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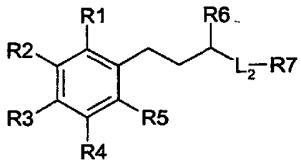
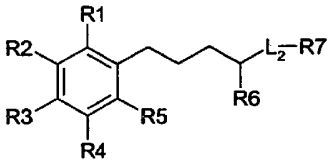


(IIa)



(IIb)

(57) Abstract: The invention related to alkanoic acid derivatives of Formula (IIa) and (IIb). These compounds of the invention were found to have activity as HDAC inhibitors.

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ALKANOIC ACID DERIVATIVES AND THEIR THERAPEUTIC USE AS HDAC INHIBITORS

The invention relates to novel compounds having pharmacological activity. The compounds can be used for treating diseases.

BACKGROUND OF THE INVENTION

Cancer is prevalent: there were about 3.2 million cancer cases diagnosed (53% men, 47% women) and 1.7 million deaths from cancer (56% men, 44% women) in Europe in 2006 (Ferlay et al. (2007) Ann. Oncol. 18(3):581-92). In the United States, the probability of developing invasive cancer is 38% for females and 46% for males that live to be 70 years older and older. There will be about 1.4 million new cases of cancer in 2006. Although the five year survival rate for cancer is now 65%, up from about 50% in the mid-nineteen seventies, cancer is deadly. It is estimated that 565,000 people in the United States will die from cancer in 2006 (American Cancer Society, Surveillance Research, 2006). Despite tremendous advances in cancer treatment and diagnosis, cancer remains a major public health concern. Accordingly, there is a need for new therapeutics with activity against cancer.

Another health crisis is facing industrialized nations. As the population in these countries ages, neurodegenerative diseases are affecting more and more people posing a tremendous economic burden to national health systems. Alzheimer's disease is the largest neurodegenerative disease; disease modifying drugs have long been sought, but to-date, none have been identified. Other neurodegenerative conditions include Parkinson's disease, Huntington disease, and Lewy Body dementia which are all characterized by disease progression which robs the patients of their abilities to perform normal daily activities, eventually leading to death.

In view of the lack of adequate treatments for conditions such as cancer and neurodegeneration, there is a desperate need for new drugs. One similar characteristic amongst many cancers and neurodegenerative

diseases is dysregulated gene expression. A number of different classes of molecules that target aspects of gene regulation have been shown to alter gene expression in models and humans. One class of compounds known to modulate gene expression and have therapeutic effects in cancer and neurodegenerative disease models are compounds referred to as histone deacetylase (HDAC) inhibitors. Histone deacetylases are a family of enzymes that can deacetylate acetyl lysines. HDACs are primarily involved in regulation of chromatin structure and gene expression via their ability to modulate histone acetylation, although they also play roles in other important cellular functions like microtubule deacetylation (see e.g., Yang et al. (2003) Cur. Opin. Gen. Dev. 13:143-153; Zhang et al. (2003) EMBO J 5:1168-1179; Drummond et al. (2005) Annu. Rev. Pharmacol. Toxicol. 45:495-528).The pharmaceutical industry is studying HDAC inhibitors intensively. One HDAC inhibitor, Vorinostat® (suberoylanilide hydroxamic acid (SAHA)) has been approved for treating cutaneous T-cell lymphoma and many more are in clinical trials. Several previously approved drugs, subsequent to approval, were found to have weak HDAC inhibition activity, namely, valproic acid, butyrate, and phenylbutyrate. These drugs are in various cancer and neurodegenerative clinical trials based on their newly discovered HDAC inhibitor activity (HDACi).

There are at least 11 human HDACs which are classified into class I, class II, class III and class IV based on their sequence homology to their yeast orthologues Rpd3, HdaI and Sir2, respectively (de Ruijter et al. (2003) *Biochem. J.* 370 737–749 and Gregoretti et al. (2004) *J. Mol. Biol.* 338 17–31). Class I, II, and Class IV HDACs are considered the classic HDACs that have an active-site zinc ion. Class III HDACs operate by an NAD+ dependent mechanism and currently are not the target of HDAC inhibitors. The active site zinc ion in the classical HDACs has proven to be a major target of drug discovery efforts.

Generally, HDAC inhibitors fall into one of several chemical classes including benzamides, hydroxamic acids, carboxylic acids, and FK228

analogs. Many of the HDACi (HDAC inhibitors) molecules in development were designed to have groups that chelate the active site zinc of the HDACs. One of the most potent zinc chelators is the hydroxamic acid moiety and this explains the intense interest in compounds that have this group; compounds with this moiety have HDAC IC50s in the low nanomolar range. Carboxylic acids also chelate zinc but in the context of HDACs they typically have much weaker affinity compared to other classes of HDACi. The carboxylic acid class of HDACi include several FDA approved drugs with activity typically in the low millimolar range (phenylbutyrate, butyrate, and valproate (Gottlicher et al. (2001) *EMBO Journal* 20:6969–6978)). Other groups have explored SAR comparisons of carboxylic acids to other types of zinc chelating moieties. Colletti et al. ((2001) *Biorg. Med. Chem. Lett.* 11:107-111) describe apicidin derivatives (HDACi) where substitution of hydroxamic acid with carboxylic acid reduces the ability of the compound to inhibit HDAC. Wada et al. ((2003) *Biorg. Med. Chem. Lett.* 11:107-111) describe a series of alpha-keto amides as HDAC inhibitors. Wada et al. found that the carboxylic acid analog of a hydroxamic acid had lost approximate 200 fold of its ability to inhibit HDAC. Vanommeslaeghe et al. ((2005) *Bioorg. & Med. Chem.* 13:6070-6082) analyzed the ability of various zinc binding groups to chelate zinc and note that hydroxamic acids appear to be the strongest zinc chelators and that finding other potent zinc chelators has been difficult, with noteworthy examples being thiols, mercaptoacetamides, and o-aminoanilides. Vanommeslaeghe et al. suggest the best replacements for hydroxamates in existing HDAC inhibitors are the N-hydroxyformamide group and the N´-hydroxyurea group. Lu et al. ((2004) *J. Med. Chem.* 47:467-474) take a different approach by starting with valproate, phenylbutyrate, and butyrate, and attaching more potent zinc chelating moieties to these molecules. Lu et al. found that some their new molecules had 1000-fold improved HDACi compared to the parent carboxylic acid.

Additionally, there are other zinc dependent enzymes that are therapeutic targets. For example, matrix metalloproteases are zinc dependent and can be inhibited by various compounds that have zinc chelating moieties (see

e.g., Ferry et al. (1998) Eur. J. Pharm. 351:225-231; EP 1348024; US 5,886,022; and Shian et al. Mol Pharmacol 64:1076-1084, 2003).

HDACi have shown activity in numerous disease models including, but not limited to, many cancers such as colon cancer (Mariadason (2008) Epigenetics. Jan-Feb;3(1):28-37), lymphoma, leukemias, lung cancer, breast cancer, prostate cancer (Glozak et al. (2007) Oncogene Aug 13;26(37):5420-32); neurogenerative disease like Spinal Muscular Atrophy (Hauke et al. (2008) Hum Mol Genet. 2008 Oct 29. [Epub ahead of print] PMID: 18971205), Huntington Disease (Thomas et al. (2008) Proc Natl Acad Sci U S A. Oct 7;105(40):15564-9), Alzheimer´s disease (Langley et al. (2005) Curr Drug Targets CNS Neurol Disord. Feb;4(1):41-50) inflammation (Adock (2007) British Journal of Pharmacology 150, 829–831 and Blanchard et al. (2005) Drug Discovery Today Vol. 10, No. 3), immune disorder including graft vs. host disorders (Tao et al. (2007) Hepatobiliary Pancreat Dis Int. Aug;6(4):348-57), in combination with other chemotherapeutics and radiotherapy as sensitizers in certain cells (Karagiannis et al. (2006) Epigenetics Jul-Sep;1(3):121-6) and radioprotectants in other cells (Paoluzzi et al. (2004) Cancer Biol Ther. Jul;3(7):612-3), Multiple Sclerosis (Gray et al. Epigenetics 2006 Apr-Jun;1(2):67-75), inflammatory lung disease (Barnes et al. (2005) Eur Respir J25:552–563), allergy and asthma (Bhavsar et al. (2008) J. Allergy Clin. Immunol. 121:580-584), renal disease (Mishra et al. (2003) J. Clin. Invest. 111:539–552), Nervous system conditions (Morrison et al. (2007) Cell. Mol. Life Sci. 64:2258–2269 and Kazantsev et al. Nat. Rev. Drug. Dis. (2008) 7:854-868), diabetes (Gray et al. (2005) Diabetes Metab Res Rev 21:416–433), malaria (Dow et al. Antimicrob. Agents Chemother. doi:10.1128/AAC.00439-08), HIV (Demonte et al. (2004) Biochemical Pharmacology 68:1231–1238), and stimulation of stem cells/ reprogramming of somatic cells to induce pluripotent stem cells (Danwei Huangfu et al. “Induction of pluripotent stem cells from primary human fibroblasts with only Oct4 and Sox2” (2008) Nat. Biotech. Published online 12 October 2008; Fuminobu Sugai et al. (2004) Eur J Neurosci

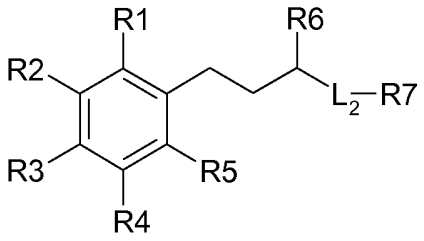
20(11):3179-83; Bug et al. (2005) Cancer Research 65(7):2537-41; Tremolizzo et al. (2005) Amyotrophic Lateral Sclerosis 6:185-186).

Although the first generation HDACi have therapeutic effects and are promising, they also have an undesirable side-effect profile. HDAC inhibitors are known to cause adverse affects in humans like bone marrow depression, diarrhea, weight loss, taste disturbances, electrolyte changes, disordered clotting, fatigue, and cardiac arrhythmias (Bruserud *et al.* (2007) *Curr. Pharm. Biotechnol.* 8:388–400). Safer HDACi are needed. Given the early success with some the initial HDAC inhibitors for treating disease, there is a need for new and improved HDAC inhibitors.

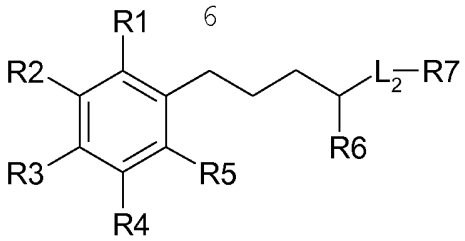
SUMMARY OF THE INVENTION

The present invention relates to novel compounds. These compounds have activity in inhibiting HDAC and are useful for treating conditions where modulating HDAC activity is desirable. Such conditions include, among other things, cancer and neurodegenerative diseases. The inventors have found that compounds of Formula IIa or IIb or Example 50 can inhibit one or more HDACs.

Thus, an aspect of the present invention is a compound of Formula IIa or IIb:

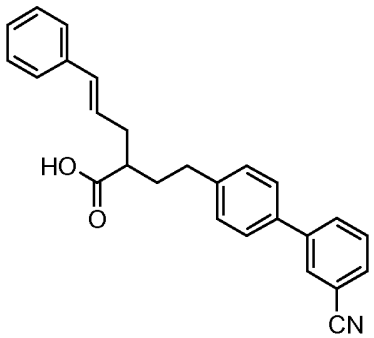


FORMULA IIa



FORMULA IIb

or a compound of formula



wherein

one of R1-R5 is a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocycle, wherein said ring one has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, N-amido, carbonyl, and C-amido; or said one R1-R5 ring is a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings;

and the others of R1-R5 are independently chosen from -H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide,

thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

R6 is –C(=O)OH or –C(=O)O(C1-C6 alkyl);

R7 is optionally substituted and is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring, being the optional substituents on R7 independently chosen from halo, alkoxy, aryl, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -C(=O)O(C_{1-6}alkyl), -C(=O)NH_2, -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl; or
R7 can be optionally substituted and is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring, being the optional substituents on R7 independently chosen from -Q-R_{25}, -Q-L_4-Q-R_{25}, and -L_4-R_{25}; wherein each Q is independently chosen from a bond, -CH_2-, -CH_2CH_2-, and -$CH_2CH_2CH_2$-; each L_4 is independently chosen from -N(R_{30})C(=O)-, -C(=O)N(R_{30})-, -N(R_{30})S(=O)$_2$-, -S(=O)$_2$N(R_{30})-, -C(=O)-, -NHC(=O)O-, -S(=O)$_2$-, -OC(=O)NH-, -NHC(=O)NH-, -N(R_{30})-, -O-, and -S-; R_{30} is chosen from –H, -C1-C4 alkyl optionally substituted with –OH or phenyl, cyclohexyl, and tetrahydropyran-4-yl;

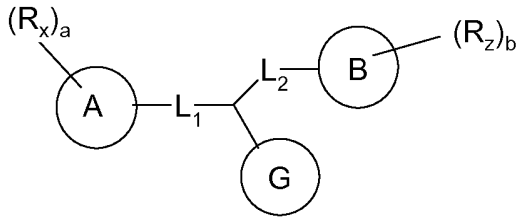
R_{25} is hydrogen; -C1-C8alkyl; or an heterocycle, heteroaryl, aryl, or carbocycle optionally substituted with one or more substituents independently chosen from -Q-heterocycle, -Q-heteroaryl, -Q-aryl, -Q-carbocycle, -C1-C8 alkyl, -OH, -Q-substituted amino, -Q-NH_2, -O-Q-substituted amino, -O-Q-NH_2, -CF_3, -OCF_3, -CN, aryloxy, alkyloxy and halo; and

L and L_2 are independently selected from the group consisting of: -$CH_2CH_2CH_2CH_2$-, –$CH_2CH_2CH_2$-, and –CH_2CH_2-;

or a pharmaceutically acceptable salt thereof.

The inventors have found that the compounds of the invention are able to efficiently inhibit HDAC, owing to the proper combination of the different radicals R_1-R_7, their three-dimensional disposition, as well as to the nature of L_2 linker. In addition, compounds of Formula IIa or IIb having as R_6 a carboxylic acid based zinc chelating moieties or analog or derivatives thereof are surprisingly potent HDAC inhibitors having IC50 values for HDACs and in some disease models much lower than other carboxylic acid based HDAC inhibitors like valproate and phenylbutyrate.

Another aspect of the invention is the provision of a method for identifying an inhibitor of HDAC comprising providing a compound of Formula I



Formula I

and assaying for the ability of said compound of Formula I to inhibit one or more HDACs targets, wherein

A is an optionally substituted ring system chosen from an aryl and heteroaryl ring;

B is an optionally substituted ring system chosen from an aryl, carbocyclic, heterocyclic, and heteroaryl ring;

G is $-C(=O)R_w$ wherein R_w is chosen from –OH, -O(C1-C6 alkyl), -$OC(R_{w1}R_{w2})C(=O)R_{w3}$, and -$NHR_{w4}$ wherein R_{w1} and R_{w2} are independently chosen from –H, C1-C6 alkyl, C2-C6 alkenyl, and halo, and R_{w3} and R_{w4} are independently chosen –H, C1-C6 alkyl, and C2-C6 alkenyl;

each R_x is independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato,

isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

each R_Z is independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

wherein the A-ring is substituted with a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocyclic, wherein said monocyclic ring substituting the A-ring has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido; or said ring substituting said A-ring is a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings which may be substituted with 1-5 optional substituents;

“a” represents the number of substituents on the A-ring and is chosen from 1, 2, 3, 4, 5 or 6;

“b” represents the number of substituents on the B-ring and is chosen from 0, 1, 2, 3, 4, 5, or 6;

each L, L_1, and L_2 can be saturated, partially saturated, or unsaturated, and is independently chosen from $-(CH_2)_n-(CH_2)_n-$, $-(CH_2)_nNH(CH_2)_n-$, $-(CH_2)_nO(CH_2)_n-$, and $-(CH_2)_nS(CH_2)_n-$, and where each n is independently chosen from 0, 1 , 2, 3, and 4, and wherein each carbon and/or nitrogen can be optionally substituted with one or more substituents independently chosen from hydroxyl, halo, alkoxy, alkyl, and amino; or

a pharmaceutically acceptable salt thereof.
In a related aspect, the invention provides a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier. In a more specific aspect, the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula I. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula I for use in the treatment of cancer. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing cancer wherein said composition comprises a therapeutically effective amount of a compound of Formula I sufficient for treating and/or preventing cancer. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula I for use in the treatment of neurodegeneration. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula I sufficient for treating and/or preventing neurodegeneration. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula I for the treatment of a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing a disease

chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis and for stimulating, reprogramming, and regenerating stem cells wherein said composition comprises a therapeutically effective amount of a compound of Formula I sufficient for treating and/or preventing the said disease or for stimulating, reprogramming, and regenerating stem cells. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula I for inhibiting HDAC.

In another related aspect, the invention provides a compound of Formula I for the treatment of a disease by modulating histone acetylation.

In another related aspect, the invention provides a compound of Formula I for the treatment of a disease characterized by aberrant gene expression.

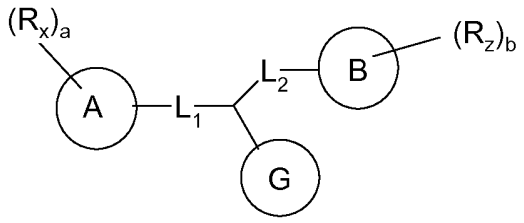
Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the finding that a group of alkanoic acid derivatives inhibit histone deacetylase (HDAC). It was found that a class of molecules having a carboxylic acid based zinc chelating group, or a derivative thereof, linked to a substituted A-ring and an optionally substituted B-ring, where the A-ring is subtituted with a monocyclic substituted ring or a multicyclic optionally substitued ring, potently inhibit HDAC. These compounds were found to have activity against cancer cell line models.

In one embodiment, the invention provides a method for identifying an inhibitor of HDAC comprising contacting an HDAC enzyme or enzymes with a compound of Formula I and determining the ability of said compound to inihibit HDAC:



Formula I

wherein

A is an optionally substituted ring system chosen from an aryl and heteroaryl ring;
B is an optionally substituted ring system chosen from an aryl, carbocyclic, heterocyclic, and heteroaryl ring;
G is $-C(=O)R_w$ wherein R_w is chosen from –OH, -O(C1-C6 alkyl), -$OC(R_{w1}R_{w2})C(=O)R_{w3}$, and -$NHR_{w4}$ wherein R_{w1} and R_{w2} are independently chosen from –H, C1-C6 alkyl, C2-C6 alkenyl, and halo, and R_{w3} and R_{w4} are independently chosen –H, C1-C6 alkyl, and C2-C6 alkenyl;
each R_x is independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino,

aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

each R_z is independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

wherein the A-ring is substituted with a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocyclic, wherein said monocyclic ring substituting the A-ring has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido; or said ring substituting said A-ring is a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings which may be substituted with 1-5 optional substituents;

“a” represents the number of substituents on the A-ring and is chosen from 1, 2, 3, 4, 5 or 6;

“b” represents the number of substituents on the B-ring and is chosen from 0, 1, 2, 3, 4, 5, or 6;

each L, L_1, and L_2 can be saturated, partially saturated, or unsaturated, and is independently chosen from $-(CH_2)_n-(CH_2)_n-$, $-(CH_2)_nNH(CH_2)_n-$, $-(CH_2)_nO(CH_2)_n-$, and $-(CH_2)_nS(CH_2)_n-$, and where each n is independently chosen from 0, 1 , 2, 3, and 4, and wherein each carbon and/or nitrogen

can be optionally substituted with one or more substituents independently chosen from hydroxyl, halo, alkoxy, alkyl, and amino; or a pharmaceutically acceptable salt thereof.

The ability to inhibit HDAC can be determined by any method known in the art, e.g., in vitro assays to measure acetylation of histones or peptides, or monitoring gene expression levels or other phenotypes related to histone acetylation.

In one embodiment of this aspect, the invention relates to a method of determining the HDAC inhibition of a compound of Formula I. According to this embodiment the method comprises providing a compound of Formula I and determining the level of inhibition of HDACs, subgroups of HDACs and/or specific HDAC isozymes. In a specific embodiment, the HDAC or HDACs are chosen from HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7, HDAC8, and HDAC9. In a specific embodiment, the HDAC is HDAC1. In a specific embodiment, the HDAC is HDAC2. In a specific embodiment, the HDAC is HDAC3. In a specific embodiment, the HDAC is HDAC4. In a specific embodiment, the HDAC is HDAC5. In a specific embodiment, the HDAC is HDAC6. In a specific embodiment, the HDAC is HDAC7. In a specific embodiment, the HDAC is HDAC8. In a specific embodiment, the HDAC is HDAC9. According to this embodiment, a compound of Formula I is an inhibitor of HDACs, subgroups of HDACs, and/or specific HDAC isozymes if it has an IC50 value of 5000 uM or less. In a more specific embodiment, the IC50 value is 2500 uM or less. In an even more specific aspect, the IC50 value is 1000 uM or less. In yet an even more specific embodiment, the IC50 value is 750 uM or less. In yet an even more specific embodiment, the IC50 value is 500 uM or less. In yet an even more specific aspect, the IC50 value is 250 uM or less. In yet an even more specific aspect, the IC50 value is 100 uM or less.

The HDAC inhibitors of Formula I can be used to prepare pharmaceutical compositions and methods of treatment as described herein.

In a more specific aspect, the compounds of Formula I include those where
the A-ring is an optionally substituted phenyl group;
the B-ring is an optionally substituted phenyl group;
G is $-C(=O)R_w$ wherein R_w is chosen from –OH, O(C1-C6 alkyl), -$OC(R_{w1}R_{w2})C(=O)R_{w3}$, and -$NHR_{w4}$ wherein R_{w1} and R_{w2} are independently chosen from –H, C1-C6 alkyl, C2-C6 alkenyl, and halo, and R_{w3} and R_{w4} are independently chosen from –H, C1-C6 alkyl and C2-C6 alkenyl;
wherein the A-ring is substituted with a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocyclic, wherein said ring substituting the A-ring has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido; or the A-ring is substituted with an aryl, heterocyclic, or heteroaryl ring system having two or more fused rings which may be optionally substituted with 1-5 substituents;
L_1 and L_2 are independently chosen from $-CH_2CH_2CH_2CH_2$-, $-CH_2CH_2CH_2$-, $-CH_2CH_2$-, and $-CH_2$-.
any other undefined variables are as defined above; or
a pharmaceutically acceptable salt thereof.

