(6-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-134);

(R)-N-hydroxy-1'-(5-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-135);

(R)-N-hydroxy-1'-(4-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-136);

(S)-N-hydroxy-1'-(4-methylpyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-137);

(R)-1'-(5-chloropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-138);

(S)-1'-(5-chloropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-139);

(R)-1'-(3-chloropyridin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-140);

(S)-1'-(3-chloropyridin-4-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-141);

(S)-N-hydroxy-1'-(4-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-142);

(R)-N-hydroxy-1'-(5-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-143);

(S)-N-hydroxy-1'-(5-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-144);

(R)-N-hydroxy-1'-(2-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-145);

(S)-N-hydroxy-1'-(2-methoxypyridin-3-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-146);

(S)-1'-(2-fluoro-5-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-147);

(S)-1'-(3-fluoro-5-methoxyphenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-148);

(R)-N-hydroxy-1'-(2-methoxypyridin-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-149);

(S)-N-hydroxy-1'-(2-methoxypyridin-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-150);

(R)-1'-(6-(dimethylamino)pyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-151);

(S)-1'-(6-(dimethylamino)pyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-152);

(S)-1'-(5-fluoropyridin-3-yl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-153);

(S)-1'-(4-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-154);

(S)-1'-(3,4-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-155);

(S)-1'-(2,3-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-156);

(S)-1'-(2-fluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-157);

(S)-N-hydroxy-1'-(3-methoxyphenyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-158);

(R)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-159);

(S)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-160);

(R)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-161);

(S)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-162);

(R)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-163);

(S)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-164);

(R)-N-hydroxy-2'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-165);

(S)-N-hydroxy-2'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-166);

(R)-1'-(2,5-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-167);

(R)-N-hydroxy-1'-(1-methyl-1H-pyrazol-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-168);

(S)-1'-(2,5-difluorophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-169);

(S)-N-hydroxy-1'-(1-methyl-1H-pyrazol-4-yl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-170);

(R)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-171);

(S)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-172);

(S)-1'-(4-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-173);

(S)-1'-(2-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-174);

(R)-1'-(2-cyanophenyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-175);

1'-benzyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-176);

N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-177);

N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-178);

(R)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-179);

(S)-N-hydroxy-1'-methyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-180);

(R)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-181);

(S)-N-hydroxy-2'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-182);

(S)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-183);

(S)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-184);

(R)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-185);

(S)-1'-(cyclobutylmethyl)-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-186);

(R)-N-hydroxy-1'-(3-methoxypropyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-187);

(S)-N-hydroxy-1'-(3-methoxypropyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-188);

(R)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-189);

(S)-N-hydroxy-1'-isobutyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-190);

(R)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-191);

(S)-N-hydroxy-1'-isopropyl-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-192);

(R)-1'-cyclopropyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-193);

(R)-1'-ethyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-194);

(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-195);

(R)-N-hydroxy-1'-(oxetan-3-ylmethyl)-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-196);

(R)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-197);

(S)-1'-cyclobutyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-198);

(R)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-199);

(S)-1'-cyclopentyl-N-hydroxy-2'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-200);

(R)-N-hydroxy-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-201);

(S)-N-hydroxy-1'-methyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-202);

(R)-N-hydroxy-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-203);

(S)-N-hydroxy-5'-oxo-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-204);

(R)-1'-(cyclobutylmethyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-205);

(R)-1'-ethyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-206);

(R)-N-hydroxy-1'-isobutyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-207);

(R)-N-hydroxy-1'-isopropyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-208);

(R)-1'-cyclopropyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-209);

(S)-1'-(cyclobutylmethyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-210);

(S)-1'-ethyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-211);

(S)-N-hydroxy-1'-isobutyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-212);

(S)-N-hydroxy-1'-isopropyl-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-213);

(S)-1'-cyclopropyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-214);

(R)-N-hydroxy-1'-(oxetan-3-ylmethyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-215);

(R)-1'-benzyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-216);

(S)-N-hydroxy-1'-(oxetan-3-ylmethyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-217);

(S)-1'-benzyl-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-218);

(R)-N-hydroxy-1'-(3-methoxypropyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-219);

(R)-N-hydroxy-5'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-220);

(R)-N-hydroxy-5'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-221);

(S)-N-hydroxy-1'-(3-methoxypropyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-222);

(S)-N-hydroxy-5'-oxo-1'-(2,2,2-trifluoroethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-223);

(S)-N-hydroxy-5'-oxo-1'-(pyridin-3-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-224);

(R)-N-hydroxy-1'-(2-methylbenzyl)-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-225);

(R)-N-hydroxy-5'-oxo-1'-(pyridin-3-ylmethyl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-226);