In one specific aspect, the compounds of Formula I have a B-ring that is an optionally substituted heterocycle. In a more specific aspect, the B-ring is an optionally substituted heterocycle chosen from morpholino, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholino, homopiperazinyl, imidazolyl, imidazolidinyl, indolyl, indazolyl, indolinyl, pyrazolidinyl, dioxanyl, dioxolanyl, pyrazolyl, pyrazinyl, pyridinyl, pyridinyl N-oxide, pyrimidinyl, thiophenyl, and thiazolyl. In an even more specific aspect, the B-ring is an

optionally substituted ring chosen from thiophenyl, pyrazolyl, furanyl, pyridinyl, indolinyl, and pyridinyl N-oxide. In one specific aspect of this embodiment, said heterocycle ring system is non-aromatic.

In one specific aspect, the compounds of Formula I have an A-ring that is a heteroaryl. In a more specific aspect, the A-ring is a heteroaryl chosen from thienyl (thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (furanyl), isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, pyridyl (pyridinyl), 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridinyl N-oxide, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7 aminoisocoumarin, pyrido[l,2-a]pyrimidin-4-one, pyrazolo[l,5-a]pyrimidinyl, pyrazolo[l,5-a]pyrimidin-3-yl, l,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl and 2-oxobenzimidazolyl. In a more specific aspect, the heteroaryl can be optionally substituted and is chosen from thiophenyl, pyrazolyl, furanyl, pyridinyl, and pyridinyl N-oxide.

In one specific aspect, the compounds of Formula I have a B-ring that is an optionally substituted heteroaryl. In a more specific aspect, the B-ring is an optionally substituted heteroaryl chosen from thienyl (thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (furanyl), isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, pyridyl (pyridinyl), 2-pyridyl, 3 -pyridyl, 4-pyridyl, pyridinyl N-oxide, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4- dihydroquinoxaline-2,3-dione, 7-

aminoisocoumarin, pyrido[l,2-a]pyrimidin-4-one, pyrazolo[l,5-a]pyrimidinyl, pyrazolo[l,5-a]pyrimidin-3-yl, l,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl and 2-oxobenzimidazolyl. In a more specific aspect, the heteroaryl can be optionally substituted and is chosen from thiophenyl, pyrazolyl, furanyl, pyridinyl, and pyridinyl N-oxide.

In one specific aspect the ring attached to the A-ring is a monocyclic aryl, monocyclic heteroaryl, or monocyclic heterocyclic ring having from 1-5 substituents independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl. In a more specific aspect, the ring attached to the A-ring is a phenyl and has 1-5 substituents independently chosen from alkyl, haloalkyl, haloalkoxy, hydroxyl, -NH_2, –CN, halo, alkoxy, tetrazolyl, -C(=O)Z, and -NH-Y, wherein Z is chosen from –OH, -O(C_{1-6} alkyl), -NH(C_{1-6} alkyl), -NH(C_{1-6} alkyl)$_2$, NH(cycloalkyl) wherein Y is chosen from alkyl and –(C=O)(C_{1-3} alkyl). In an even more specific aspect, the ring attached to the A-ring is a phenyl and has 1-5 substituents independently chosen from –CN, chloro, fluoro, methoxy, ethoxy, hydroxyl, methyl, tetrazolyl, -OCF_3, -C(=O)OH, -C(=O)O-alkyl, -NC(=O)CH_3, -C(=O)NH_2, -C(=O)CH_3, and -C(=O)NH-cyclopropyl.

In one specific aspect, the compounds of Formula I have a B-ring that is an optionally substituted aryl. In a more specific aspect, the B-ring is an optionally substituted aryl chosen from phenyl and napthyl.

In one specific aspect, the compounds of Formula I have each L (e.g., L, L_1, and L_2) independently chosen from -CH_2OCH_2-, -CH_2NHCH_2-, -CH_2SCH_2-,-$CH_2CH_2CH_2$-,-CH_2CH_2NH-, -CH_2CH_2S-, -CH_2CH_2-, -CH_2S-, -CH_2O-, -$CH_2CH_2CH_2CH_2$-, -$CH_2CH_2CH{=}CH_2$-, -$CH_2CH{=}CH_2CH_2$-, -$CH_2CH_2NHCH_2$-, -$CH_2CH_2SCH_2$-, and -$CH_2CH_2OCH_2$-. In a more specific

aspect, the compounds of Formula I have each L (e.g., L, L_1, L_2, L_3) independently chosen from $–CH_2CH_2CH_2CH_2$-, $–CH_2CH_2CH_2$-, $–CH_2CH_2$-, and $–CH_2$-.

In one specific aspect, the compounds of Formula I have a number of bonds directly connecting the A-ring to the B-ring in a linear manner chosen from 5, 6, 7, 8, 9, and 10 bonds. In a more specific aspect, the number of bonds is chosen from 6, 7, 8, or 9. In this context, a double bond is equivalent to one single bond (i.e., a double bond does not count as two bonds).

In one specific aspect, the compounds of Formula I have a sum of n-values for L_1 and L_2 chosen from 4, 5, 6, 7, and 8.

In another embodiment, the B-ring is chosen from aryl, carbocycle, heteroaryl, and heterocycle each of which may be optionally substituted with 1-3 optional substituents wherein said optional substituents are independently chosen from -Q-R_{25}, -Q-L_4-Q-R_{25}, and -L_4-$R_{25;}$ wherein each Q is independently chosen from a bond, $-CH_2$-, $-CH_2CH_2$-, and $-CH_2CH_2CH_2$-; each L_4 is independently chosen from -N(R_{30})C(=O)-, -C(=O)N(R_{30})-, -N(R_{30})S(=O)$_2$-, -S(=O)$_2$N(R_{30})-, -C(=O)-, -NHC(=O)O-, -S(=O)$_2$-, -OC(=O)NH-, -NHC(=O)NH-, -N(R_{30})-, -O-, and -S-; R_{30} is chosen from –H, -C1-C4 alkyl optionally substituted with –OH or phenyl, cyclohexyl, and tetrahydropyran-4-yl; R_{25} is hydrogen; -C1-C8alkyl; or an heterocycle, heteroaryl, aryl, or carbocycle optionally substituted with one or more substituents independently chosen from -Q-heterocycle, -Q-heteroaryl, -Q-aryl, -Q-carbocycle, -C1-C8 alkyl, -OH, -Q-substituted amino, -Q-NH_2, -O-Q-substituted amino, -O-Q-NH_2, $-CF_3$, $-OCF_3$, -CN, aryloxy, alkyloxy and halo; any other variables are as defined above; or a pharmaceutically acceptable salt thereof.

In a related aspect, the invention provides a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier. In a more specific aspect, the pharmaceutical composition

comprises a therapeutically effective amount of a compund of Formula I. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula I for use in the treatment of cancer. This aspect can be formulated as the use of a compound of Formula I for the manufacture of a medicament for treating cancer. In a specific aspect, the invention provides a method for treating an individual having cancer by identifying a patient with cancer and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula I sufficient for treating and/or preventing cancer. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula I for use in the treatment of neurodegeneration. This aspect can be formulated as the use of a compound of Formula I for the manufacture of a medicament for treating neurodegeneration. In a specific aspect, the invention provides a method for treating an individual having a neurodegenerative condition by identifying a patient with a neurodegenerative condition and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula I sufficient for treating and/or preventing neurodegeneration. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

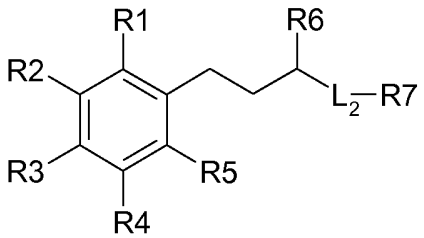
In another related aspect, the invention provides a compound of Formula I for the treatment of a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. This aspect can be formulated as the use of a compound of Formula I for the manufacture of a medicament for treating a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells.. In a specific aspect, the invention provides a method for treating an individual having a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis by identifying a patient with said disease and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis and for stimulating, reprogramming, and regenerating stem cells wherein said composition comprises a therapeutically effective amount of a compound of Formula I sufficient for treating and/or preventing the said disease or for stimulating, reprogramming, and regenerating stem cells. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula I for inhibiting HDAC. This aspect can be formulated as the use of compound of Formula I for the manufacture of a medicament for inhibiting HDAC. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by HDAC inhibition by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I.

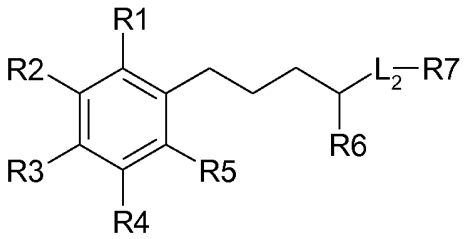
In another related aspect, the invention provides a compound of Formula I for the treatment of a disease by modulating histone acetylation. This aspect can be formulated as the use of a compound of Formula I for the manufacture of a medicament for modulating histone acetylation. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by modulating histone acetylation by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I.

In another related aspect, the invention provides a compound of Formula I for the treatment of a disease characterized by aberrant gene expression. This aspect can be formulated as the use of a compound of Formula I for the manufacture of a medicament modulating gene expression. In a specific aspect, the invention provides a method for treating an individual having disease characterized in part by having aberrant gene expression by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I.

In another aspect, the invention provide a compound of Formula IIa and/or IIb as mentioned above of formulas

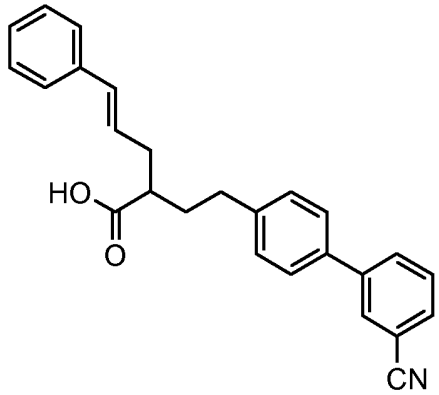


FORMULA IIa



FORMULA IIb

or a compound of formula:



In a preferred embodiment, is one of formula IIa or IIb, wherein:
one of R1-R5 is a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocycle, wherein said ring one has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-

carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido; or said one R1-R5 ring is a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings;

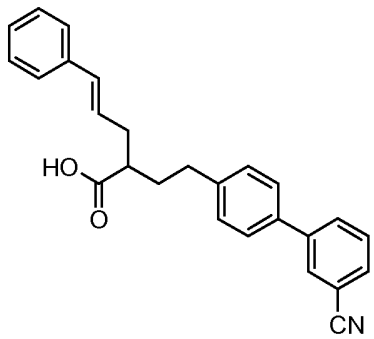
and the others of R1-R5 are independently chosen from -H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

R6 is –C(=O)OH or –C(=O)O(C1-C6 alkyl);

R7 is optionally substituted and is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring; being the optional substituents on R7 independently chosen from -Q-R_{25}, -Q-L_4-Q-R_{25}, and -L_4-$R_{25;}$ wherein each Q is independently chosen from a bond, -CH_2-, -CH_2CH_2-, and -$CH_2CH_2CH_2$-; each L_4 is independently chosen from -N(R_{30})C(=O)-, -C(=O)N(R_{30})-, -N(R_{30})S(=O)$_2$-, -S(=O)$_2$N(R_{30})-, -C(=O)-, -NHC(=O)O-, -S(=O)$_2$-, -OC(=O)NH-, -NHC(=O)NH-, -N(R_{30})-, -O-, and -S-; R_{30} is chosen from –H, -C1-C4 alkyl optionally substituted with –OH or phenyl, cyclohexyl, and tetrahydropyran-4-yl; R_{25} is hydrogen; -C1-C8alkyl; or an heterocycle, heteroaryl, aryl, or carbocycle optionally substituted with one or more substituents independently chosen from -Q-heterocycle, -Q-heteroaryl, -Q-aryl, -Q-carbocycle, -C1-C8 alkyl, -OH, -Q-substituted amino, -Q-NH_2, -O-Q-substituted amino, -O-Q-NH_2, -CF_3, -OCF_3, -CN, aryloxy, alkyloxy and halo; and

L and L_2 are independently selected from the group consisting of: $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, and $-CH_2CH_2-$;

or the compound



or a pharmaceutically acceptable salt thereof.

In another embodiment, the compound of formula IIa or IIb is one wherein:

R3 is chosen from a monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocycle, wherein said ring has from 1-5 substituents; or R3 is chosen from a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings; and

R7 is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring each of which being optionally substituted with 1-5 independently chosen optional substituents selected from the group consisting of: hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, $-N(C_{1-3}\text{ alkyl})_2$, $-NH(C_{1-3}\text{ alkyl})$, $-NHC(=O)(C_{1-3}\text{ alkyl})$, $-C(=O)OH$, $-C(=O)O(C_{1-6}\text{alkyl})$, $-C(=O)(C_{1-3}\text{ alkyl})$, $-C(=O)NH_2$, $-C(=O)NH(C_{1-3}\text{ alkyl})$, $-C(=O)NH(\text{cycloalkyl})$, $-C(=O)N(C_{1-3}\text{ alkyl})_2$, $-S(=O)_2(C_{1-3}\text{alkyl})$, $-S(=O)_2NH_2$, $-S(=O)_2N(C_{1-3}\text{ alkyl})_2$, $-S(=O)_2NH(C_{1-3}\text{ alkyl})$, $-CHF_2$, $-OCF_3$, $-OCHF_2$, $-SCF_3$, $-CF_3$, $-CN$, $-NH_2$, $-NO_2$, and tetrazolyl.

In one aspect, in the compounds of Formula IIa and IIb, the optional substituents on R7 are independently chosen from -Q-R_{25}, -Q-L_4-Q-R_{25}, and -L_4-$R_{25;}$ wherein each Q is independently chosen from a bond, -CH_2-, -CH_2CH_2-, and -$CH_2CH_2CH_2$-; each L_4 is independently chosen from -N(R_{30})C(=O)-, -C(=O)N(R_{30})-, -N(R_{30})S(=O)$_2$-, -S(=O)$_2$N(R_{30})-, -C(=O)-, -NHC(=O)O-, -S(=O)$_2$-, -OC(=O)NH-, -NHC(=O)NH-, -N(R_{30})-, -O-, and -S-; R_{30} is chosen from –H, -C1-C4 alkyl optionally substituted with –OH or phenyl, cyclohexyl, and tetrahydropyran-4-yl; R_{25} is hydrogen; -C1-C8alkyl; or an heterocycle, heteroaryl, aryl, or carbocycle optionally substituted with one or more substituents independently chosen from -Q-heterocycle, -Q-heteroaryl, -Q-aryl, -Q-carbocycle, -C1-C8 alkyl, -OH, -Q-substituted amino, -Q-NH_2, -O-Q-substituted amino, -O-Q-NH_2, -CF_3, -OCF_3, -CN, aryloxy, alkyloxy and halo.

In one aspect, the invention provides a compound of Formula IIa and/or IIb, wherein R3 is a phenyl having from 1-5 substituents independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl. In a more specific aspect, R3 is a phenyl and has 1-5 substituents independently chosen from alkyl, haloalkyl, haloalkoxy, hydroxyl, -NH_2, –CN, halo, alkoxy, tetrazolyl, -C(=O)Z, and -NH-Y, wherein Z is chosen from –OH, -O(C_{1-6} alkyl), -NH(C_{1-6} alkyl), -NH(C_{1-6} alkyl)$_2$, -NH(cycloalkyl) wherein Y is chosen from alkyl and –(C=O)(C_{1-3} alkyl). In an even more specific aspect, R3 is a phenyl and has 1-5 substituents independently chosen from –CN, chloro, fluoro, methoxy, ethoxy, hydroxyl, methyl, tetrazolyl, -OCF_3, -C(=O)OH, -C(=O)O-alkyl, -NC(=O)CH_3, -C(=O)NH_2, -C(=O)CH_3, and -C(=O)NH-cyclopropyl. In one specific aspect, the compounds of Formula IIa and IIb have L_2 chosen from -CH_2OCH_2-, -CH_2NHCH_2-, -CH_2SCH_2-,-$CH_2CH_2CH_2$-,-CH_2CH_2NH-, -CH_2CH_2S-, -CH_2CH_2-, -CH_2S-, -CH_2O-, -$CH_2CH_2CH_2CH_2$-, -

$CH_2CH_2CH=CH_2$-, -$CH_2CH=CH_2CH_2$-, -$CH_2CH_2NHCH_2$-, -$CH_2CH_2SCH_2$-, and -$CH_2CH_2OCH_2$-. In a more specific aspect, L_2 is chosen from –$CH_2CH_2CH_2CH_2$-, –$CH_2CH_2CH_2$-, –CH_2CH_2-, and –CH_2-.

In one specific aspect, the invention provides compounds of Formula IIa and/or IIb where R1 and R5 are each hydro, and the other variables are as defined herein. In a more specific aspect, the invention provides compounds of Formula IIa and IIb where R1, R2, R4, R5 are each hydro.

In one specific aspect, the compounds of Formula IIa and/or IIb have a number of bonds directly connecting the A-ring to R7 in a linear manner chosen from 5, 6, 7, 8, 9, and 10 bonds. In a more specific aspect, the number of bonds is chosen from 6, 7, 8, or 9. In this context, a double bond (or triple) is equivalent to one single bond (i.e., a double bond does not count as two bonds).

In one specific aspect, the compounds of Formula IIa and/or IIb have a sum of n-value for L_2 chosen from 2, 3, and 4.

In one aspect, the invention provides compounds of Formula IIa and/or IIb, wherein

R3 is chosen from a monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocycle, wherein said ring one has from 1-5 substituents; or R3 is chosen from a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings which may be substituted with 1-5 optional substituents;
R6 is chosen from –C(=O)OH and –C(=O)O(C1-C6 alkyl);
R7 is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring each of which can be optionally substituted with 1-5 independently chosen optional substituents;
L_2 is chosen from –$CH_2CH_2CH_2CH_2$-, –$CH_2CH_2CH_2$-, –CH_2CH_2-, and –CH_2-; any other variables are as defined above; and pharmaceutically acceptable salts thereof. In a more specific aspect, the optional

substituents on R7 are independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl; provided said R7 is not a mono-substitued phenyl group having a –CH_2CH_2COOH or –$CH_2CH_2COOCH_2CH_3$ group para to the remainder of the molecule. In an even more specific aspect, the substituents on R7 are independently chosen from –CN, chloro, fluoro, methoxy, ethoxy, hydroxyl, methyl, tetrazolyl, -OCF_3, -C(=O)OH, -C(=O)O-alkyl, -NC(=O)CH_3, -C(=O)NH_2, -C(=O)CH_3, and -C(=O)NH-cyclopropyl. In another aspect of this embodiment, R7 is substituted with 2 or 3 substituents independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl.

In a related aspect, the invention provides a pharmaceutical composition comprising a compound of Formula IIa and/or IIb and a pharmaceutically acceptable carrier. In a more specific aspect, the pharmaceutical composition comprises a therapeutically effective amount of a compund of Formula II and/or IIb. In an even more specific aspect, the therapeutically effective amount of a compound of Formula IIa or IIb is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula IIa and/or IIb for use in the treatment of cancer. This aspect can be formulated as the use of a compound of Formula IIa and/or IIb for the manufacture of a medicament for treating cancer. In a specific aspect, the invention provides a method for treating an individual having cancer by identifying a patient with cancer and administering to the individual a

pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IIa or IIb. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula II and/or IIb sufficient for treating and/or preventing cancer. In an even more specific aspect, the therapeutically effective amount of a compound of Formula IIa and/or IIb is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula IIa or IIb for use in the treatment of neurodegeneration. This aspect can be formulated as the use of a compound of Formula IIa or IIb for the manufacture of a medicament for treating neurodegeneration. In a specific aspect, the invention provides a method for treating an individual having a neurodegenerative condition by identifying a patient with a neurodegenerative condition and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IIa or IIb. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula I sufficient for treating and/or preventing neurodegenration. In an even more specific aspect, the therapeutically effective amount of a compound of Formula I is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula IIa or IIb for the treatment of a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. This aspect can be formulated as the use of a compound of Formula IIa or IIb for the manufacture of a medicament for treating a disease chosen from breast cancer, lung cancer, prostate

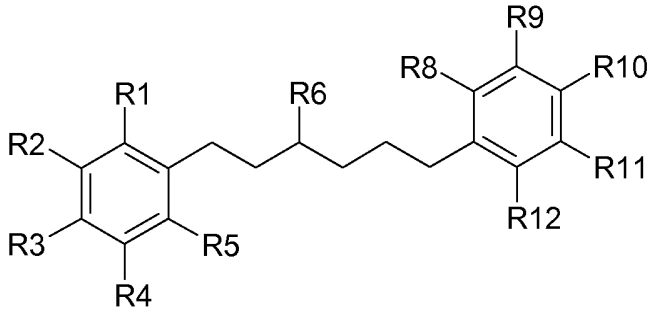
cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. In a specific aspect, the invention provides a method for treating an individual having a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis by identifying a patient with said disease and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IIa or IIb. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis and for stimulating, reprogramming, and regenerating stem cells wherein said composition comprises a therapeutically effective amount of a compound of Formula IIa and/or IIb sufficient for treating and/or preventing the said disease or for stimulating, reprogramming, and regenerating stem cells. In an even more specific aspect, the therapeutically effective amount of a compound of Formula II and/or IIb is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula IIa and/or IIb for inhibiting HDAC. This aspect can be formulated as the use of compound of Formula IIa or IIb for the manufacture of a medicament for inhibiting HDAC. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by HDAC inhibition by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IIa and/or IIb.

In another related aspect, the invention provides a compound of Formula IIa and/or IIb for the treatment of a disease by modulating histone acetylation. This aspect can be formulated as the use of a compound of Formula IIa and/or IIb for the manufacture of a medicament for modulating histone acetylation. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by modulating histone acetylation by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IIa and/or IIb.

In another related aspect, the invention provides a compound of Formula IIa and/or IIb for the treatment of a disease characterized by aberrant gene expression. This aspect can be formulated as the use of a compound of Formula IIa and/or IIb for the manufacture of a medicament modulating gene expression. In a specific aspect, the invention provides a method for treating an individual having disease characterized in part by having aberrant gene expression by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IIa and/or IIb.

In another embodiment, the invention provides a compound of Formula III:



wherein

one of R1-R5 and R8-R12 is a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocyclic, wherein said one ring has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido; or said one ring is a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings which may be substituted with 1-5 optional substituents;

the others of R1-R5 and R8-R12 are independently chosen from -H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

R6 is $-C(=O)R_w$ wherein R_w is chosen from –OH, -O(C1-C6 alkyl), -$OC(R_{w1}R_{w2})C(=O)R_{w3}$, and -$NHR_{w4}$ wherein R_{w1} and R_{w2} are independently chosen from –H, C1-C6 alkyl, C2-C6 alkenyl, and halo, and R_{w3} and R_{w4} are independently chosen –H, C1-C6 alkyl and C2-C6 alkyl;

each L can be saturated, partially saturated, or unsaturated, is independently chosen from $-(CH_2)_n-(CH_2)_n-$, $-(CH_2)_nNH(CH_2)_n-$, $-(CH_2)_nO(CH_2)_n-$, and $-(CH_2)_nS(CH_2)_n-$, and where each n is independently chosen from 0, 1 , 2, 3, and 4, and wherein each carbon and/or nitrogen can be optionally substituted with one or more substituents independently chosen from hydroxyl, halo, alkoxy, alkyl, and amino; and pharmaceutically acceptable salts thereof.

Preferably, the compound of Formula III is one wherein:

at least one of R3 and R10 is a ring chosen from a monocyclic aryl, monocyclic heteroaryl and monocyclic heterocycle, each having from 1-5 susbtituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido; or at least one R3 and R10 is chosen from an aryl, heteroaryl, and heterocycle ring having two or more fused rings that can have from 1-5 optional substituents.

In one aspect, the invention provides compounds of Formula III, wherein R3 and/or R10 is a phenyl having from 1-5 substituents independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl. In a more specific aspect, R3 and/or R10 is a phenyl and has 1-5 substituents independently chosen from alkyl, haloalkyl, haloalkoxy, hydroxyl, -NH_2, –CN, halo, alkoxy, tetrazolyl, -C(=O)Z, and -NH-Y, wherein Z is chosen from –OH, -O(C_{1-6} alkyl), -NH(C_{1-6} alkyl), -NH(C_{1-6} alkyl)$_2$, -NH(cycloalkyl) wherein Y is chosen from alkyl and –(C=O)(C_{1-3} alkyl). In an even more specific aspect, R3 and/or R10 is a phenyl and has 1-5 substituents independently chosen from –CN, chloro, fluoro, methoxy, ethoxy, hydroxyl, methyl, tetrazolyl, -OCF_3, -C(=O)OH, -C(=O)O-alkyl, -NC(=O)CH_3, -C(=O)NH_2, -C(=O)CH_3, and -C(=O)NH-cyclopropyl.

In a related aspect, the invention provides a pharmaceutical composition comprising a compound of Formula III and a pharmaceutically acceptable carrier. In a more specific aspect, the pharmaceutical composition comprises a therapeutically effective amount of a compund of Formula III. In an even more specific aspect, the therapeutically effective amount of a compound of Formula III is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula III for use in the treatment of cancer. This aspect can be formulated as the use of a compound of Formula III for the manufacture of a medicament for treating cancer. In a specific aspect, the invention provides a method for treating an individual having cancer by identifying a patient with cancer and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula III. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula III sufficient for treating and/or preventing cancer. In an even more specific aspect, the therapeutically effective amount of a compound of Formula III is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula III for use in the treatment of neurodegeneration. This aspect can be formulated as the use of a compound of Formula III for the manufacture of a medicament for treating neurodegeneration. In a specific aspect, the invention provides a method for treating an individual having a neurodegenerative condition by identifying a patient with a neurodegenerative condition and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula III. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula III sufficient for treating and/or preventing neurodegeneration. In an even more specific aspect, the

therapeutically effective amount of a compound of Formula III is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula III for the treatment of a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. This aspect can be formulated as the use of a compound of Formula III for the manufacture of a medicament for treating a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells.. In a specific aspect, the invention provides a method for treating an individual having a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis by identifying a patient with said disease and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula III. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis and for stimulating, reprogramming, and regenerating stem cells wherein said composition comprises a therapeutically effective amount of a compound of Formula III sufficient for treating and/or preventing the said disease or for stimulating, reprogramming, and regenerating stem cells. In an even more specific

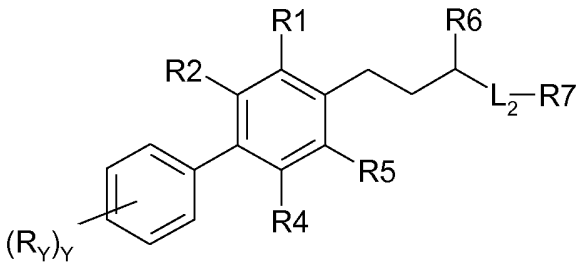
aspect, the therapeutically effective amount of a compound of Formula III is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula III for inhibiting HDAC. This aspect can be formulated as the use of compound of Formula III for the manufacture of a medicament for inhibiting HDAC. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by HDAC inhibition by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula III.

In another related aspect, the invention provides a compound of Formula III for the treatment of a disease by modulating histone acetylation. This aspect can be formulated as the use of a compound of Formula III for the manufacture of a medicament for modulating histone acetylation. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by modulating histone acetylation by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula III.

In another related aspect, the invention provides a compound of Formula III for the treatment of a disease characterized by aberrant gene expression. This aspect can be formulated as the use of a compound of Formula III for the manufacture of a medicament modulating gene expression. In a specific aspect, the invention provides a method for treating an individual having disease characterized in part by having aberrant gene expression by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula III.

In one embodiment, the invention provides a compound of Formula IV:



wherein

R1-R4 are independently chosen from –H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

R6 is $–C(=O)R_w$ wherein R_w is chosen from –OH, -O(C1-C6 alkyl), $-OC(R_{w1}R_{w2})C(=O)R_{w3}$, and $-NHR_{w4}$ wherein R_{w1} and R_{w2} are independently chosen from –H, C1-C6 alkyl, C2-C6 alkenyl, and halo, and R_{w3} and R_{w4} are independently chosen –H, C1-C6 alkyl and C2-C6 alkenyl;

R7 can be optionally substituted and is chosen from a carbocyclic, heterocyclic, heteroaryl, and aryl ring;

each L and L_2 can be saturated, partially saturated, or unsaturated, and are independently chosen from $-(CH_2)_n-(CH_2)_n-$, $-(CH_2)_nNH(CH_2)_n-$, $-(CH_2)_nO(CH_2)_n-$, and $-(CH_2)_nS(CH_2)_n-$, and where each n is independently chosen from 0, 1 , 2, 3, and 4, and wherein each carbon and/or nitrogen can be optionally substituted with one or more substituents independently chosen from hydroxyl, halo, alkoxy, alkyl, and amino;

at least one R_Y is chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano,

cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;
and the other R_Y are chosen from –H, -halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;
Y is chosen from 1, 2, 3, 4, 5; or a pharmaceutically acceptable salt thereof.

In a related aspect, the invention provides a pharmaceutical composition comprising a compound of Formula IV and a pharmaceutically acceptable carrier. In a more specific aspect, the pharmaceutical composition comprises a therapeutically effective amount of a compund of Formula IV. In an even more specific aspect, the therapeutically effective amount of a compound of Formula IV is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula IV for use in the treatment of cancer. This aspect can be formulated as the use of a compound of Formula IV for the manufacture of a medicament for treating cancer. In a specific aspect, the invention provides a method for treating an individual having cancer by identifying a patient with cancer and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IV. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula IV sufficient for treating and/or preventing cancer. In an even

more specific aspect, the therapeutically effective amount of a compound of Formula IV is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula IV for use in the treatment of neurodegeneration. This aspect can be formulated as the use of a compound of Formula IV for the manufacture of a medicament for treating neurodegeneration. In a specific aspect, the invention provides a method for treating an individual having a neurodegenerative condition by identifying a patient with a neurodegenerative condition and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IV. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula IV sufficient for treating and/or preventing neurodegeneration. In an even more specific aspect, the therapeutically effective amount of a compound of Formula IV is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula IV for the treatment of a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. This aspect can be formulated as the use of a compound of Formula IV for the manufacture of a medicament for treating a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. In a specific aspect, the invention provides a method for treating an individual having a disease chosen from breast cancer, lung cancer,

prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis by identifying a patient with said disease and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IV. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis and for stimulating, reprogramming, and regenerating stem cells wherein said composition comprises a therapeutically effective amount of a compound of Formula IV sufficient for treating and/or preventing the said disease or for stimulating, reprogramming, and regenerating stem cells. In an even more specific aspect, the therapeutically effective amount of a compound of Formula IV is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula IV for inhibiting HDAC. This aspect can be formulated as the use of compound of Formula IV for the manufacture of a medicament for inhibiting HDAC. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by HDAC inhibition by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IV.

In another related aspect, the invention provides a compound of Formula IV for the treatment of a disease by modulating histone acetylation. This aspect can be formulated as the use of a compound of Formula IV for the manufacture of a medicament for modulating histone acetylation. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by modulating histone acetylation by identifying

a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IV.

In another related aspect, the invention provides a compound of Formula IV for the treatment of a disease characterized by aberrant gene expression. This aspect can be formulated as the use of a compound of Formula IV for the manufacture of a medicament modulating gene expression. In a specific aspect, the invention provides a method for treating an individual having disease characterized in part by having aberrant gene expression by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula IV.

In one aspect, R7 is an optionally substituted heteroaryl. In a more specific one aspect, R7 can be optionally substituted and is a heteroaryl chosen from thienyl (thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (furanyl), isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, pyridyl (pyridinyl), 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridinyl N-oxide, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7 aminoisocoumarin, pyrido[l,2-a]pyrimidin-4-one, pyrazolo[l,5-a]pyrimidinyl, pyrazolo[l,5-a]pyrimidin-3-yl, l,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl and 2-oxobenzimidazolyl. In a more specific aspect, the heteroaryl can be optionally substituted and is chosen from thiophenyl, pyrazolyl, furanyl, pyridinyl, and pyridinyl N-oxide.

In one aspect, R7 is an optionally substituted heterocycle. In a more specific one aspect, R7 can be optionally substituted and is a heterocycle chosen from morpholino, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholino, homopiperazinyl, imidazolyl, imidazolidinyl, indolyl, indazolyl, indolinyl, pyrazolidinyl, dioxanyl, dioxolanyl, pyrazolyl, pyrazinyl, pyridinyl, pyridinyl N-oxide, pyrimidinyl, thiophenyl, and thiazolyl. In a more specific aspect, the heterocycle can be optionally substituted and is chosen from thiophenyl, pyrazolyl, furanyl, pyridinyl, indolinyl, and pyridinyl N-oxide. In another specific aspect, the heterocycle is a non-aromatic heterocycle.

In one aspect, R7 is an optionally substituted aryl. In a more specific one aspect, R7 can be optionally substituted and is an aryl group chosen from phenyl and naphthyl.

In one aspect, R7 is an optionally substituted carbocyclic group. In a more specific aspect, R7 is an optionally substituted carbocycle chosen from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl and cycloheptyl.

In one aspect, the optional substituents on R7 are chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido. In a more specific aspect, the optional substituents on R7 are independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3}

alkyl), $-CHF_2$, $-OCF_3$, $-OCHF_2$, $-SCF_3$, $-CF_3$, -CN, $-NH_2$, $-NO_2$, and tetrazolyl.

In one aspect, the invention provides compounds of Formula IV, wherein each R_Y is independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, $-N(C_{1-3}$ alkyl$)_2$, $-NH(C_{1-3}$ alkyl), $-NHC(=O)(C_{1-3}$ alkyl), -C(=O)OH, $-C(=O)O(C_{1-6}$alkyl), $-C(=O)(C_{1-3}$ alkyl), $-C(=O)NH_2$, $-C(=O)NH(C_{1-3}$ alkyl), -C(=O)NH(cycloalkyl), $-C(=O)N(C_{1-3}$ alkyl$)_2$, $-S(=O)_2(C_{1-3}$alkyl), $-S(=O)_2NH_2$, $-S(=O)_2N(C_{1-3}$ alkyl$)_2$, - $S(=O)_2NH(C_{1-3}$ alkyl), $-CHF_2$, $-OCF_3$, $-OCHF_2$, $-SCF_3$, $-CF_3$, -CN, $-NH_2$, $-NO_2$, and tetrazolyl. In a more specific aspect, each R_Y is independently chosen from alkyl, haloalkyl, haloalkoxy, hydroxyl, $-NH_2$, –CN, halo, alkoxy, tetrazolyl, -C(=O)Z, and -NH-Y, wherein Z is chosen from –OH, $-O(C_{1-6}$ alkyl), $-NH(C_{1-6}$ alkyl), $-NH(C_{1-6}$ alkyl$)_2$, -NH(cycloalkyl) wherein Y is chosen from alkyl and $-(C=O)(C_{1-3}$ alkyl). In an even more specific aspect, each R_Y is independently chosen from –CN, chloro, fluoro, methoxy, ethoxy, hydroxyl, methyl, tetrazolyl, $-OCF_3$, -C(=O)OH, -C(=O)O-alkyl, $-NC(=O)CH_3$, $-C(=O)NH_2$, $-C(=O)CH_3$, and -C(=O)NH-cyclopropyl.

In one aspect, in the compounds of Formula IV, the optional substituents on R7 are independently chosen from $-Q-R_{25}$, $-Q-L_4-Q-R_{25}$, and $-L_4-R_{25;}$ wherein each Q is independently chosen from a bond, $-CH_2-$, $-CH_2CH_2-$, and $-CH_2CH_2CH_2-$; each L_4 is independently chosen from $-N(R_{30})C(=O)-$, $-C(=O)N(R_{30})-$, $-N(R_{30})S(=O)_2-$, $-S(=O)_2N(R_{30})-$, -C(=O)-, -NHC(=O)O-, $-S(=O)_2-$, -OC(=O)NH-, -NHC(=O)NH-, $-N(R_{30})-$, -O-, and -S-; R_{30} is chosen from –H, -C1-C4 alkyl optionally substituted with –OH or phenyl, cyclohexyl, and tetrahydropyran-4-yl; R_{25} is hydrogen; -C1-C8alkyl; or an heterocycle, heteroaryl, aryl, or carbocycle optionally substituted with one or more substituents independently chosen from -Q-heterocycle, -Q-heteroaryl, -Q-aryl, -Q-carbocycle, -C1-C8 alkyl, -OH, -Q-substituted amino, $-Q-NH_2$, -O-Q-substituted amino, $-O-Q-NH_2$, $-CF_3$, $-OCF_3$, -CN, aryloxy, alkyloxy and halo.

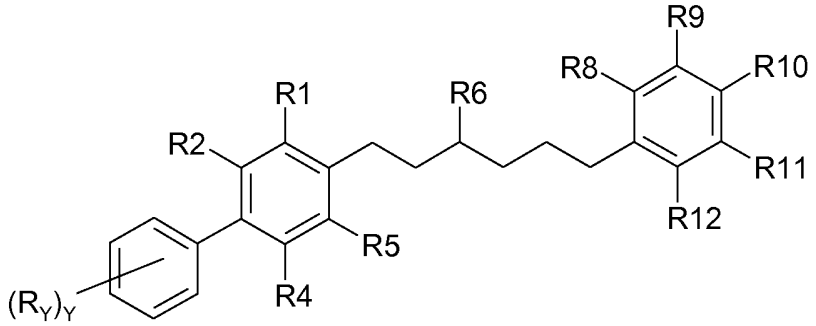
In one specific aspect, the invention provides compounds of Formula IV, wherein R1 and R5 are hydro, and the other variables are as defined herein. In a more specific aspect, R1, R2, R4, and R5 are hydro.

In one specific aspect of the compounds of Formula IV, when R7 is phenyl, L_2 is $–CH_2CH_2CH_2$-, and R6 is COOH, y is 1, para to the linkage to the rest of the molecule R_Y is not $–CH_2CH_2COOH$ or $-CH_2CH_2C(=O)OCH_2CH_3$.

In one specific aspect of the compounds of Formula IV, R6 is –COOH or a pharmaceutically acceptable salt thereof.

In one specific aspect of the compounds of Formula IV, L_2 is chosen from $–CH_2CH_2CH_2CH_2$-, $–CH_2CH_2CH_2$-, $–CH_2CH_2$-, and $–CH_2$-.

In one embodiment, the invention provides a compound of Formula V:



wherein R1, R2, R4, R5, and R8-R12 are each independently chosen from –H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

R6 is –C(=O)R_w wherein R_w is chosen from –OH, -O(C1-C6 alkyl), -OC($R_{w1}R_{w2}$)C(=O)R_{w3}, and -NHR_{w4} wherein R_{w1} and R_{w2} are independently chosen from –H, C1-C6 alkyl, C2-C6 alkenyl, and halo, and R_{w3} and R_{w4} are independently chosen –H, C1-C6 alkyl and C2-C6 alkenyl;

each R_Y is chosen from –H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido, wherein at least one R_Y is not hydro; or two R_Y can be taken together to form an optionally substituted aryl, heterocyclic or heteroaryl ring system having two or more fused rings;

Y is chosen from 1, 2, 3, 4, 5;

each L can be saturated, partially saturated, or unsaturated, and is independently chosen from -$(CH_2)_n$-$(CH_2)_n$-, -$(CH_2)_n$NH$(CH_2)_n$-, -$(CH_2)_n$O$(CH_2)_n$-, and -$(CH_2)_n$S$(CH_2)_n$-, and where each n is independently chosen from 0, 1 , 2, 3, and 4, and wherein each carbon and/or nitrogen can be optionally substituted with one or more substituents independently chosen from hydroxyl, halo, alkoxy, alkyl, and amino; or a pharmaceutically acceptable salt thereof.

In a specific aspect, the invention provides a compound of Formula V wherein each L is independently chosen from –$CH_2CH_2CH_2CH_2$-, –$CH_2CH_2CH_2$-, –CH_2CH_2-, and –CH_2-.

In a specific aspect, the invention provides a compound of Formula V wherein each R_Y is independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$,

-S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2$NH$_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF$_2$, -OCF$_3$, -OCHF$_2$, -SCF$_3$, -CF$_3$, -CN, -NH$_2$, -NO$_2$, and tetrazolyl. In a more specific aspect, the R_Y is a phenyl and has 1-5 substituents independently chosen from alkyl, haloalkyl, haloalkoxy, hydroxyl, -NH$_2$, –CN, halo, alkoxy, tetrazolyl, -C(=O)Z, and -NH-Y, wherein Z is chosen from –OH, -O(C_{1-6} alkyl), -NH(C_{1-6} alkyl), -NH(C_{1-6} alkyl)$_2$, -NH(cycloalkyl) wherein Y is chosen from alkyl and –(C=O)(C_{1-3} alkyl). In an even more specific aspect, R_Y is a phenyl and has 1-5 substituents independently chosen from –CN, chloro, fluoro, methoxy, ethoxy, hydroxyl, methyl, tetrazolyl, -OCF$_3$, -C(=O)OH, -C(=O)O-alkyl, -NC(=O)CH$_3$, -C(=O)NH$_2$, -C(=O)CH$_3$, and -C(=O)NH-cyclopropyl. In another specific aspect, there are 2 or 3 R_Y on the compound of Formula V.

In a specific aspect, the invention provides a compound of Formula V wherein R10 is chosen from sulphonamide, -CH$_2$(carbocycle), -CH$_2$(aryl), and -CH$_2$(heterocycle), and O-benzyl.

In a related aspect, the invention provides a pharmaceutical composition comprising a compound of Formula V and a pharmaceutically acceptable carrier. In a more specific aspect, the pharmaceutical composition comprises a therapeutically effective amount of a compund of Formula V. In an even more specific aspect, the therapeutically effective amount of a compound of Formula V is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula V for use in the treatment of cancer. This aspect can be formulated as the use of a compound of Formula III for the manufacture of a medicament for treating cancer. In a specific aspect, the invention provides a method for treating an individual having cancer by identifying a patient with cancer and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound

of Formula V sufficient for treating and/or preventing cancer. In an even more specific aspect, the therapeutically effective amount of a compound of Formula V is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula V for use in the treatment of neurodegeneration. This aspect can be formulated as the use of a compound of Formula V for the manufacture of a medicament for treating neurodegeneration. In a specific aspect, the invention provides a method for treating an individual having a neurodegenerative condition by identifying a patient with a neurodegenerative condition and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing neurodegeneration wherein said composition comprises a therapeutically effective amount of a compound of Formula V sufficient for treating and/or preventing neurodegeneration. In an even more specific aspect, the therapeutically effective amount of a compound of Formula V is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula V for the treatment of a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. This aspect can be formulated as the use of a compound of Formula V for the manufacture of a medicament for treating a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis, and for stimulating, reprogramming, and regenerating stem cells. In a specific aspect, the invention provides a method for treating an

individual having a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS) and rheumatoid arthritis by identifying a patient with said disease and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V. In a related aspect, the invention provides a pharmaceutical composition for treating and/or preventing a disease chosen from breast cancer, lung cancer, prostate cancer, colon cancer, leukemia, lymphoma, Alzheimer's disease, Parkinson's disease, Huntington disease, Lewy Body dementia, inflammation, thalassemias, acne, asthma, fungal infections, HIV (and/or AIDS), and rheumatoid arthritis and for stimulating, reprogramming, and regenerating stem cells wherein said composition comprises a therapeutically effective amount of a compound of Formula V sufficient for treating and/or preventing the said disease or for stimulating, reprogramming, and regenerating stem cells. In an even more specific aspect, the therapeutically effective amount of a compound of Formula V is an amount effective to inhibit HDAC.