(R)-1'-(4-fluorophenyl)-N-hydroxy-5'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-227);

(R)-N-hydroxy-5'-oxo-1'-(pyridin-4-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-228);

(R)-N-hydroxy-5'-oxo-1'-(pyridin-2-yl)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidine]-6-carboxamide (I-229);

N-hydroxy-2'-oxo-1'-(pyridin-4-ylmethyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-230);

N-hydroxy-2'-oxo-1'-phenylspiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-231);

1'-benzyl-N-hydroxy-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-232);

N-hydroxy-2'-oxo-1'-(pyridin-3-yl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-233);

N-hydroxy-2'-oxo-1'-((tetrahydro-2H-pyran-4-yl)methyl)spiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-234);

N-hydroxy-1'-isopropyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-235);

N-hydroxy-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-236);

N-hydroxy-1'-methyl-2'-oxospiro[chromane-2,3'-pyrrolidine]-6-carboxamide (I-237);

N-hydroxy-2-oxo-1-phenylspiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-238);

1-benzyl-N-hydroxy-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-239);

N-hydroxy-2-oxo-1-(pyridin-3-yl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-240);

N-hydroxy-2-oxo-1-((tetrahydro-2H-pyran-4-yl)methyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-241);

N-hydroxy-2-oxo-1-(pyridin-4-ylmethyl)spiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-242);

N-hydroxy-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-243); and

N-hydroxy-1-methyl-2-oxospiro[pyrrolidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-244).

23. A compound of claim 15 selected from the group consisting of:

N-hydroxy-1'-(4-methoxybenzyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-1);

1'-((1H-benzo[d]imidazol-2-yl)methyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-2);

1'-(cyclohexanecarbonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-3);

N-hydroxy-1'-(4-methoxybenzoyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-4);

N-hydroxy-1'-((4-methoxyphenyl)sulfonyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-5);

1'-(cyclohexylsulfonyl)-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-6);

N6-hydroxy-N1'-phenylspiro[chromane-2,4'-piperidine]-1',6-dicarboxamide (II-7;

1'-cyclohexyl-N-hydroxyspiro[chromane-2,4'-piperidine]-6-carboxamide (II-8); and

N-hydroxy-1'-(2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-1-carbonyl)spiro[chromane-2,4'-piperidine]-6-carboxamide (II-9).

24. A compound of claim 1 selected from the group consisting of:

N-hydroxy-1'-methyl-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-245);

N-hydroxy-1-methyl-3',4'-dihydro-1'H-spiro[azepane-3,2'-naphthalene]-6'-carboxamide (I-246);

N-hydroxy-1-methyl-3',4'-dihydro-1'H-spiro[azocane-3,2'-naphthalene]-6'-carboxamide (I-247);

N-hydroxy-1-methyl-2-oxo-3',4'-dihydro-1'H-spiro[azepane-3,2'-naphthalene]-6'-carboxamide (I-248);

N-hydroxy-1-methyl-2-oxo-3',4'-dihydro-1'H-spiro[azocane-3,2'-naphthalene]-6'-carboxamide (I-249);

N-hydroxy-1'-methyl-6'-oxo-3,4-dihydro-1H-spiro[naphthalene-2,3'-piperidine]-6-carboxamide (I-250);

N-hydroxy-1-methyl-7-oxo-3',4'-dihydro-1'H-spiro[azepane-3,2'-naphthalene]-6'-carboxamide (I-251);

N-hydroxy-1-methyl-8-oxo-3',4'-dihydro-1'H-spiro[azocane-3,2'-naphthalene]-6'-carboxamide (I-252);

N-hydroxy-1'-methyl-2'-oxospiro[chromane-2,3'-piperidine]-6-carboxamide (I-253);

N-hydroxy-1-methyl-2-oxospiro[azepane-3,2'-chromane]-6'-carboxamide (I-254);

N-hydroxy-1-methyl-2-oxospiro[azocane-3,2'-chromane]-6'-carboxamide (I-255);

N-hydroxy-1-methyl-2-oxospiro[piperidine-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-256);

N-hydroxy-1-methyl-2-oxospiro[azepane-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-257); and

N-hydroxy-1-methyl-2-oxospiro[azocane-3,2'-thiochromane]-6'-carboxamide 1',1'-dioxide (I-258).