In another related aspect, the invention provides a compound of Formula V for inhibiting HDAC. This aspect can be formulated as the use of compound of Formula V for the manufacture of a medicament for inhibiting HDAC. In a specific aspect, the invention provides a method for treating an individual having a disease treatable by HDAC inhibition by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V.

In another related aspect, the invention provides a compound of Formula V for the treatment of a disease by modulating histone acetylation. This aspect can be formulated as the use of a compound of Formula V for the manufacture of a medicament for modulating histone acetylation. In a specific aspect, the invention provides a method for treating an individual

having a disease treatable by modulating histone acetylation by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V.

In another related aspect, the invention provides a compound of Formula V for the treatment of a disease characterized by aberrant gene expression. This aspect can be formulated as the use of a compound of Formula V for the manufacture of a medicament modulating gene expression. In a specific aspect, the invention provides a method for treating an individual having disease characterized in part by having aberrant gene expression by identifying a patient in need of such treatment and administering to the individual a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula V.

In one aspect of the invention, the compound of Formulae I-V is used as a radiosensitizer and/or a chemosensitizer.

In one aspect, the invention provides a method that involves identifying a patient having a neurodegenerative disease or CNS related condition and treating the individual with a therapeutically effective amount of a compound of Formulae I-V. In aspect of this embodiment, the neurodegenerative disease is chosen from Alzheimer's disease, Huntington disease, Parkinson's disease, Dementia, Lewy Body Dementia, and Amyloid Lateral Sclerosis (ALS). In another aspect of this embodiment, the condition is chosen from depression, epilepsy, and mood disorders. In one aspect, the disease is a polyglutamine-repeat diseases.

In another aspect the invention provides a method,comprising identifying a patient having cancer and administering to said patient a therapeutically effective amount of a compound of a formula chosen from Formula I, II, III, IV, and V. In one aspect, the cancer is chosen from breast cancer, colon cancer, prostate cancer, pancreatic cancer, leukemias, lymphomas,

ovarian cancers, neuroblastomas, head and neck cancer, lung cancer, and melanoma.

In yet another aspect of this embodiment, the invention provides a method comprising identifying a patient having a disease which is chosen from inflammatory diseases/immune system disorders, angiofibroma, cardiovascular diseases (e.g. restenosis, arteriosclerosis), thalassaemias, fibrotic diseases (e.g. liver fibrosis), diabetes, and autoimmune diseases and administering to said patient a therapeutically effective amount of a compound of a formula chosen from Formula I, II, III, IV, and V

In one aspect, in the compounds of the invention each L (e.g., L, L_1, and L_2) is independently chosen from $-CH_2OCH_2-$, $-CH_2NHCH_2-$, $-CH_2SCH_2-$, $--CH_2CH_2CH_2-$,$-CH_2CH_2NH-$, $-CH_2CH_2S-$, $-CH_2CH_2-$, $-CH_2S-$, $-CH_2O-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH{=}CH_2-$, $-CH_2CH{=}CH_2CH_2-$, $-CH_2CH_2NHCH_2-$, $-CH_2CH_2SCH_2-$, and $-CH_2CH_2OCH_2-$. In a more specific aspect, each L (e.g., L, L_1, and/or L_2) is independently chosen from $CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, and $-CH_2CH_2-$.

In one aspect, in the compounds of the invention, the number of bonds directly connecting the A-ring to the B-ring in a linear manner is chosen from 6, 7, or 8.

In one aspect, in the compounds of the invention the sum on n-values for L_1 and L_2 is 4, 5, 6, or 7.

In one aspect, R_Y is an optionally substituted heteroaryl. In a more specific one aspect, R_Y can be optionally substituted and is a heteroaryl independently chosen from thienyl (thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (furanyl), isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, pyrrolyl, including without limitation 2H-pyrrolyl, imidazolyl, pyrazolyl, pyridyl (pyridinyl) 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridinyl N-oxide, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl,

isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4- dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[l,2-a]pyrimidin-4-one, pyrazolo[l,5-a]pyrimidinyl, including without limitation pyrazolo[l,5-a]pyrimidin-3-yl, l,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl and 2 oxobenzimidazolyl.

In one aspect, R_Y is an optionally substituted heterocycle. In a more specific one aspect, R_Y can be optionally substituted and is a heterocycle independently chosen from morpholino, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholino, homopiperazinyl, imidazolyl, imidazolidinyl, pyrazolidinyl, dioxanyl and dioxolanyl.

In one aspect, R_Y is an optionally substituted aryl. In a more specific one aspect, R_Y can be optionally substituted and is an aryl group independently chosen from phenyl, naphthyl and anthracenyl. In a more specific aspect, the optional substituent(s) on R_Y is chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, -S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl.

In one aspect, each R_Y can be optionally substituted and is independently chosen from thiophenyl, furanyl, phenyl, pyridinyl, and pyrazole.
In one aspect, the optional substituents on R_Y are chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl,

sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido. In a more specific aspect, the optional substituents are independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl.

In one aspect, the optional substituents on R_Y are independently chosen from –CN, halo, alkyl provided said alkyl is not substituted with a carboxylate or ester thereof, alkoxy, haloalkyl, haloalkoxy, and -C(=O)NH(cyclopropyl).

In some aspects of the embodiments of the invention, e.g., the compounds of Formulae I-V, do not include those having a structure as in CAS registry no.179544-25-3 (4'-(3-Ethoxy-3-oxopropyl)-α-(3-phenylpropyl)[1,1'-biphenyl]-4-butanoic acid), CAS registry no. 179544-26-4 (4'-(2-Carboxyethyl)-α-(3-phenylpropyl)[1,1'-biphenyl]-4-butanoic acid), CAS registry no. 382605-84-7 ([1,1'-Biphenyl]-4-butanoic acid, α-(3,4-dichlorophenyl)-), and CAS registry no. 189218-03-9 ([1,1'-Biphenyl]-4-butanoic acid, 4'-fluoro-α-[(2S)-2-[(phenylmethoxy)methyl]hexyl]-, (α R)-).

In some aspects of the compounds of the invention, e.g., of Formulae I-V, the ring system attached to the A-ring has 1-5 substituents independently chosen from hydroxyl, halo, alkyl provided it is not an ethyl substituted with a carboxylate or ester thereof, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl.

In some aspects of the compounds of the invention, e.g., of Formulae I-V, the ring system attached to the A-ring has 1-5 substituents chosen from alkyl, haloalkyl, haloalkoxy, hydroxyl, $-NH_2$, –CN, halo, alkoxy, tetrazolyl, -C(=O)Z, and -NH-Y, wherein Z is chosen from –OH, -O(C_{1-6} alkyl), -NH(C_{1-6} alkyl), -NH(C_{1-6} alkyl)$_2$, -NH(cycloalkyl) wherein Y is chosen from alkyl and –(C=O)(C_{1-3} alkyl).

In some aspects of the compounds of the invention, e.g., of Formulae I-V, the ring system attached to the A-ring has 1-5 substituents chosen from -CN, chloro, fluoro, methoxy, ethoxy, hydroxyl, methyl, tetrazolyl, $-OCF_3$, -C(=O)OH, -C(=O)O-alkyl, $-NC(=O)CH_3$, $-C(=O)NH_2$, $-C(=O)CH_3$, and -C(=O)NH-cyclopropyl.

In an embodiment, the invention provides a compound of Formulae I-V or a pharmaceutically acceptable salt thereof, wherein said compound is chosen from 5-(1-Naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid; 2-{2-[3'-(Aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-Trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-Cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-Acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(4'-Fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(4'-Methoxy, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate; Methyl 2-{2-[(4'-fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate; 2-{2-[2'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid ; Methyl 2-{2-[2'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate; 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; Methyl 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate; 2-{2-[(1-Methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid; 2-{2-[(2'-Methoxypyridinyl)-1,1'-

biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[2'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[2'-Trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-Chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-([3'-Cyano-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoic acid; or an ester thereof.

In one embodiment, the invention provides a compound of Formulae I-V or a pharmaceutically acceptable salt thereof, wherein said compound is chosen from 2-{2-[4-(1H-tetrazol-5-yl)phenyl]ethyl}-5-phenyl-pentanoic acid; 2-{2-[2'-hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-([2'-cyano-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoic acid; 2-{2-[3'-hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-(tert-butoxycarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-(Aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(2'-Fluoro, 5'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(2'-Fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(2'-Chloro, 5'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 5-[4-(benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid; 5-[(1,1'-biphenyl-4-yl)]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid; 4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(1,1'-biphenyl-4-yl)butanoic acid; or an ester thereof.

In a preferred embodiment the invention provides a compound or a pharmaceutically acceptable salt thereof chosen from 2-{2-([3'-Cyano-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoic acid;
2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[4'-Chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;

2-{2-[3'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[2'-Trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[2'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[(2'-Methoxypyridinyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[(1-Methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenyl pentanoic acid;
2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[2'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[(4'-Methoxy, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[(4'-Fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-Acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[4'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[4'-Cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-Trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[4'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-(Aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
5-(1-Naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl- 4-yl)]ethyl}pentanoic acid;
2-{2-[4-(1-Oxidopyridin-3-yl)phenyl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-nitrile-1,1'-biphenyl-4-yl]ethyl}-5-phenylpent-4-enoic acid;
5-[3-(4-methylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid;
4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(4-benzyloxybenzyl)butanoic acid.;
5-[4-(Anilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid;
2-{2-[3'-Hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
5-[4-(Benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid;
5-(1,1'-Biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid;
2-(4-Bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoic acid;

2-(1,1'-Biphenyl-4-ylmethyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoic acid;
2-[2-(6-Benzyloxy-1,1'-biphenyl-3-yl)ethyl]-5-phenylpentanoic acid;
5-(1-Naphthyl)-2-[2-(4'-trifluoro-1,1'-biphenyl-4-yl)ethyl]-pentanoic acid;
5-(1-Naphthyl)-2-{2-[3'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid;
5-(1-Naphthyl)-2-{2-[4'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid;
5-(1-Naphthyl)-2-{2-[4'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid;
2-{2-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid;
2-(2-{[1-Isobutyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[(2-Ethoxy-2-oxoethyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[1-Methyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[1-Benzyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[1-(4-Methoxybenzyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[3,5-Dimethyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-{2-[(1-Ethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid;and
2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid.
In a related aspect, of this embodiment, a pahrmaceutical composition is provided comprising a compound or pharmaceutically acceptable salt as described above and a pharmaceutically acceptable carrier.

In a preferred embodiment the invention provides a compound or a salt thereof chosen from
Methyl 2-{2-[3'-cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[2'-trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[2'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[(2'-methoxypyridinyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;

Methyl 2-{2-[(1-methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[2'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[(4'-fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
2-{2-[(4'-Methoxy, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-(acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-(aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 5-(1-naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl-4-yl)]ethyl}-pentanoate;
Methyl 2-{2-[4-(1-oxidopyridin-3-yl)phenyl]ethyl}-5-phenylpentanoate;
Methyl 4-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)butanoate;
Methyl 2-{2-[3'-nitrile-1,1'-biphenyl-4-yl]ethyl}-5-phenylpent-4-enoate;
Methyl 5-[3-(tert-butoxycarbonyl-4-methylanilinosulfonyl) phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-ynoate;
Methyl 5-[3-(tert-butoxycarbonyl-4-methylanilinosulfonyl) phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate;
Methyl 5-[4-(tert-butoxycarbonylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-ynoate;
Methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(4-benzyloxybenzyl)butanoate;
Methyl 5-[4-(tert-butoxycarbonylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate;
Methyl 2-{2-[3'-hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;

Methyl 5-[4-(benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate;
Methyl (4E)-5-(4-bromophenyl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-enoate;
Methyl (4E)-5-(1,1'-biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-enoate;
Methyl 5-(1,1'-biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate;
Methyl 2-(4-bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate;
Methyl 2-(1,1'-biphenyl-4-ylmethyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate;
Methyl 2-[2-(6-benzyloxy-1,1'-biphenyl-3-yl)ethyl]-5-phenylpentanoate;
Methyl 5-(1-naphthyl)-2-[2-(4'-trifluoro-1,1'-biphenyl-4-yl)ethyl]-pentanoate;
Methyl 5-(1-naphthyl)-2-{2-[3'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoate;
Methyl 5-(1-naphthyl)-2-{2-[4'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoate;
Methyl 5-(1-naphthyl)-2-{2-[4'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoate;
Methyl 2-{2-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate;
Methyl 2-(2-{[1-isobutyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-(2-{[(2-ethoxy-2-oxoethyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-(2-{[1-methyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-(2-{[1-benzyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-(2-{[1-(4-methoxybenzyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-{2-(4-[3,5-dimethyl-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)]phenyl)ethyl}-5-phenylpentanoate;
Methyl 2-(2-{[3,5-dimethyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Ethyl 2-{2-[(1-ethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate; and

Methyl 2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compounds of this embodiment can be used as synthetic intermediates and/or as ester prodrugs.

In another embodiment, the invention provides a method for synthesizing a compound of Formulae I-V, see scheme I below. Commercially available carboxylic acid derivatives of formula (VI) were transformed to the methyl ester derivatives of formula (VII) by 3 successive reactions as shown in the Scheme below. First, the methyl ether was removed using hydrobromic acid to give the phenol, which was esterified using methanol and a strong acid like hydrochloric or sulphuric acid. Finally methyl ester derivatives were benzylated with benzyl bromide under basic conditions to afford the compounds of formula (VII).

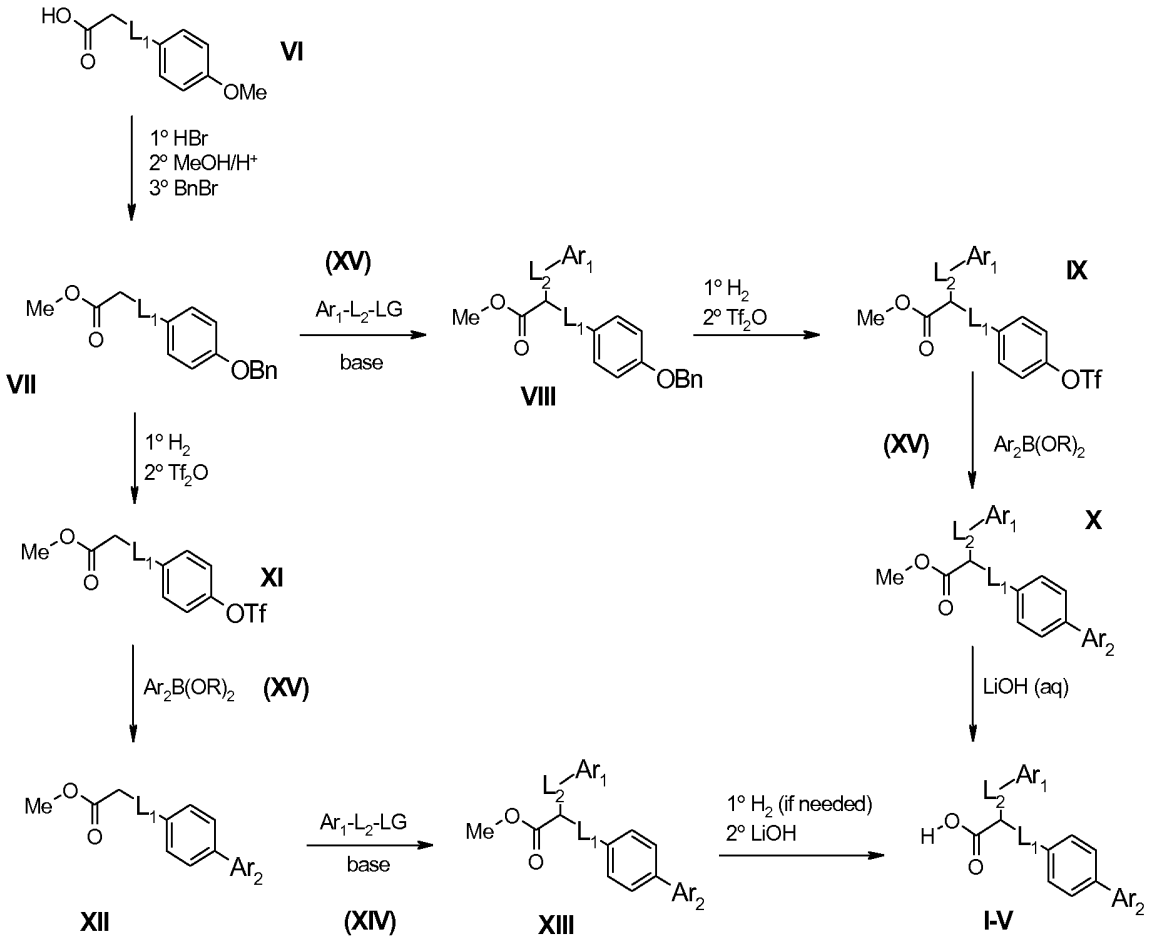
Alkylation of the derivatives of formula (VII) using a strong base and an alkylating agent of formula (XIV) leads to the formation of the derivatives of formula (VIII). The benzylic group was then removed by catalytic hydrogenation, and the resulting free hydroxyl group was allowed to react with triflic anhydride under basic conditions to afford the triflates of formula (IX). Standard Suzuki coupling reactions of compounds of formula (IX) with commercially available boronic acids of formula (XIV) results in the formation of the derivatives of formula (X). Hydrolysis of the methyl ester of these derivatives using lithium hydroxide afforded the compounds of formula (I-V), which are subject of the present invention.

On the other hand, cleavage of the benzylic group of the compounds of formula (VII) and triflate formation of the free phenol lead to the formation of the compounds of formula (XI). Reaction of these compounds with commercially available boronic acids of formula (XIV) under standard Suzuki coupling reactions conditions results in the formation of the derivatives of formula (XII). Alkylation of the derivatives of formula (VII) using a strong base and an alkylating agent of formula (XIV) leads to the formation of the derivatives of formula (XIII). Again, hydrolysis of the methyl ester of the derivatives of formula (XIII) using lithium hydroxide

afforded the compounds of formula (I-V), which are subject of the present invention.

In the synthetic scheme triflate is used as a leaving group in order to react with boronic-based reagents. In this step other leaving groups such as bromine and others known to the skilled artisan can be used instead of triflate.

The invention also provides compounds as defined in the synthetic schemes below as intermediates. These intermediates are useful for synthesizing compounds of the invention.



Scheme I

Definitions

As used herein, the term "alkyl" refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. In a more specific definition, the alkyl group has 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; e.g., "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). In another more specific definition, it is a medium size alkyl having 1 to 10 carbon atoms. In yet another more specific definition, it is a lower alkyl having 1 to 6 carbon atoms, and in a more specific embodiment, 1 to 4 carbon atoms.

As used herein, the term "alkenyl" refers to an unsaturated hydrocarbon including straight chain and/or branched chain groups, comprising at least one carbon-to-carbon double bond. In a more specific definition, the alkenyl group is further defined as having 2 to 20 carbon atoms. In another more specific definition, it is an alkenyl having 2 to 10 carbon atoms. In yet another more specific definition, it is an alkenyl having 2 to 6 carbon atoms, and in yet another more specific definition, it is an alkenyl having 2 to 4 carbon atoms.

As used herein, the term "alkynyl" refers to an unsaturated hydrocarbon including straight chain and/or branched chain groups, comprising at least one carbon-to-carbon triple bond. In a more specific definition, the alkynyl group is further defined as having 2 to 20 carbon atoms. In another more specific definition, it is an alkynyl having 2 to 10 carbon atoms. In yet another more specific definition, it is an alkynyl having 2 to 6 carbon atoms, and in yet another more specific definition, it is an alkynyl having 2 to 4 carbon atoms.

As used herein, the term "halo" refers to chloro, fluoro, bromo, and iodo.

As used herein, the term "hydro" refers to a hydrogen atom (-H group).

As used herein, the term "hydroxy" or “hydroxyl” refers to an -OH group.

As used herein, the term "alkoxy" refers to both an -O-alkyl and an -O-cycloalkyl group, as defined herein. Lower alkoxy refers to -O-lower alkyl groups.

As used herein, the term "aryloxy" refers to both an -O-aryl.

As used herein, the term “heteroaryloxy” refers to an -O-heteroaryl group, as defined herein.

As used herein, the term "mercapto" group refers to an -SH group.

As used herein, the term "alkylthio" group refers to both an S-alkyl and an -S-cycloalkyl group, as defined herein.

As used herein, the term "arylthio" group refers to both an -S-aryl and an -S- heteroaryl group, as defined herein.

As used herein, the term "carbonyl" group refers to a -C(=O)R" group, where R" is selected from the group consisting of hydro, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heterocyclic (bonded through a ring carbon), as defined herein.

As used herein, the term "aldehyde" group refers to a carbonyl group where R" is hydro.

As used herein, the term "cycloketone" refer to a cycloalkyl group in which one of the carbon atoms which form the ring has a "=O" bonded to it; i.e. one of the ring carbon atoms is a -C(=O)-group.

As used herein, the term "thiocarbonyl" group refers to a -C(=S)R" group, with R" as defined herein.

As used herein, the term "O-carboxy" group refers to a R"C(=O)O-group, with R" as defined herein.

As used herein, the term "C-carboxy" group refers to a -C(=O)OR" groups with R" as defined herein.

As used herein, the term "ester" is a C-carboxy group, as defined herein, wherein R" is as defined herein other than hydro.

As used herein, the term "C-carboxy salt" refers to a $-C(=O)O^-M^+$ group wherein M^+ is selected from the group consisting of lithium, sodium, magnesium, calcium, potassium, barium, iron, zinc and quaternary ammonium.

As used herein, the term "acetyl" group refers to a $-(C=O)CH_3$ group.

As used herein, the term "carboxyalkyl" refers to $-(CH_2)_rC(=O)OR"$ wherein r is 1-6 and R" is as defined herein.

As used herein, the term "carboxyalkyl salt" refers to a $-(CH_2)_rC(=O)O^-M^+$ wherein M^+ is selected from the group consisting of lithium, sodium, potassium, calcium, magnesium, barium, iron, zinc and quaternary ammonium.

As used herein, the term "carboxylic acid" refers to a C-carboxy group in which R" is hydro.

As used herein, the term "haloalkyl" refers to an alkyl group substituted with 1 to 6 halo groups. In a preferred defintion, haloalkyl is a $-CX_3$ group wherein X is a halo group. The halo groups can be independently selected.

As used herein, the term "trihalomethanesulfonyl" refers to a $X_3CS(=O)_2$-group with X as defined above.

As used herein, the term "cyano" refers to a -C≡N group.

As used herein, the term "cyanato" refers to a -CNO group.

As used herein, the term "isocyanato" refers to a -NCO group.

As used herein, the term "thiocyanato" refers to a -CNS group.

As used herein, the term "isothiocyanato" refers to a -NCS group.

As used herein, the term "sulfinyl" refers to a -S(=O)R" group, with R" as defined herein.

As used herein, the term "sulfonyl" refers to a $-S(=O)_2R"$ group, with R" as defined herein.

As used herein, the term "sulfonamido" or “sulfonamide” refers to a $-S(=O)_2\ NR_{17}R_{18}$. R_{17} and R_{18} are independently chosen from hydro, alkyl, aryl, carbocycle, heterocycle, $-(CH_2)$aryl, $-(CH_2)$carbocycle, and $-(CH_2)$heterocycle.

As used herein, the term "trihalomethanesulfonamido" refers to a $X_3CS(=O)_2NR_{17}-$ group with X and R_{17} as defined herein.

As used herein, the term "O-carbamyl" refers to a $-OC(=O)NR_{17}R_{18}$ group with R_{17} and R_{18} as defined herein.

As used herein, the term "N-carbamyl" refers to a $R_{18}OC(=O)NR_{17}-$ group, with R_{17} and R_{18} as defined herein.

As used herein, the term "O-thiocarbamyl" refers to a $-OC(=S)NR_{17}\ R_{18}$ group with R_{17} and R_{18} as defined herein.

As used herein, the term "N-thiocarbamyl" refers to a $R_{17}O(C=S)NR_{18}$- group, with R_{17} and R_{18} as defined herein.

As used herein, the term "amino" refers to a -NRR group, with R and R both being hydro.

As used herein, the term “substituted amino” refers to a $–NR_{22}R_{23}$ wherein R_{22} and R_{23} are independently chosen from –H, C1-C8 alkyl, and phenyl wherein at least one of R_{22} and R_{23} is not –H.

As used herein, the term "C-amido" refers to a $-C(=0)NR_{17}R_{18}$ group with R_{17} and R_{18} as defined herein.

An "N-amido" refers to a $R_{17}C(=0)NR_{18}$- group with R_{17} and R_{18} as defined herein.

As used herein, the term "nitro" refers to a $-NO_2$ group.

As used herein, the term "quaternary ammonium" refers to a $–NR_{20}R_{21}$ R_{22} group wherein R_{20}, R_{21}, and R_{22} are independently selected from the group consisting of hydro and unsubstituted lower alkyl.

As used herein, the term "methylenedioxy" refers to a $-OCH_2O$- group wherein the oxygen atoms are bonded to adjacent ring carbon atoms.

As used herein, the term "ethylenedioxy" refers to a $-OCH_2CH_2O$- group wherein the oxygen atoms are bonded to adjacent ring carbon atoms.

As used herein, the term "carbocyclic" refers to an all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group wherein one or more of the rings does not have a completely conjugated pi-electron system. Examples, without limitation, of carbocyclic groups are cycloalkyls such as cyclopropane, cyclobutane, cyclopentane,

cyclohexane, adamantane, cycloheptane and cycloalkenes such as cycloheptatriene, cyclopentene, and cyclohexadiene.

As used herein, the term "cycloalkyl" refers to an all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group wherein one or more of the rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclohexane, adamantane, and cycloheptane.

As used herein, the term "heterocycle" or heterocyclic" refers to a saturated or partially saturated 3-7 membered monocyclic, or 7-10 membered bicyclic ring system, which consists of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Non- limiting saturated or partially saturated heterocyclic groups include tetrahydrofuranyl, pyranyl, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, isochromanyl, chromanyl, pyrazolidinyl, pyrazolinyl, tetronoyl and tetramoyl groups. Example of "heterocycles" or "heterocyclic" rings also include, but are not limited to, morpholino, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholino, homopiperazinyl, imidazolyl, imidazolidinyl, pyrazolidinyl, dioxanyl and dioxolanyl. "Heterocycle" can include heteroaryls when the pi-electron system of a heterocycle is completely conjugated.

As used herein, the term "aryl" refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system.

Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl.

As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms; 6, 10 or 14 pi electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms. Non-limiting heteroaryl groups include thienyl (thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (furanyl), isobenzofuranyl, chromenyl, xanthenyl, phenoxanthiinyl, pyrrolyl, including without limitation 2H-pyrrolyl, imidazolyl, pyrazolyl, pyridyl (pyridinyl), including without limitation 2-pyridyl, 3 -pyridyl, and 4-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, quinolyl, phthalzinyl, naphthyridinyl, quinozalinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acrindinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7 aminoisocoumarin, pyrido[l,2-a]pyrimidin-4-one, pyrazolo[l,5-a]pyrimidinyl, including without limitation pyrazolo[l,5-a]pyrimidin-3-yl, l,2-benzoisoxazol-3-yl, benzimidazolyl, 2-oxindolyl and 2 oxobenzimidazolyl. When the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the form of an N-oxide, e.g., a pyridyl N-oxide, pyrazinyl N-oxide and pyrimidinyl N-oxide.

As used herein, the term "arylalkyl" refers to an alkyl group asdefined herein above substituted by an aryl group as defined herein above. In a preferred definition “arylalkyl” refers to a C_{l-10} alkyl grou
p (an alkyl group having 1-10 carbon atoms), as defined herein above, substituted by a C_{6-14} aryl group (an aryl group having 6 to 14 carbon atoms), as defined herein above. Non-limiting examples of arylalkyl groups include benzyl, phenethyl, and naphthylmethyl.

As used herein, the term "arylalkenyl" refers to an alkenyl group as defined herein above substituted by an aryl group as defined herein. In a preferred definition “arylalkenyl” refers to a C_{2-10} alkenyl group substituted

by a C_{6-14} aryl group (an aryl group having 6 to 14 carbon atoms), as defined herein above.

As used herein, the term "arylalkynyl" refers to an alkynyl group as defined herein above substituted with an aryl group as defined herein above. In a preferred definition “arylalkynyl” refers to a C_{2-10} alkynyl group substituted by a C_{6-14} aryl group (an aryl group having 6 to 14 carbon atoms), as defined herein above.

As used herein, the term "arylalkoxy" refers to an alkoxy group as defined herein above substituted by an aryl group as defined herein above. In a preferred definition “arylalkoxy” refers to a C_{l-10} alkoxy group, as defined herein above, substituted by an aryl group, as defined herein above. Examples of arylalkoxy groups include benzyloxy and phenethyloxy.

As used herein, the term "heteroarylalkoxy" refers to an alkoxy group as defined herein above substituted by an heteroaryl group as defined herein above. In a preferred definition “heteroarylalkoxy” refers to a C_{l-10} alkoxy group, as defined herein above, substituted by an heteroaryl group, as defined herein above. Examples of arylalkoxy groups include benzyloxy and phenethyloxy.

As used herein, the term "haloalkoxy" refers to an alkoxy group which is substituted with 1 to 6 halo groups, wherein the alkoxy group and the halo groups are as defined herein above, and further wherein the halo groups are independently selected.

As used herein, the term "haloaryl" refers to an aryl group which is substituted with 1 to 6 halo groups, wherein the aryl group and the halo groups are as defined herein above, and further wherein the halo groups are independently selected.

As used herein, the term "acylamino" refers to an $-N(R_{17})C(=O)R_{18}$ group, wherein R_{17} and R_{18} are as defined herein above.

As used herein, the term "acyloxy" refers to an -O-C(=O)R_{17} group, wherein R_{17} is as defined herein above.

Unless otherwise specified, as used herein the term “optional substituent” or “optionally substituted” refers to one or more substituents covalently linked the parent group where said substituents are independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido, wherein L is defined herein as indicated in its broadest embodiment. In an alternative definition, the optional substituents are chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl.

As used herein, the term "preventing an increase in a symptom" refers to both not allowing a symptom to increase or worsen, as well as reducing the rate of increase in the symptom. For example, a symptom can be measured as the amount of particular disease marker, i.e., a protein. In another example the symptom can be cognitive decline. Preventing an increase, according to the definition provided herein, means that the amount of symptom (e.g., protein or cognitive decline) does not increase or that the rate at which it increases is reduced.

As used herein, the term "treating a disease or disorder" refers to a slowing of or a reversal of the progress of the disease. Treating a disease or disorder includes treating a symptom and/or reducing the symptoms of the disease.

As used herein, the term "preventing a disease or disorder" refers to a slowing of the disease or of the onset of the disease or the symptoms thereof. Preventing a disease or disorder can include stopping the onset of the disease or symptoms thereof. As used herein, the term "unit dosage form" refers to a physically discrete unit, such as a capsule or tablet suitable as a unitary dosage for a human patient. Each unit contains a predetermined quantity of a compound of Formulae I-V, which was discovered or believed to produce the desired pharmacokinetic profile which yields the desired therapeutic effect. The dosage unit is composed of a compound of Formulae I-V in association with at least one pharmaceutically acceptable carrier, salt, excipient, or combination thereof.

As used herein, the term "dose" or "dosage" refers the amount of active ingredient that an individual takes or is administered at one time. For example, a 40 mg dose of a compound of Formulae I-V refers to, in the case of a twice-daily dosage regimen, a situation where the individual takes 40 mg of a compound of Formulae I-V twice a day, e.g., 40 mg in the morning and 40 mg in the evening. The 40 mg of a compound of Formulae I-V dose can be divided into two or more dosage units, e.g., two 20 mg dosage units of a compound of Formulae I-V in tablet form or two 20 mg dosage units of a compound of Formulae I-V in capsule form.

"A pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound.

"A pharmaceutically active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the

body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein.

"A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound for use in the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrophosphates, dihydrophosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4 dioates, hexyne-l,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

As used herein, a “pharmaceutically acceptable carrier” refers to a non-API (API refers to Active Pharmaceutical Ingredient) substances such as disintegrators, binders, fillers, and lubricants used in formulating pharmaceutical products. They are generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration and the European Medical Agency.

As is understood by the skilled artisan, certain variables in the list of substituents are repetitive (different name for the same substituent), generic to other terms in the list, and/or partially overlap in content with other terms. In the compounds of the invention, the skilled artisan recognizes that substituents may be attached to the remainder of the molecule via a number of positions and the preferred positions are as illustrated in the Examples.

Additionally, the compounds of Formulae I-V can contain asymmetric carbon atoms and can therefore exist in racemic and optically active forms. Thus, optical isomers or enantiomers, racemates, tautomers, and diastereomers are also encompassed in the compounds of Formulae I-V. The methods of present invention include the use of all such isomers and mixtures thereof. Methods of separation of enantiomeric and diastereomeric mixtures are well known to one skilled in the art. The present invention encompasses any isolated racemic or optically active form of compounds described in Formulae I-V, or any mixture thereof. For oral delivery, the active compounds can be incorporated into a formulation that includes pharmaceutically acceptable carriers such as binders (e.g., gelatin, cellulose, gum tragacanth), excipients (e.g., starch, lactose), lubricants (e.g., magnesium stearate, silicon dioxide), disintegrating agents (e.g., alginate, Primogel, and corn starch), and sweetening or flavoring agents (e.g., glucose, sucrose, saccharin, methyl salicylate, and peppermint). The formulation can be orally delivered in the form of enclosed gelatin capsules or compressed tablets. Capsules and tablets can be prepared in any conventional techniques. The capsules and tablets can also be coated with various coatings known in the art to modify the flavors, tastes, colors, and shapes of the capsules and tablets. In addition, liquid carriers such as fatty oil can also be included in capsules. Suitable oral formulations can also be in the form of suspension, syrup, chewing gum, wafer, elixir, and the like. If desired, conventional agents for modifying flavors, tastes, colors, and shapes of the special forms can also be included. In addition, for convenient administration by enteral feeding

tube in patients unable to swallow, the active compounds can be dissolved in an acceptable lipophilic vegetable oil vehicle such as olive oil, corn oil and safflower oil.

The active compounds can also be administered parenterally in the form of solution or suspension, or in lyophilized form capable of conversion into a solution or suspension form before use. In such formulations, diluents or pharmaceutically acceptable carriers such as sterile water and physiological saline buffer can be used. Other conventional solvents, pH buffers, stabilizers, anti-bacteria agents, surfactants, and antioxidants can all be included. For example, useful components include sodium chloride, acetates, citrates or phosphates buffers, glycerin, dextrose, fixed oils, methyl parabens, polyethylene glycol, propylene glycol, sodium bisulfate, benzyl alcohol, ascorbic acid, and the like. The parenteral formulations can be stored in any conventional containers such as vials and ampoules.

Routes of topical administration include nasal, bucal, mucosal, rectal, or vaginal applications. For topical administration, the active compounds can be formulated into lotions, creams, ointments, gels, powders, pastes, sprays, suspensions, drops and aerosols. Thus, one or more thickening agents, humectants, and stabilizing agents can be included in the formulations. Examples of such agents include, but are not limited to, polyethylene glycol, sorbitol, xanthan gum, petrolatum, beeswax, or mineral oil, lanolin, squalene, and the like. A special form of topical administration is delivery by a transdermal patch. Methods for preparing transdermal patches are disclosed, e.g., in Brown, et al., (1988) Annual Review of Medicine, 39:221-229, which is incorporated herein by reference.

Subcutaneous implantation for sustained release of the active compounds may also be a suitable route of administration. This entails surgical procedures for implanting an active compound in any suitable formulation into a subcutaneous space, e.g., beneath the anterior abdominal wall. See, e.g., Wilson et al., (1984) J. Clin. Psych. 45:242-247. Hydrogels can

be used as a carrier for the sustained release of the active compounds. Hydrogels are generally known in the art. They are typically made by crosslinking high molecular weight biocompatible polymers into a network, which swells in water to form a gel like material. Preferably, hydrogels are biodegradable or biosorbable. For purposes of this invention, hydrogels made of polyethylene glycols, collagen, or poly(glycolic-co-L-lactic acid) may be useful. See, e.g., Phillips et al., (1984) J. Pharmaceut. Sci., 73: 1718- 1720.

The compounds of Formulae I-V also include prodrugs and metabolites thereof. The active compounds for example, can be conjugated, to a water soluble non- immunogenic non-peptidic high molecular weight polymer to form a polymer conjugate. For example, an active compound is covalently linked to polyethylene glycol to form a conjugate. Typically, such a conjugate exhibits improved solubility, stability, and reduced toxicity and immunogenicity. Thus, when administered to a patient, the active compound in the conjugate can have a longer half-life in the body, and exhibit better efficacy. See generally, Burnham (1994) Am. J. Hosp. Pharm. 15:210-218. PEGylated proteins are currently being used in protein replacement therapies and for other therapeutic uses. For example, PEGylated interferon (PEG-INTRON A®) is clinically used for treating Hepatitis B. PEGylated adenosine deaminase (ADAGEN®) is being used to treat severe combined immunodeficiency disease (SCIDS). PEGylated L-asparaginase (ONCAPSPAR®) is being used to treat acute lymphoblastic leukemia (ALL). It is preferred that the covalent linkage between the polymer and the active compound and/or the polymer itself is hydrolytically degradable under physiological conditions. Such conjugates known as "prodrugs" can readily release the active compound inside the body. Controlled release of an active compound can also be achieved by incorporating the active ingredient into microcapsules, nanocapsules, or hydrogels generally known in the art. Other pharmaceutically acceptable prodrugs of the compounds of this invention include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases,

Schiff bases, aminoacid conjugates, phosphate esters, metal salts and sulfonate esters.

Liposomes can also be used as carriers for the active compounds of the present invention. Liposomes are micelles made of various lipids such as cholesterol, phospholipids, fatty acids, and derivatives thereof. Various modified lipids can also be used. Liposomes can reduce the toxicity of the active compounds, and increase their stability. Methods for preparing liposomal suspensions containing active ingredients therein are generally known in the art. See, e.g., U.S. Patent No. 4,522,81 1 ; Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N. Y. (1976).

The active compounds can also be administered in combination with another active agent that synergistically treats or prevents the same symptoms or is effective for another disease or symptom in the patient treated so long as the other active agent does not interfere with or adversely affect the effects of the active compounds of this invention. Such other active agents include but are not limited to anti-inflammation agents, antiviral agents, antibiotics, antifungal agents, antithrombotic agents, cardiovascular drugs, cholesterol lowering agents, anti-cancer drugs, hypertension drugs, and the like.

The following examples are provided by way of illustration and are not intended to limit the scope of the invention.

Molecule names were generated using IsisDraw version 2.4. For molecules larger than 50 atoms, the molecule was fragmented to generate the name. In the case of a conflict between a name and a drawing of the structure, the drawing is controlling.

EXAMPLES

Example 1: Synthesis of Intermediates A and B.

Synthesis of Intermediate A: Methyl 2-{2-(4-{[(trifluoromethyl)sulfonyl] oxy}phenyl)ethyl}-5-phenylpentanoate.
4-(4-Hydroxyphenyl)butanoic acid. A suspension of 4-(4-methoxyphenyl) butanoic acid (2.0 g, 9.603 mmol) in HBr (20 mL, 48% aqueous solution) was refluxed for 2 h. The reaction mixture was allowed to reach r.t., poured into H_2O (150 mL) and extracted with EtOAc (200 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated, to give 1.81 g of 4-(4-hydroxyphenyl)butanoic acid (white solid). The crude residue was submitted to the next step without purification.

Methyl 4-(4-hydroxyphenyl)butanoate. H_2SO_4 (2 mL, 37.32 mmol) was added to a solution of 4-(4-hydroxyphenyl)butanoic acid (9.603 mmol) in MeOH (40 mL). The reaction mixture was refluxed for 1 h, allowed to reach r.t., and poured into H_2O (150 mL). It was extracted with CH_2Cl_2 (200 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated, to give 1.59 g of crude methyl 4-(4-hydroxyphenyl)butanoate (colourless oil, yield: 85%). The compound was submitted to next step without further purification. ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.02 (d, *J* = 7.9 Hz, 2H), 6.75 (d, *J* = 7.9 Hz, 2H), 5.47 (bs, 1H), 3.67 (s, 3H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.32 (t, *J* = 7.7 Hz, 2H), 1.92 (m, 2H).

Methyl 4-[4-(benzyloxy)phenyl]butanoate. BnBr (2.5 mL, 21.018 mmol) was added to a suspension of K_2CO_3 (3.0 g, 21.706 mmol) and methyl 4-(4-hydroxyphenyl)butanoate (2.10 g, 10.812 mmol) in CH_3CN (100 mL). The reaction mixture was stirred at r.t. overnight (18 h). It was poured into H_2O (200 mL) and extracted with EtOAc (150 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was flash chromatographed on SiO_2 (0→5% EtOAc/hexanes), to afford 3.05 g of methyl 4-[4-(benzyloxy)phenyl]butanoate (colourless oil,

yield: 99%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.38 (m, 5H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.05 (s, 2H), 3.66 (s, 3H), 2.59 (m, 2H), 2.31 (m, 2H), 1.92 (m, 2H).

Methyl (4E)-2-[2-(4-benzyloxyphenyl)ethyl]-5-phenylpent-4-enoate. Method A: Alkylation. A solution of methyl 4-[4-(benzyloxy)phenyl]butanoate (3.0 g, 10.550 mmol) in THF (5 mL) was added to a -78 °C cooled solution of LDA (13 mL, 1 M THF solution, 13 mmol) in THF (30 mL). The reaction mixture was stirred at low temperature for 2 min, and a solution of [(1E)-3-bromoprop-1-enyl]benzene (3.30 g, 16.744 mmol) in THF (5 mL) was added. The reaction was allowed to reach r.t. overnight (18 h). It was poured into H_2O (150 mL), taken up to pH = 2 with HCl and extracted with EtOAc (150 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was flash chromatographed on SiO_2 (2→4% EtOAc/hexanes), to give 3.51 g of methyl (4E)-2-[2-(4-benzyloxyphenyl)ethyl]-5-phenylpent-4-enoate (colourless oil, yield: 83%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.43-7.11 (m, 11H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.99 (s, 2H), 3.63 (s, 3H), 2.56-2.23 (m, 5H), 1.89 (m, 1H), 1.75 (m, 1H).

Methyl 2-[2-(4-hydroxyphenyl)ethyl]-5-phenylpentanoate. Method E: Hydrogenation. Methyl (4E)-2-[2-(4-benzyloxyphenyl)ethyl]-5-phenylpent-4-enoate (3.45 g, 8.613 mmol) was added to a suspension of Pd/C (900 mg, 10% Pd/C, 0.845 mmol) in MeOH (60 mL). The reaction mixture was stirred under H_2 atmosphere (balloon) for 8 h. It was filtered through Celite (eluted with EtOAc) and solvent was concentrated off. The crude residue was flash chromatographed on SiO_2 (20% EtOAc/hexanes), to furnish 2.34 g of methyl 2-[2-(4-hydroxyphenyl)ethyl]-5-phenylpentanoate (white solid, yield: 87%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.28-7.07 (m, 5H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.00 (bs, 2H), 3.64 (s, 3H), 2.59-2.32 (m, 5H), 1.88 (m, 1H), 1.75-1.43 (m, 5H).