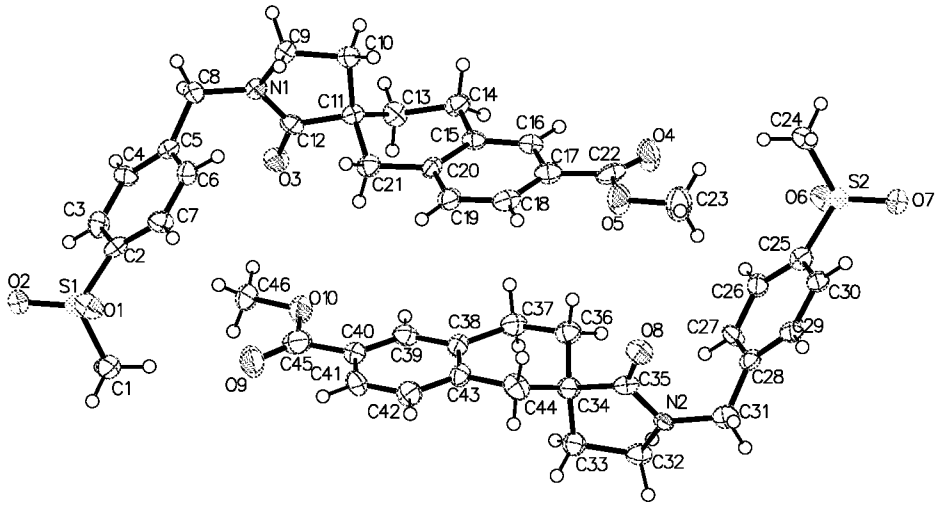
25. A pharmaceutical composition comprising a compound of any one of claims 1 to 24 and a pharmaceutically acceptable carrier.

26. A method of treating a disease associated with HDAC6 modulation in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1 to 24.
27. The method of claim 26, wherein the disease is cancer, neurodegenerative disease, neurodevelopmental disorder, inflammatory or autoimmune disease, infection, metabolic disease, hematologic disease, or cardiovascular disease.
28. The method of claim 27, wherein the cancer is melanoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, multiple myeloma, leukemia, lung, ovarian, breast, prostate, pancreatic, hepatocellular or renal cancer.
29. The method of claim 27, wherein the neurodegenerative disease is Alzheimer's, Huntington's, Parkinson's, Amyotrophic Lateral Sclerosis, or spinal muscular atrophy.
30. The method of claim 27, wherein the neurodevelopmental disorder is Rett syndrome.
31. The method of claim 27, wherein the inflammatory or autoimmune disease is rheumatoid arthritis, spondylitis arthritis, psoriatic arthritis, psoriasis, multiple sclerosis, systemic lupus erythematosus, inflammatory bowel diseases, graft versus host disease, transplant rejection or fibrotic disease.
32. The method of claim 26, wherein the compound inhibits a histone deacetylase.
33. The method of claim 32, wherein the compound inhibits a zinc-dependent histone deacetylase.
34. The method of claim 33, wherein the compound inhibits the HDAC6 isozyme zinc-dependent histone deacetylase.
35. A compound of any one of claims 1 to 24 for use in treating or preventing a disease associated with HDAC6 modulation.

36. Use of a compound of any one of claims 1 to 24 in the manufacture of a medicament for treating or preventing a disease associated with HDAC6 modulation.

FIGURES

Figure 1.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/027842

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D221/20 C07D209/96 C07D401/04 C07D401/06 C07D403/04
C07D403/06 C07D405/04 C07D405/06 C07D413/06 C07D417/06
C07D471/04 C07D491/107 C07D495/10 C07D519/00 A61K31/438

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARIO VARASI ET AL: "Discovery, Synthesis, and Pharmacological Evaluation of Spiropiperidine Hydroxamic Acid Based Derivatives as Structurally Novel Histone Deacetylase (HDAC) Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, vol. 54, no. 8, 2011, pages 3051-3064, XP055274318, ISSN: 0022-2623, DOI: 10.1021/jm200146u the whole document schemes 1-6; tables 1-3; compounds 13a-13d -----	1-14,22, 24-36
Y	WO 2011/045265 A2 (DAC SRL [IT]; VARASI MARIO [IT]) 21 April 2011 (2011-04-21) page 14, line 22 - page 16, line 18; claims 1,4-9; examples; tables 1,2 ----- -/--	1-14,22, 24-36

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2016	12/08/2016

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/027842

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/127609 A1 (DAC SRL [IT]; VARASI MARIO [IT]) 22 October 2009 (2009-10-22) page 20, line 27 - page 22, line 16; claims 1,5,6; examples; tables 1,2 -----	1-14,22, 24-36

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/027842

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-14, 22, 24(completely); 25-36(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14, 22, 24(completely); 25-36(partially)

   relating to compounds of formula I

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2. claims: 17-21, 23(completely); 15, 16, 25-36(partially)

   relating to compounds of formula II wherein X1 is -CR1R2-

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3. claims: 15, 16, 25-36(all partially)

   relating to compounds of formula II wherein X1 is -NR3-, -O-, -SO2-, -S(O)- or -S-

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/027842

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