Intermediate A: Methyl 2-{2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)ethyl}-5-phenylpentanoate. Trifluoromethanesulfonic anhydride (2.60 g, 9.21 mmol) was added to a -18 °C cooled solution of methyl 2-[2-(4-hydroxyphenyl)ethyl]-5-phenylpentanoate (2.30 g, 7.361 mmol) and DIPEA (2.6 mL, 15.187 mmol) in CH_2Cl_2 (45 mL). The reaction mixture was allowed to react at low temperature for 10 min, poured into H_2O (150 mL), taken up to pH = 3 with HCl and extracted with CH_2Cl_2 (120 mL). The crude residue was purified by flash chromatography on SiO_2 (2→6% EtOAc/hexanes), to give 3.04 g of methyl 2-{2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)ethyl}-5-phenylpentanoate (colourless oil, yield: 93%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.37-7.17 (m, 9H), 3.73 (s, 3H), 2.63 (m, 4H), 2.45 (m, 1H), 1.99 (m, 1H), 1.86-1.48 (m, 5H).

Synthesis of Intermediate B Methyl 2-[2-(4-{[(trifluoromethyl)sulfonyl] oxy}phenyl)ethyl]-5-(1-naphthyl)pentanoate.

Methyl 2-[2-(4-benzyloxyphenyl)ethyl]-5-(1-naphthyl)pent-4-ynoate. A solution of methyl 4-[4-(benzyloxy)phenyl]butanoate (1.5 g, 5.27 mmol) in THF (5 mL) was added to a -78 °C cooled solution of LDA (6 mL, 1 M THF solution, 6 mmol) in THF (30 mL). The reaction mixture was stirred at low temperature for 3 min, and a solution of 1-(3-bromoprop-1-ynyl)naphthalene (1.68 g, 6.86 mmol) in THF (5 mL) was added. The reaction was allowed to reach r.t. and stirred for 6 h. It was poured into H_2O (100 mL), taken up to pH = 2 with HCl and extracted with EtOAc (2x100 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was flash chromatographed on SiO_2 (5→10% EtOAc/hexanes), to furnish 950 mg of methyl 2-[2-(4-benzyloxyphenyl)ethyl]-5-(1-naphthyl)pent-4-ynoate (colourless oil, yield: 40%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.29 (m, 1H), 7.80 (m, 3H), 7.62-7.48 (m, 3H), 7.47-7.32 (m, 5H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.04 (s, 2H), 3.75 (s, 3H), 2.82 (m, 3H), 2.67 (m, 2H), 2.13 (m, 2H).

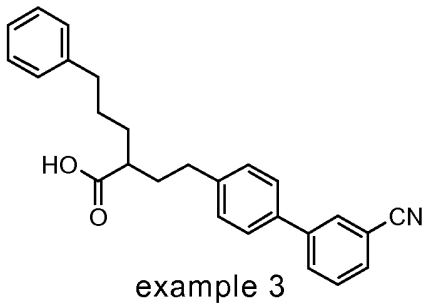
Methyl 2-[2-(4-hydroxyphenyl)ethyl]-5-(1-naphthyl)pentanoate. Methyl 2-[2-(4-benzyloxyphenyl)ethyl]-5-(1-naphthyl)pent-4-ynoate (940 mg, 2.095 mmol) was added to a suspension of Pd/C (220 mg, 10% Pd/C, 0.210 mmol) in MeOH (20 mL). The reaction mixture was stirred under H_2 atmosphere (balloon) for 2 h. It was filtered through Celite (eluted with EtOAc) and solvent was concentrated off. The crude residue was flash chromatographed on SiO_2 (20→30% EtOAc/hexanes), to furnish 579 mg of methyl 2-[2-(4-hydroxyphenyl)ethyl]-5-(1-naphthyl)pentanoate (colourless oil, yield: 76%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.99 (m, 1H), 7.84 (m, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.48 (m, 2H), 7.39 (m, 1H), 7.27 (m, 1H), 7.01 (d, *J* = 7.4 Hz, 2H), 6.74 (d, *J* = 7.4 Hz, 2H), 5.10 (bs, 1H), 3.67 (s, 3H), 3.04 (m, 2H), 2.49 (m, 3H), 1.93 (m, 1H), 1.73 (m, 5H).

Intermediate B: Methyl 2-[2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)ethyl]-5-(1-naphthyl)pentanoate. Trifluoromethanesulfonic anhydride (530 mg, 1.89 mmol) was added to a -18 °C cooled solution of methyl 2-[2-(4-hydroxyphenyl)ethyl]-5-(1-naphthyl)pentanoate (570 mg, 1.57 mmol) and DIPEA (430 mg, 3.37 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was allowed to react at low temperature for 15 min, poured into H_2O (150 mL), taken up to pH = 3 with HCl and extracted with CH_2Cl_2 (100 mL). The crude residue was purified by flash chromatography on SiO_2 (2→10% EtOAc/hexanes), to give 645 mg of methyl 2-[2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)ethyl]-5-(1-naphthyl)pentanoate (colourless oil, yield: 83%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.99 (m, 1H), 7.85 (m, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.48 (m, 2H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.28 (m, 1H), 7.18 (m, 4H), 3.66 (s, 3H), 3.05 (m, 2H), 2.59 (m, 2H), 2.44 (m, 1H), 1.96 (m, 1H), 1.74 (m, 5H).

Example 2: Methyl 2-{2-[3'-cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. Method F: Suzuki coupling.

$Pd(PPh_3)_4$ (34 mg, 0.029 mmol) was added to a suspension of methyl 2-{2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)ethyl}-5-phenylpentanoate (250 mg, 0.562 mmol), Cs_2CO_3 (365 mg, 1.12 mmol) and 3-cyanophenylboronic

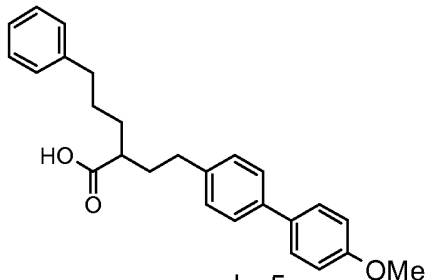
acid (130 mg, 0.884 mmol) in DMF (14 mL). The reaction mixture was stirred at 90 °C until no unreacted Intermediate A was detected by TLC analysis. It was allowed to reach r.t., poured into H_2O (100 mL) and extracted with Et_2O (100 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes), to afford 234 mg of methyl 2-{2-([3'-(cyano)-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoate (colourless oil, yield: quantitative). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.78 (m, 2H), 7.60-7.40 (m, 4H), 7.28-7.05 (m, 7H), 3.67 (s, 3H), 2.54 (m, 4H), 2.41 (m, 1H), 1.94 (m, 1H), 1.80-1.44 (m, 5H).



example 3

Example 3: 2-{2-([3'-Cyano-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoic acid . Method B: ester hydrolysis.LiOH (4 mL, 2M solution in H_2O, 8 mmol) was added to a solution of methyl 2-{2-[3'-cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate (234 mg, 0.562 mmol) in a mixture of THF (14 mL) and MeOH (14 mL). It was warmed up to reflux, and stirred until no unreacted ester was detected by TLC analysis (2 h). The reaction mixture was allowed to reach r.t. and poured into H_2O (100 mL). It was acidified with HCl (10% aqueous solution) until pH 2-3, and extracted with EtOAc (150 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was purified by flash chromatography on SiO_2 (10→80% EtOAc/hexanes) to furnish 2-{2-([3'-cyano-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoic acid (51 mg, white solid, yield: 24%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.85 (m, 2H), 7.67-7.48 (m, 4H), 7.37-7.16 (m, 7H), 2.69 (m, 4H), 2.51 (m, 1H), 2.04 (m, 1H), 1.92-1.56 (m, 5H). EI MS: *m/z* = 382 (M-1).

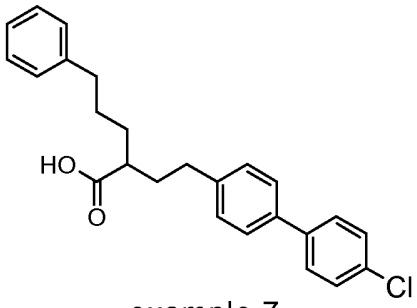
Example 4: Methyl 2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 4-methoxyphenylboronic acid following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (2→10% EtOAc/hexanes) to give a colourless oil (yield: 64%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.39 (m, 4H), 7.21-7.00 (m, 7H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.73 (s, 3H), 3.60 (s, 3H), 2.48 (m, 4H), 2.34 (m, 1H), 1.88 (m, 1H), 1.75-1.36 (m, 5H).



example 5

Example 5: 2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→40% EtOAc/hexanes) to give a white solid (yield: 60%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.43 (m, 4H), 7.26-7.05 (m, 7H), 6.90 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H), 2.56 (m, 4H), 2.40 (m, 1H), 1.94 (m, 1H), 1.83-1.39 (m, 5H). EI MS: *m/z* = 389 (M+1), 406 (M+18).

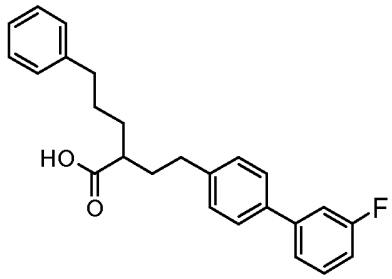
Example 6: Methyl 2-{2-[4'-chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 4-chlorophenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (2→4% EtOAc/hexanes) to give a white solid (yield: 80%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.34 (m, 4H), 7.25 (m, 2H), 7.19-6.98 (m, 7H), 3.57 (s, 3H), 2.46 (m, 4H), 2.34 (m, 1H), 1.86 (m, 1H), 1.73-1.36 (m, 5H).



example 7

Example 7: 2-{2-[4'-Chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[4'-chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→60% EtOAc/hexanes) to give a white solid (yield: 73%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.32 (m, 4H), 7.23 (m, 2H), 7.15-6.97 (m, 7H), 2.45 (m, 4H), 2.29 (m, 1H), 1.84 (m, 1H), 1.75-1.36 (m, 5H). EI MS: *m/z* = 391 (M-1).

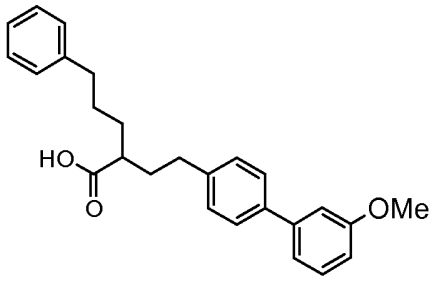
Example 8: Methyl 2-{2-[3'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-fluorophenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5% EtOAc/hexanes) to give a colourless oil (yield: 70%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.49 (d, *J* = 8.5 Hz, 2H), 7.44-7.11 (m, 10H), 7.03 (m, 1H), 3.70 (s, 3H), 2.61 (m, 4H), 2.45 (m, 1H), 1.99 (m, 1H), 1.77-1.54 (m, 5H).



example 9

Example 9: 2-{2-[3'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[3'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→50% EtOAc/hexanes) to give an off-white solid (yield: 60%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.48 (d, *J* = 7.9 Hz, 2H), 7.40-7.10 (m, 10H), 7.00 (m, 1H), 2.62 (m, 4H), 2.46 (m, 1H), 2.02 (m, 1H), 1.89-1.48 (m, 5H). EI MS: *m/z* = 375 (M-1).

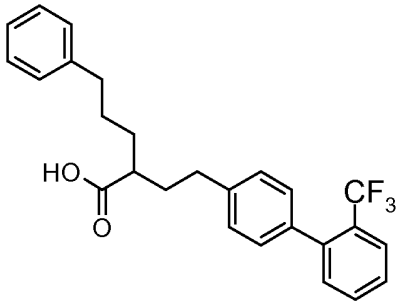
Example 10: Methyl 2-{2-[3'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-methoxyphenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (0→10% EtOAc/hexanes) to give a yellow coloured oil (yield: 83%). EI MS: *m/z* = 403 (M+1), 420 (M+18).



example 11

Example 11: 2-{2-[3'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[3'methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→40% EtOAc/hexanes) to afford a yellow coloured oil (yield: 50%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.42 (m, 2H), 7.13 (m, 10H), 6.80 (m, 1H), 3.78 (s, 3H), 2.68-2.43 (m, 4H), 2.44-2.34 (m, 1H), 2.0-1.88 (m, 1H), 1.80-1.51 (m, 5H). EI MS: *m/z* = 389 (M+1), 406 (M+18).

Example 12: Methyl 2-{2-[2'-trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 2-(trifluoromethyl)benzeneboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a colourless oil (yield: 62%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.85-7.68 (m, 2H), 7.63-7.43 (m, 4H), 7.34-7.12 (m, 7H), 3.71 (s, 3H), 2.66-2.49 (m, 4H), 2.44 (m, 1H), 2.07-1.87 (m, 1H), 1.82-1.58 (m, 5H).

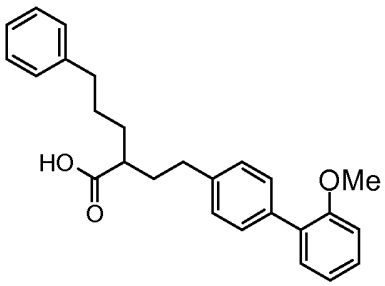


example 13

Example 13: 2-{2-[2'-Trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[2'-trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→40% EtOAc/hexanes) to afford a yellow coloured oil (yield: 52%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.74-7.73 (m, 2H), 7.53-7.41 (m, 4H), 7.19 (m, 4H), 7.14-7.06 (m, 3H), 2.72-2.48 (m, 4H), 2.39 (m, 1H), 2.02-1.87 (m, 1H), 1.74-1.53 (m, 5H). EI MS: *m/z* = 425 (M-1).

Example 14: Methyl 2-{2-[2'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 2-methoxyphenylboronic acid pinacol ester, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→10% EtOAc/hexanes) to give a yellow coloured oil (yield: 64%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.45 (d, *J* = 8.2 Hz, 2H), 7.34-

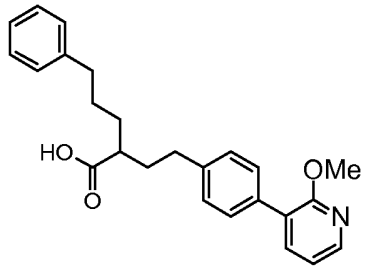
7.12 (m, 8H), 7.05-6.82 (m, 3H), 3.81 (s, 3H), 3.69 (s, 3H), 2.60 (m, 4H), 2.47 (m, 1H), 1.99 (m, 1H), 1.86-1.60 (m, 5H).



example 15

Example 15: 2-{2-[2'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-(4-[2'-methoxy-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→40% EtOAc/hexanes) to give a colourless oil (yield: 68%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.54 (d, *J* = 7.9 Hz, 2H), 7.43-7.18 (m, 9H), 7.14-7.01 (m, 2H), 3.87 (s, 3H), 2.71 (m, 4H), 2.57 (m, 1H), 2.11 (m, 1H), 1.93- 1.60 (m, 5H). EI MS: *m/z* = 406 (M+18).

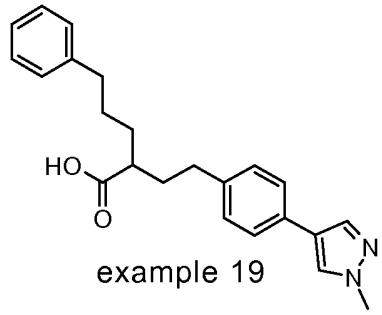
Example 16: Methyl 2-{2-[(2'-methoxypyridinyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 2-methoxypyridine-3-boronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→50% EtOAc/hexanes) to give an orange coloured oil (yield: 55%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.96 (m, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 7.09-6.93 (m, 7H), 6.76 (m, 1H), 3.76 (s, 3H), 3.49 (s, 3H), 2.49-2.34 (m, 4H), 2.27 (m, 1H), 1.78 (m, 1H), 1.46- 1.33 (m, 5H).



example 17

Example 17: 2-{2-[(2'-Methoxypyridinyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[(2'-methoxypyridinyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (30→50% EtOAc/hexanes) to give a colourless oil (yield: 51%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.15 (m, 1H), 7.60 (m, 1H), 7.47 (d, *J* = 7.9, 2H), 7.29-7.12 (m, 7H), 6.96 (m, 1H), 3.96 (s, 3H), 2.79-2.57 (m, 4H), 2.49 (m, 1H), 2.02 (m, 1H), 1.80-1.49 (m, 5H). EI MS: *m/z* = 390 (M+1).

Example 18: Methyl 2-{2-[(1-methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 1-methylpyrazole-4-boronic acid pinacol ester, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (30→50% EtOAc/hexanes) to give an orange coloured oil (yield: 48%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.72 (s, 1H), 7.37 (s, 1H), 7.37 (m, 2H), 7.24 (m, 2H), 7.14 (m, 5H), 3.93 (s, 3H), 3.67 (s, 3H), 2.55 (m, 4H), 2.40 (m, 1H), 1.95-1.48 (m, 6H).

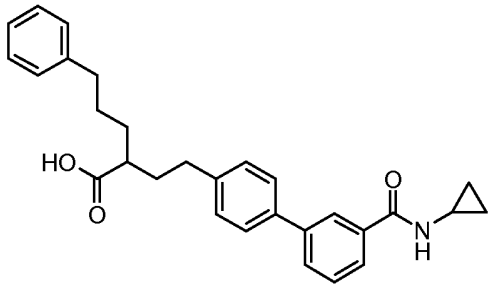


example 19

Example 19:. 2-{2-[(1-Methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenyl pentanoic acid

The compound was synthesized from methyl 2-{2-[(1-methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (0→10% MeOH/EtOAc) to furnish an off-white solid (yield: 35%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.73 (s, 1H), 7.57 (s, 1H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.31- 7.12 (m, 7H), 3.93 (s, 3H), 2.61 (m, 4H), 2.45 (m, 1H), 2.01 (m, 1H), 1.79-1.52 (m, 5H). EI MS: *m/z* = 363 (M+1).

Example 20: Methyl 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-(*N*-cyclopropylaminocarbonyl)phenylboronic acid, pinacol ester, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (20→70% EtOAc/hexanes) to afford a yellow coloured oil (yield: 19%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.77 (m, 1H), 7.50 (m, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.14-6.93 (m, 8H), 6.23 (s, 1H), 3.52 (s, 3H), 2.74 (m, 1H), 2.43 (m, 4H), 2.26 (m, 1H), 1.79 (m, 1H), 1.44 (m, 5H), 0.70 (m, 4H).

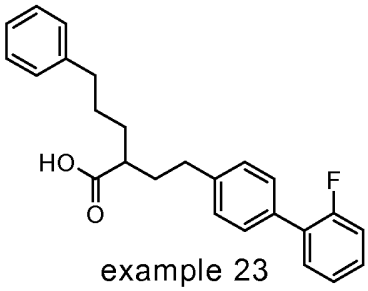


example 21

Example 21: 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→100% EtOAc/hexanes) to give a white solid (yield: 33%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.75 (s, 1H), 7.45 (bs, 2H), 7.27-6.91 (m, 10 H), 6.54 (bs, 1H), 2.77 (m, 1H), 2.40 (m,

4H), 1.80-1.29 (m, 7H), 0.73 (m, 2H), 0.51 (m, 2H). EI MS: *m/z* = 442 (M+1).

Example 22: Methyl 2-{2-[2'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 2-fluorophenylboronic acid following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→10% EtOAc/hexanes) to give a colourless oil (yield: 80%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.34 (m, 3H), 7.22-6.95 (m, 10H), 3.58 (s, 3H), 2.48 (m, 4H), 2.35 (m, 1H), 1.88 (m, 1H), 1.76-1.31 (m, 5H).

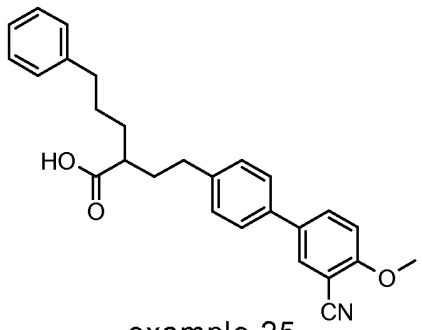


example 23

Example 23: 2-{2-[2'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[2'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→50% EtOAc/hexanes) to give a colourless oil (yield: 75%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.34-7.22 (m, 3H), 7.18-7.04 (m, 6H), 7.04-6.94 (m, 4H), 2.63-2.39 (m, 4H), 2.31 (m, 1H), 1.83 (m, 1H), 1.66 (m, 1H), 1.59-1.40 (m, 4H). EI MS: *m/z* = 394 (M+18).

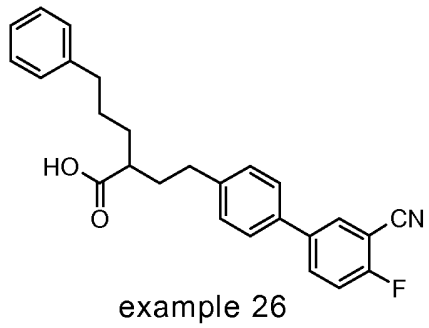
Example 24: Methyl 2-{2-[(4'-fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-cyano-4-fluorophenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a yellow-coloured oil (yield: 99%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.80 (m, 2H), 7.41 (m, 2H), 7.32-

7.11 (m, 8H), 3.69 (s, 3H), 2.60 (m, 4H), 2.44 (m, 1H), 1.96 (m, 1H), 1.85-1.45 (m, 5H).



example 25

Example 25: 2-{2-[(4'-Methoxy, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[(4'-fluoro,3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (25→30% EtOAc/hexanes) to give a white solid (yield: 39%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.75 (m, 2H), 7.42 (m, 2H), 7.33-7.12 (m, 7H), 7.03 (m, 1H), 3.96 (s, 3H), 2.63 (m, 4H), 2.45 (m, 1H), 1.99 (m, 1H), 1.90-1.51 (m, 5H). EI MS: *m/z* = 414 (M+1), 431 (M+18).

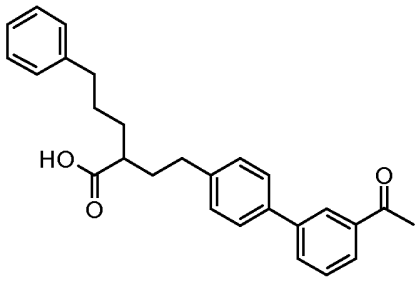


example 26

Example 26: 2-{2-[(4'-Fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[(4'-fluoro,3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B, by using a mixture of H_2O and THF as reaction solvent (MeOH was not present). It was purified by flash chromatography on SiO_2 (25→30% EtOAc/hexanes) to give a colourless oil (yield:22%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.77 (m, 2H),

7.43 (m, 2H), 7.34-7.12 (m, 8H), 2.66 (m, 4H), 2.47 (m, 1H), 2.04 (m, 1H), 1.89-1.52 (m, 5H). EI MS: *m/z* = 402 (M+1), 419 (M+18).

Example 27: Methyl 2-{2-[3'-acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-acetylphenylboronic acid following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a colourless oil (yield: 25%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.16 (bs, 1H), 7.92 (m, 1H), 7.77 (m, 1H), 7.54 (m, 3H), 7.34-7.11 (m, 7H), 3.69 (s, 3H), 2.66 (s, 3H), 2.61 (m, 4H), 2.46 (m, 1H), 1.96 (m, 1H), 1.84-1.50 (m, 5H).

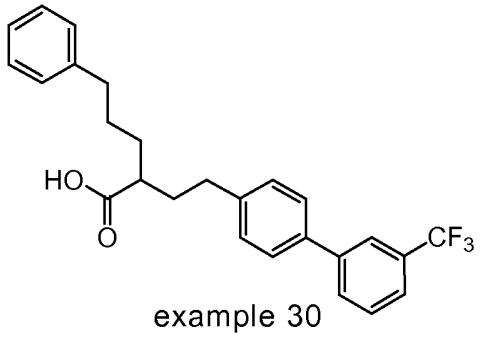


example 28

Example 28: 2-{2-[3'-Acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[3'-acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→50% EtOAc/hexanes) to give a colourless oil (yield: 86%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.17 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.54 (m, 3H), 7.34-7.25 (m, 4H), 7.17 (m, 3H), 2.75-2.49 (m, 8H), 2.01 (m, 1H), 1.84-1.55 (m, 6H). EI MS: *m/z* = 401 (M+1), 418 (M+18).

Example 29: Methyl 2-{2-[3'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-(trifluoromethyl)phenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography

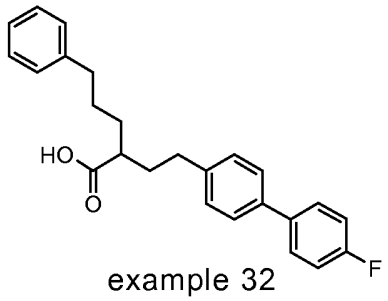
on SiO_2 (2→4% EtOAc/hexanes) to give a colourless oil (yield: 88%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.63 (bs, 1H), 7.56 (m, 1H), 7.34 (m, 4H), 7.08 (m, 4H), 6.97 (m, 3H), 3.52 (s, 3H), 2.41 (m, 4H), 2.25 (m, 1H), 1.80 (m, 1H), 1.65-1.28 (m, 5H).



example 30

Example 30: 2-{2-[3'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[3'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (5→30% EtOAc/hexanes) to give a white solid (yield: 87%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.81 (bs, 1H), 7.74 (m, 1H), 7.53 (m, 4H), 7.27 (m, 4H), 7.18 (m, 3H), 2.62 (m, 4H), 2.46 (m, 1H), 2.02 (m, 1H), 1.90-1.49 (m, 5H). EI MS: *m/z* = 425 (M-1).

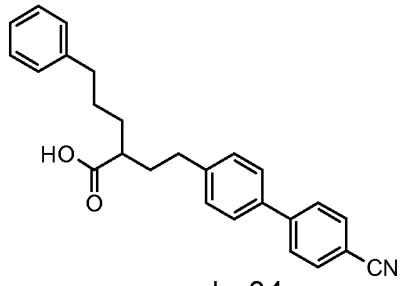
Example 31: Methyl 2-{2-[4'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 4-fluorophenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (0→5% EtOAc/hexanes) to give a white solid (yield: 91%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.5-7.4 (m, 4H), 7.3-7.05 (m, 9H), 3.67(s, 3H), 2.58 (m, 4H), 2.42 (m, 1H), 1.94 (m, 1H), 1.85-1.57 (m, 5H).



example 32

Example 32: 2-{2-[4'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[4'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (5→30% EtOAc/hexanes) to give a white solid (yield: 45%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.49 (m, 4H), 7.37-7.01 (m, 9H), 2.67-2.39 (m, 4H), 2.20 (m, 1H), 1.81 (m, 1H), 1.67-1.40 (m, 5H). EI MS: *m/z* = 375 (M-1).

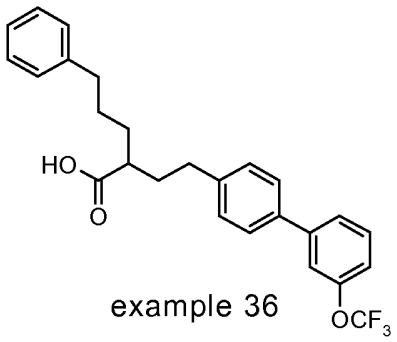
Example 33: Methyl 2-{2-[4'-cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 4-cyanophenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→7% EtOAc/hexanes) to furnish a yellow coloured oil (yield: 27%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.69 (m, 3H), 7.51 (m, 2H), 7.26 (m, 5H), 7.21-7.12 (m, 3H), 3.69 (s, 3H), 2.60 (m, 4H), 2.45 (m, 1H), 1.96 (m, 1H), 1.70-1.61 (m, 5H).



example 34

Example 34: 2-{2-[4'-Cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[4'-cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a white solid (yield: 18%). ^1H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.67 (m, 3H), 7.51 (m, 2H), 7.29 (m, 6H), 7.16 (m, 2H), 2.60 (m, 4H), 2.45 (m, 1H), 1.99 (m, 1H), 1.91-1.39 (m, 5H). EI MS: *m/z* = 382 (M-1).

Example 35: Methyl 2-{2-[3'-trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-(trifluoromethoxy)benzeneboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (0→10% EtOAc/hexanes) to give an orange coloured oil (yield: 67%). EI MS: *m/z* = 457 (M+1).

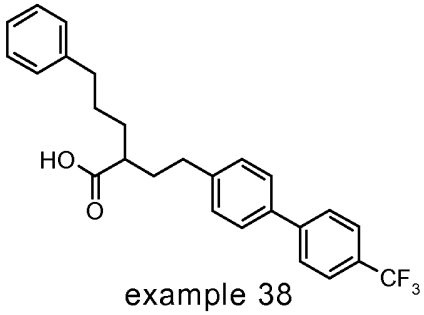


example 36

Example 36: 2-{2-[3'-Trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-

[3'-trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a waxy solid (yield: 26%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.49 (d, *J* = 8.2 Hz, 3H), 7.42 (d, *J* = 7.4Hz, 1 H), 7.26 (m, 5H), 7.17 (m, 4H), 2.60 (m, 4H), 2.45 (m, 1H), 2.01 (m, 1H), 1.65 (m, 5H).

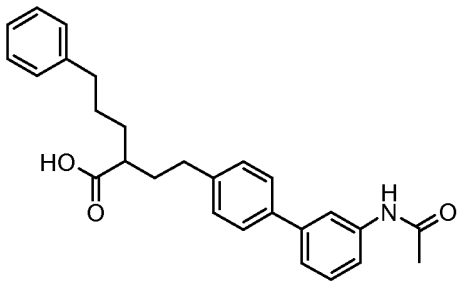
Example 37: Methyl 2-{2-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 4-(trifluoromethyl)benzeneboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (0→10% EtOAc/hexanes) to give a white solid (yield: 56%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.69 (bs, 3H), 7.53 (m, 2H), 7.31 (m, 6H), 7.18 (m, 2H), 3.71 (s, 3H), 2.64 (m, 4H), 2.47 (m, 1H), 1.98 (m, 1H), 1.87-1.50 (m, 5H).



example 38

Example 38: 2-{2-[4'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a white solid (yield: 58%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.83 (bs, 3H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.44 (m, 6H), 7.33 (m, 2H), 2.79 (m, 4H), 2.62 (m, 1H), 2.19 (m, 1H), 2.07-1.64 (m, 5H). EI MS: *m/z* = 425 (M-1).

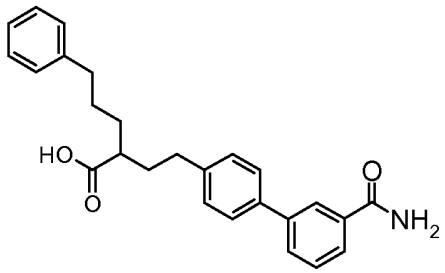
Example 39: Methyl 2-{2-[3'-(acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-acetamidophenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (20→80% EtOAc/hexanes) to give a colourless oil (yield: 98%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.51 (bs, 1H), 7.32 (m, 3H), 7.30-7.02 (m, 10H), 3.51 (s, 3H), 2.47-2.35 (m, 4H), 2.27 (m, 1H), 2.03 (s, 3H), 1.90 (m, 1H), 1.75-1.43 (m, 5H).



example 40

Example 40: 2-{2-[3'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[3'-(acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (0→20% MeOH/EtOAc) to give a brown-coloured solid (yield: 26%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.57 (s, 1H), 7.37 (m, 2H), 7.30-7.02 (m, 10H), 2.63-2.45 (m, 4H), 2.36 (m, 1H), 2.09 (s, 3H), 1.90 (m, 1H), 1.75-1.43 (m, 5H). EI MS: *m/z* = 416 (M+1).

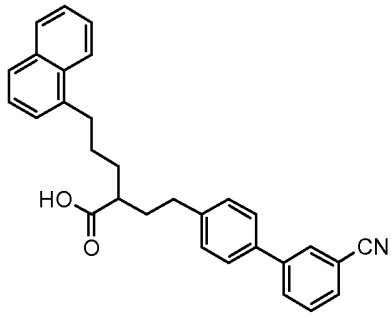
Example 41: Methyl 2-{2-[3'-(aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate. The compound was synthesized from Intermediate A and 3-carbamoylphenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (30→80% EtOAc/hexanes) to give a yellow-coloured oil (yield: 52%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.04 (bs, 1H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.53 (m, 3H), 7.31-7.11 (m, 9H), 3.69 (s, 3H), 2.59 (m, 4H), 2.43 (m, 1H), 1.99 (m, 1H), 1.80-1.47 (m, 5H).



example 42

Example 42: 2-{2-[3'-(Aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[3'-(aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (0→10% MeOH/CH_2Cl_2) to give a colourless oil (yield: 42.6%). ^{1}H NMR (MeOD, 250 MHz) δ ppm: 8.17 (bs, 1H), 7.85 (t, J = 9.6 Hz, 2H), 7.68-7.49 (m, 3H), 7.39-7.09 (m, 7H), 2.64 (m, 4H), 2.40 (m, 1H), 1.99 (m, 1H), 1.86-1.50 (m, 5H). EI MS: *m/z* = 402 (M+1).

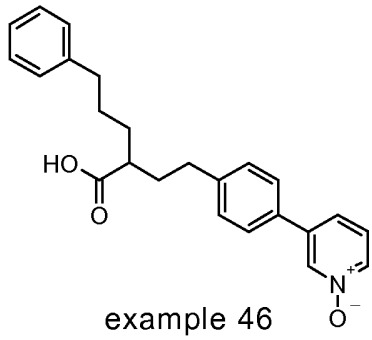
Example 43: Methyl 5-(1-naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl-4-yl)]ethyl}-pentanoate. The compound was synthesized from Intermediate B and 3-cyanophenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a yellow coloured oil (yield: 47%). EI MS: *m/z* = 448 (M+1).



example 44

Example 44: 5-(1-Naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid. The compound was synthesized from methyl 5-(1-naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl-4-yl)]ethyl}-pentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (30→70% MeOH/EtOAc) to give a colourless oil (yield: 51%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.02- 7.58 (m, 6H), 7.57-7.08 (m, 9H), 2.85 (m, 2H), 2.53-2.08 (m, 3H), 1.82 (m, 1H), 1.64-1.44 (m, 5H).

Example 45: Methyl 2-{2-[4-(1-oxidopyridin-3-yl)phenyl]ethyl}-5-phenylpentanoate. H_2O_2 (35% aqueous solution, 0.16 mL, 1.75 mmol) was added to a solution of methyl 2-[2-(4-pyridin-3'-ylphenyl)ethyl]-5-phenylpentanoate (132 mg, 0.353 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at r.t. for 32 h. It was poured into H_2O (20 mL), taken up to pH= 10 and extracted with CH_2Cl_2 (3x10 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated to give 117 mg of methyl 2-{2-[4-(1-oxidopyridin-3-yl)phenyl]ethyl}-5-phenylpentanoate (colourless oil, yield: 88%). It was submitted to next step without further purification. ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.45 (s, 1H), 8.18 (d, J = 6.3 Hz, 1H), 7.63-7.40 (m 3H), 7.39-7.07 (m, 8H), 3.68 (s, 3H), 2.59 (m, 4H), 2.42 (m, 1H), 1.99 (m, 1H), 1.84-1.41 (m, 5H).



example 46

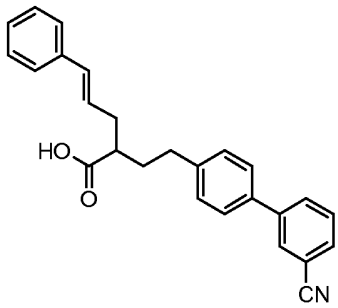
Example 46: 2-{2-[4-(1-Oxidopyridin-3-yl)phenyl]ethyl}-5-phenylpentanoic acid. The compound was synthesized from methyl 2-{2-[4-(1-oxidopyridin-3-yl)phenyl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography

on SiO_2 (0→7% MeOH/CH_2Cl_2), and slurred with hexanes to give a white solid (yield: 38%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.86 (bs, 1H), 8.58 (m, 1H), 7.89 (d, *J* = 10.1 Hz, 1H), 7.56-7.07 (m, 10H), 2.65 (m, 4H), 2.47 (m, 1H), 2.03 (m, 1H), 1.90-1.47 (m, 5H). EI MS: *m/z* = 360 (M+1).

Example 47: Methyl 4-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)butanoate. Trifluoromethanesulfonic anhydride (1.68 g, 5.94 mmol) was added to a -18 °C cooled solution of methyl 4-(4-hydroxyphenyl)butanoate (1.0 g, 5.148 mmol) and DIPEA (1.7 mL, 9.930 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was allowed to react at low temperature for 5 min, poured into H_2O (100 mL), taken up to pH= 3 with HCl and extracted with CH_2Cl_2 (120 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was purified by flash chromatography on SiO_2 (5→10% EtOAc/hexanes), to give 1.63 g of methyl 4-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)butanoate (colourless oil, yield: 97%). EI MS: *m/z* = 327 (M+1).

Example 48: Methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate. The compound was synthesized from methyl 4-(4-{[(trifluoromethyl)sulfonyl] oxy}phenyl)butanoate and 3-cyanophenylboronic acid following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a white solid (yield: 81%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.61 (m, 2H), 7.42-7.23 (m, 4H), 7.07 (m, 2H), 3.47 (s, 3H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.16 (t, *J* = 7.6 Hz, 2H), 1.79 (m, 2H).

Example 49: Methyl 2-{2-[3'-nitrile-1,1'-biphenyl-4-yl]ethyl}-5-phenylpent-4-enoate. The compound was synthesized from methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate and [(1E)-3-bromoprop-1-enyl]benzene following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a yellow-coloured oil (yield: 76%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.84-7.76 (m, 2H), 7.66-7.46 (m, 4H), 7.29-7.16 (m, 7H), 6.42 (m, 1H), 6.12 (m, 1H), 3.73 (s, 3H), 2.76-2.32 (m, 4H), 1.87 (m, 1H), 1.62 (m, 2H).



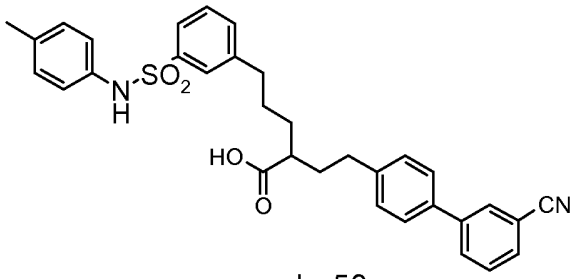
example 50

Example 50: 2-{2-[3'-nitrile-1,1'-biphenyl-4-yl]ethyl}-5-phenylpent-4-enoic acid. The compound was synthesized from methyl 2-{2-[3'-nitrile-1,1'-biphenyl-4-yl]ethyl}-5-phenylpent-4-enoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (30→70% MeOH/EtOAc) to give a white solid (yield: 22%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.83-7.73 (m, 2H), 7.61-7.42 (m, 4H), 7.35-7.15 (m, 7H), 6.44 (d, J = 15.0 Hz, 1H), 6.12 (m, 1H), 2.83-2.36 (m, 5H), 2.13-1.81 (m, 2H). EI MS: *m/z* = 382 (M+1), 399 (M+18).

Example 51: Methyl 5-[3-(tert-butoxycarbonyl-4-methylanilinosulfonyl) phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-ynoate. The compound was synthesized from methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate and tert-butyl [3-(3-bromoprop-1-ynyl)phenyl]sulfonyl(4-methylphenyl)carbamate, following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (10→40% EtOAc/hexanes) to give a white solid (yield: 95%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.00 (m, 1H), 7.83 (m, 4H), 7.60 (m, 2H), 7.49 (m, 3H), 7.34-7.20 (m, 4H), 7.14 (m, 2H), 3.76 (s, 3H), 2.72 (m, 5H), 2.37 (s, 3H), 2.14 (m, 2H), 1.33 (s, 9H).

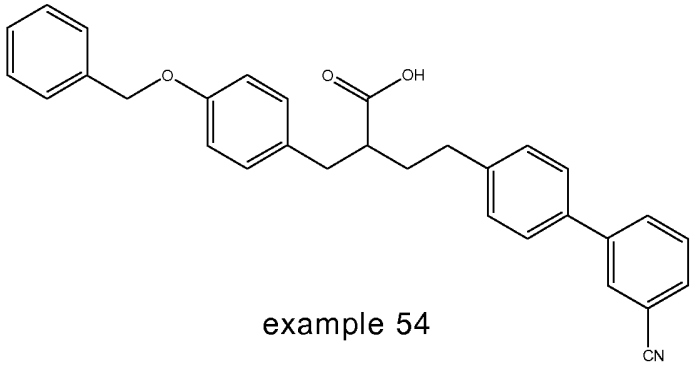
Example 52: Methyl 5-[3-(tert-butoxycarbonyl-4-methylanilinosulfonyl) phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate. The compound was synthesized from methyl 5-[3-(tert-butoxycarbonyl-4-methylanilino sulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-ynoate following the experimental procedure detailed in Method E. It was purified

by flash chromatography on SiO_2 (10→20% MeOH/EtOAc) to give a white solid (yield: 22%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.80 (m, 4H), 7.64-7.38 (m, 6H), 7.24 (m, 4H), 7.12 (m, 2H), 3.70 (s, 3H), 2.66 (m, 4H), 2.45 (m, 1H), 2.37 (m, 1H), 1.99 (m, 1H), 1.84-1.54 (m, 5H), 1.33 (s, 9H).



example 53

Example 53: 5-[3-(4-methylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid. The compound was synthesized from methyl 5-[3-(tert-butoxycarbonyl-4-methylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→40% MeOH/EtOAc) to give a white solid (yield: 56%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.76 (m, 2H), 7.60-7.39 (m, 6H), 7.24 (m, 5H), 6.94 (m, 4H), 2.61 (m, 4H), 2.41 (m, 1H), 2.20 (s, 3H), 1.97 (m, 1H), 1.83-1.43 (m, 5H). EI MS: *m/z* = 553 (M+1), 570 (M+18).



example 54

Example 54: 4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(4-benzyloxybenzyl)butanoic acid.

$NaBH_4$ (820 mg, 21.68 mmol) was added in portions to a 0 °C cooled solution of 4-(benzyloxy)benzaldehyde in MeOH (50 mL). The reaction

mixture was stirred at low temperature for 10 min and pored into H_2O (100 mL). The mixture was taken to pH= 3 and extracted with CH_2Cl_2 (2x150 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated, to give 4.50 g of [4-(benzyloxy)phenyl]methanol (white solid, yield: 97%). The crude residue was submitted to next step without purification. ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.38 (m, 7H), 7.02 (d, *J* = 8.5 Hz, 2H), 5.12 (s, 2H), 4.67 (s, 2H).

1-(Benzyloxy)-4-(bromomethyl)benzene. PBr_3 (0.66 mL, 7.00 mmol) was added to a -18 °C cooled solution of [4-(benzyloxy)phenyl]methanol (1.0 g, 4.667 mmol) in Et_2O (20 mL). The reaction was stirred at low temperature for 5 min and poured into H_2O (100 mL). It was extracted with Et_2O (100 mL), and washed with $NaHCO_3$ (200 mL, saturated aqueous solution). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was purified slurred with Et_2O (10 mL), to give 734 mg of 1-(benzyloxy)-4-(bromomethyl)benzene (white solid, yield: 57%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.37 (m, 7H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.07 (s, 2H), 4.43 (s, 2H).

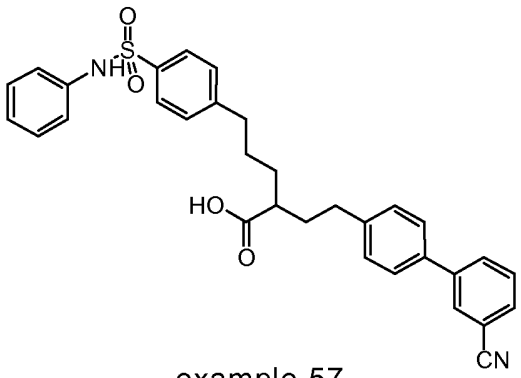
Methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(4-benzyloxybenzyl)butanoate. The compound was synthesized from methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate and 1-(benzyloxy)-4-(bromomethyl)benzene, following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a colourless oil (yield: 78%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.81 (m, 2H), 7.64-7.19 (m, 11H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 5.03 (s, 2H), 3.63 (s, 3H), 2.92 (m, 1H), 2.69 (m, 4H), 1.82 (m, 1H), 1.67 (m, 1H).

4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(4-benzyloxybenzyl)butanoic acid. The compound was synthesized from methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(4-benzyloxybenzyl)butanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (5→80% EtOAc/hexanes) to give a white solid (yield: 52%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.72 (m, 2H), 7.56-7.13 (m, 11H), 7.03 (d, *J* =

8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.93 (s, 2H), 2.90 (m, 1H), 2.64 (m, 4H), 1.94 (m, 1H), 1.79 (m, 1H).

Example 55: Methyl 5-[4-(tert-butoxycarbonylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-ynoate. The compound was synthesized from methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate and tert-butyl [4-(3-bromoprop-1-ynyl)phenyl]sulfonyl(phenyl)carbamate, following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a white solid (yield: 62%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.90-7.67 (m, 4H), 7.62-7.32 (m, 8H), 7.31-7.09 (m, 5H), 3.71 (s, 3H), 2.68 (m, 5H), 2.07 (m, 2H), 1.29 (s, 9H).

Example 56: Methyl 5-[4-(tert-butoxycarbonylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate. The compound was synthesized from methyl 5-[4-(tert-butoxycarbonylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-ynoate following the experimental procedure detailed in Method E. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a white solid (yield: 63%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.85-7.65 (m, 4H), 7.53-7.30 (m, 7H), 7.15 (m, 6H), 3.61 (s, 3H), 2.60 (m, 4H), 2.36 (m, 1H), 1.82-1.38 (m, 6H), 1.28 (s, 9H).



example 57

Example 57: 5-[4-(Anilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid. The compound was synthesized from methyl 5-[4-(tert-butoxycarbonylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (40→100% EtOAc/hexanes) to give a white solid (yield: 68%). ^{1}H NMR (DMSO-d_6, 250 MHz) δ ppm: 12.18 (bs, 1H), 10.17 (bs, 1H), 8.09 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.60 (m, 5H), 7.33-6.90 (m, 9H), 2.52 (m, 4H), 2.20 (m, 1H), 1.77-1.30 (m, 6H). EI MS: *m/z* = 539 (M+1), 556 (M+18).

Example 58: Methyl 2-{2-[3'-hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate

Synthesis of methyl 2-[2-(4-bromophenyl)ethyl]-5-phenylpentanoate.

Methyl 4-(4-bromophenyl)butanoate

H_2SO_4 (0.35 mL, 6.49 mmol) was added to a solution of 4-(4-bromophenyl)butanoic acid (5.26 g, 21.64 mmol) in MeOH (100 mL). The reaction mixture was stirred at r.t. for 16 h, and poured into H_2O (120 mL). It was extracted with CH_2Cl_2 (150 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated, to give 5.50 g of methyl 4-(4-bromophenyl)butanoate (colourless oil, yield: 98%). The compound was submitted to next step without further purification.

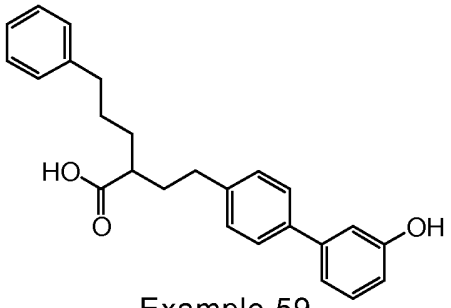
Methyl 2-[2-(4-bromophenyl)ethyl]-5-phenylpentanoate

The compound was synthesized from methyl 4-(4-bromophenyl)butanoate and (3-iodopropyl)benzene following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (0→5% EtOAc/hexanes) to give a colourless oil (yield: 76%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.40 (m, 2H), 7.28 (m, 2H), 7.16 (m, 3H), 7.05 (m, 2H), 3.68 (s, 3H), 2.71-2.48 (m, 4H), 2.39 (m, 1H), 1.94 (m, 1H), 1.76-1.50 (m, 5H).

The title compound Example 58 was synthesized from methyl 2-[2-(4-bromophenyl)ethyl]-5-phenylpentanoate and 3-hydroxyphenylboronic acid following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→30% EtOAc/hexanes) to give a yellow-coloured oil (yield: 76%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.47 (m, 2H), 7.34-7.01 (m, 10H), 6.78 (m, 1H), 5.04 (bs, 1H), 3.69 (s, 3H), 2.69-2.32 (m, 5H), 1.98 (m, 1H), 1.86-1.49 (m, 5H).



Example 59

Example 59: 2-{2-[3'-Hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid

The compound was synthesized from methyl 2-{2-[3'-hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (5→30% EtOAc/hexanes) to give a white solid (yield: 53%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.37 (d, *J* = 7.7 Hz, 2H), 7.25-6.98 (m, 10H), 6.70 (d, *J* = 8.5 Hz, 1H), 2.52 (m, 4H), 2.37 (m, 1H), 1.92 (m, 1H), 1.79-1.37 (m, 5H).

EI MS: *m/z* = 373 (M-1).

Example 60: Methyl 5-[4-(benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate

<u>Synthesis of</u> 1-(benzyloxy)-4-(3-iodopropyl)benzene

Methyl (2E)-3-[4-(benzyloxy)phenyl]acrylate

Trimethyl phosphonoacetate (6.43 g, 35.35 mmol) was dropwise added to a 0 °C cooled suspension of NaH (1.50 g, 60% suspension in mineral oil, 37.72 mmol) in THF (200 mL). The mixture was stirred for 15 min, and 4-(benzyloxy)benzaldehyde (5.0 g, 23.57 mmol) was added in portions. The reaction was allowed to reach r.t. and stirred for 2 h. It was poured into H_2O (400 mL), taken up to pH = 2 with HCl (10% aqueous solution) and extracted with EtOAc (400 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was slurred with hexanes (50 mL), to give 6.35 g of methyl (2E)-3-[4-(benzyloxy)phenyl]acrylate (white solid, yield: quantitative).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.49 (d, *J* = 15.9 Hz, 1H), 7.35-7.15 (m, 7H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.15 (d, *J* = 15.9 Hz, 1H), 4.94 (s, 2H), 3.63 (s, 3H).

Methyl 3-(4-hydroxyphenyl)propanoate

The compound was synthesized from methyl (2E)-3-[4-(benzyloxy)phenyl]acrylate following the experimental procedure detailed in Method E. It was purified by flash chromatography on SiO_2 (10→50% EtOAc/hexanes) to give a colourless oil (yield: 75%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.05 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 5.56 (bs, 1H), 3.68 (s, 3H), 2.88 (t, *J* = 7.7 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H).

Methyl 3-[4-(benzyloxy)phenyl]propanoate

BnBr (4.39 g, 25.64 mmol) was added to a suspension of K_2CO_3 (3.55 g, 25.64 mmol) and methyl 3-(4-hydroxyphenyl)propanoate (1.54 g, 8.55 mmol) in CH_3CN (40 mL). The reaction mixture was warmed up to reflux, and allowed to react for 1 h. It was poured into H_2O (120 mL), taken up to pH = 2 with HCl (10% aqueous solution) and extracted with EtOAc (2x100 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was flash chromatographed on SiO_2 (0→5% EtOAc/hexanes) to give 2.01 g of methyl 3-[4-(benzyloxy)phenyl]propanoate (white solid, yield: 88%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.51-7.29 (m, 5H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 2H), 3.69 (s, 3H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H).

3-[4-(Benzyloxy)phenyl]propan-1-ol

A solution of methyl 3-[4-(benzyloxy)phenyl]propanoate (2.01 g, 7.43 mmol) in THF (10 mL) was dropwise added to a -78 °C cooled suspension of $LiAlH_4$ (560 mg, 14.86 mmol) in THF (30 mL). The reaction mixture was allowed to reach r.t., poured into H_2O (100 mL) and taken up to pH = 2 with HCl (10% aqueous solution). It was extracted with EtOAc (100 mL) and the organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was slurred with hexanes (30 mL), to give 1.60 g of 3-[4-(benzyloxy)phenyl]propan-1-ol (white solid, yield: 89%).

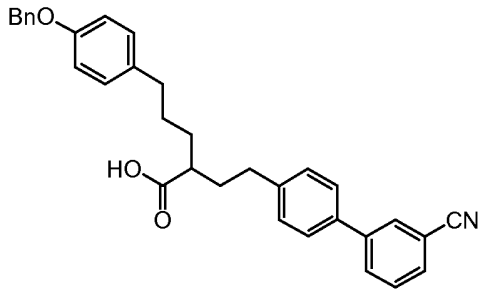
^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.41 (m, 5H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.05 (s, 2H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.66 (t, *J* = 7.4 Hz, 2H), 1.87 (m, 2H), 1.27 (bs, 1H).

1-(Benzyloxy)-4-(3-iodopropyl)benzene

I_2 (3.80 g, 14.98 mmol) was added to a solution of 3-[4-(benzyloxy)phenyl]propan-1-ol (3.30 g, 13.62 mmol), Ph_3P (3.57 g, 13.62 mmol) and imidazole (1.48 g, 21.79 mmol) in THF (60 mL). The reaction mixture was stirred at r.t. for 15 min, poured into H_2O (100 mL) and extracted with EtOAc (100 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was flash chromatographed on SiO_2 (0→20% EtOAc/hexanes) to give 3.40 g of 1-(benzyloxy)-4-(3-iodopropyl)benzene (white solid, yield: 71%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.38 (m, 5H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.05 (s, 2H), 3.16 (t, *J* = 6.8 Hz, 2H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.08 (m, 2H).

The title compound of Example 60 was synthesized from methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate and 1-(benzyloxy)-4-(3-iodopropyl)benzene following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a colourless oil (yield: 38%).
^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.92 (m, 2H), 7.56 (m, 11H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.12 (s, 2H), 3.73 (s, 3H), 2.64 (m, 5H), 2.12 (m, 1H), 1.75 (m, 5H).



Example 61

Example 61: 5-[4-(Benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid

The compound was synthesized from methyl 5-[4-(benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→40% EtOAc/hexanes) to give a white solid (yield: 35%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.64 (m, 2H), 7.53-7.14 (m, 11H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J*= 8.5 Hz, 2H), 4.90 (s, 2H), 2.63-2.23 (m, 5H), 1.89 (m, 1H), 1.74-1.37 (m, 5H).

EI MS: *m/z* = 488 (M-1).

Example 62: 1-Bromo-4-[(1E)-3-bromoprop-1-enyl]benzene

PBr_3 (0.70 mL) was added to a – 18 °C cooled solution of (2E)-3-(4-bromophenyl)prop-2-en-1-ol (1.30 g, 6.10 mmol) in Et_2O (50 mL). The reaction mixture was stirred at low temperature for 10 min, poured into H_2O (100 mL) and extracted with Et_2O (100 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated, to give 940 mg of 1-bromo-4-[(1E)-3-bromoprop-1-enyl]benzene, that was submitted to next step without purification (white solid, yield: 59%).

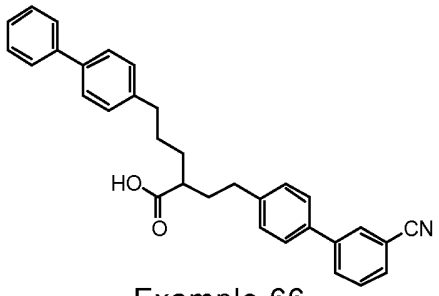
^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.61 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5, 2H), 6.80 (m, 1H), 6.50 (m, 1H), 4.50 (m, 2H).

Example 63: Methyl (4E)-5-(4-bromophenyl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-enoate

The compound was synthesized from methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate and 1-bromo-4-[(1E)-3-bromoprop-1-enyl]benzene following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a colourless oil (yield: 40%). EI MS: *m/z* = 492 (M+18).

Example 64: Methyl (4E)-5-(1,1'-biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-enoate
The compound was synthesized from methyl (4E)-5-(4-bromophenyl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-enoate and phenylboronic acid following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a white solid (yield: 71%). EI MS: *m/z* = 479 (M+18).

Example 65: Methyl 5-(1,1'-biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate
The compound was synthesized from methyl (4E)-5-(1,1'-biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-enoate following the experimental procedure detailed in Method E. The crude residue was submitted to next step without purification (white solid, yield: 56%).
EI MS: *m/z* = 491 (M+18).



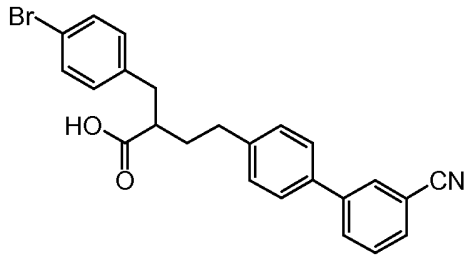
Example 66

Example 66: 5-(1,1'-Biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid
The compound was synthesized from methyl 5-(1,1'-biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (0→60% EtOAc/hexanes) to give a white solid (yield: 36%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.65-6.97 (m, 17H), 2.60-2.35 (s, 4H), 2.30 (s, 1H), 1.87 (s, 1H), 1.67-1.34 (m, 5H). EI MS: *m/z* = 477 (M+18).

Example 67: Methyl 2-(4-bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate

The title compound of Example 67 was synthesized from methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate and 1-bromo-4-(bromomethyl)benzene (commercially available from e.g., Fluka ref.: 16460)following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (5→15% EtOAc/hexanes) to give a colourless oil (yield: 56%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.80 (m, 2H), 7.64-7.35 (m, 6H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H), 3.63 (s, 3H), 2.92 (m, 1H), 2.65 (m, 4H), 1.97 (m, 1H), 1.81 (m, 1H).



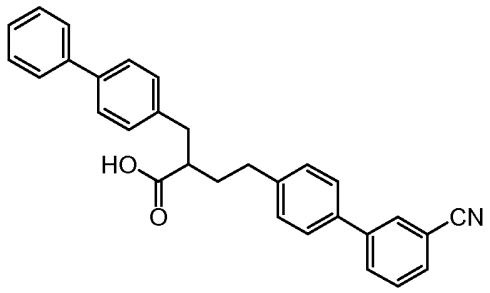
Example 68

Example 68: 2-(4-Bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoic acid

The compound was synthesized from methyl 2-(4-bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (0→60% EtOAc/hexanes) to give a white solid (yield: 51%).
^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.71 (m, 2H), 7.56-7.26 (m, 6H), 7.16 (d, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 2.87 (m, 1H), 2.75-2.48 (m, 4H), 1.94 (m, 1H), 1.75 (m, 1H). EI MS: *m/z* = 432, 434 (M-1).

Example 69: Methyl 2-(1,1'-biphenyl-4-ylmethyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate

The compound was synthesized from methyl 2-(4-bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate and phenylboronic acid following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a colourless oil (yield: 38%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.87-7.21 (m, 17H), 3.70 (s, 3H), 3.11-3.56 (m, 5H), 2.06 (m, 2H).



Example 70

Example 70: 2-(1,1'-Biphenyl-4-ylmethyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoic acid

The compound was synthesized from methyl 2-(1,1'-biphenyl-4-ylmethyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→60% EtOAc/hexanes) to give a white solid (yield: 33%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 12.18 (bs, 1H), 8.11-7.03 (m, 17H), 2.77-2.38 (m, 5H), 1.60 (m, 2H). EI MS: *m/z* = 430 (M-1).

Example 71: Methyl 2-[2-(6-benzyloxy-1,1'-biphenyl-3-yl)ethyl]-5-phenylpentanoate

Synthesis of Methyl 2-[2-(3-bromo-4-benzyloxyphenyl)ethyl]-5-phenylpentanoate

Methyl 2-[2-(4-benzyloxyphenyl)ethyl]-5-phenylpentanoate

K_2CO_3 (1.40 mmol) was added to a solution of methyl 2-[2-(4-hydroxyphenyl)ethyl]-5-phenylpentanoate (describe in the synthesis of intermediate A) (1.60 g, 5.121 mmol) and BnBr (1 mL, 8.407 mmol) in CH_3CN (30 mL). The reaction mixture was stirred at r.t. for 6 h, poured

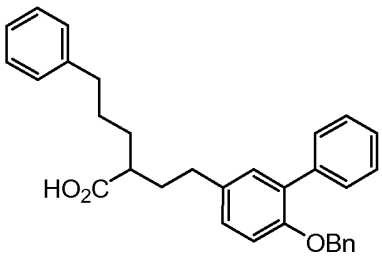
into H_2O (120 mL) and extracted with EtOAc (150 mL). The organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes), to give 1.73 g of methyl 2-[2-(4-benzyloxyphenyl)ethyl]-5-phenylpentanoate (colourless oil, yield: 84%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.44-7.19 (m, 7H), 7.18-7.08 (m, 3H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.01 (s, 2H), 3.64 (s, 3H), 2.60-2.32 (m, 5H), 1.90 (m, 1H), 1.76-1.44 (m, 5H).

Methyl 2-[2-(3-bromo-4-benzyloxyphenyl)ethyl]-5-phenylpentanoate

NBS (276 mg, 1.55 mmol) was added to a solution of methyl 2-[2-(4-benzyloxyphenyl)ethyl]-5-phenylpentanoate (567 mg, 1.408 mmol) in CH_3CN (30 mL). The reaction mixture was refluxed for 1 h, allowed to reach r.t. and poured into H_2O (100 mL). It was extracted with EtOAc (2x100 mL), and the organic layer was dried over Na_2SO_4 (anhydrous), filtered and concentrated. The crude residue was flash chromatographed on SiO_2 (10→20% EtOAc/hexanes) to give a yellow-coloured oil (yield: 69%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.57-7.16 (m, 13H), 5.13 (s, 2H), 3.66 (s, 3H), 2.59 (m, 5H), 1.89 (m, 1H), 1.61 (m, 5H).

The title compound of Example 71 was synthesized from methyl 2-[2-(3-bromo-4-benzyloxyphenyl)ethyl]-5-phenylpentanoate and phenylboronic acid following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a yellow-coloured oil (yield: 65%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.72-6.99 (m, 18 H), 5.18 (s, 2H), 3.82 (s, 3H), 2.79-2.49 (m, 5H), 2.36 (m, 1H), 1.75 (m, 5H).



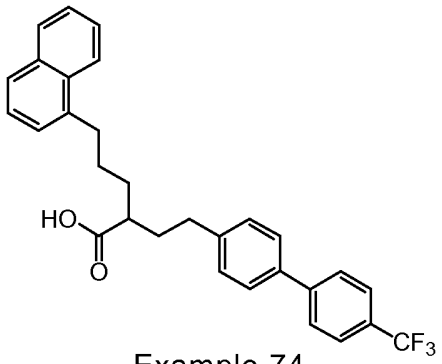
Example 72

Example 72: 2-[2-(6-Benzyloxy-1,1'-biphenyl-3-yl)ethyl]-5-phenylpentanoic acid

The compound was synthesized from methyl 2-[2-(6-benzyloxy-1,1'-biphenyl-3-yl)ethyl]-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→50% EtOAc/hexanes) to give a colourless oil (yield: 48%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.48 (m, 2H), 7.13-6.96 (m, 15H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.96 (s, 2H), 2.61-2.40 (m, 5H), 2.36 (m, 1H), 1.75 (m, 5H). EI MS: *m/z* = 463 (M-1).

Example 73: Methyl 5-(1-naphthyl)-2-[2-(4'-trifluoro-1,1'-biphenyl-4-yl)ethyl]-pentanoate

The compound was synthesized from Intermediate B and 4-(trifluoromethyl)phenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (7→10% EtOAc/hexanes) to afford a yellow-coloured oil (yield: 56%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.13 (d, *J* = 7.9 Hz, 1H), 8.00-7.25 (m, 14H), 3.81 (s, 3H), 3.18 (m, 2H), 2.82-2.59 (m, 3H), 2.15 (m, 1H), 1.88 (m, 5H).



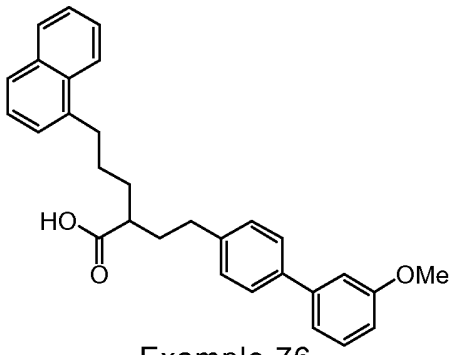
Example 74

Example 74: 5-(1-Naphthyl)-2-[2-(4'-trifluoro-1,1'-biphenyl-4-yl)ethyl]-pentanoic acid

The compound was synthesized from methyl 5-(1-naphthyl)-2-[2-(4'-trifluoro-1,1'-biphenyl-4-yl)ethyl]-pentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→40% EtOAc/hexanes) to give a white solid (yield: 66%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.96 (d, *J* = 7.9 Hz, 1H), 7.8-7.16 (m, 14H), 3.01 (m, 2H), 2.69-2.36 (m, 3H), 1.95 (m, 1H), 1.75 (m, 5H).
EI MS: *m/z* = 475 (M-1).

Example 75: Methyl 5-(1-naphthyl)-2-{2-[3'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoate
The compound was synthesized from Intermediate B and 3-methoxyphenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (4→8% EtOAc/hexanes) to afford a colourless oil (yield: 55%).
^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.29-7.93 (m, 3H), 7.78-7.32 (m, 11H), 7.12 (m, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 3.29 (m, 2H), 2.83 (m, 3H), 2.02 (m, 1H), 1.80 (m, 5H).



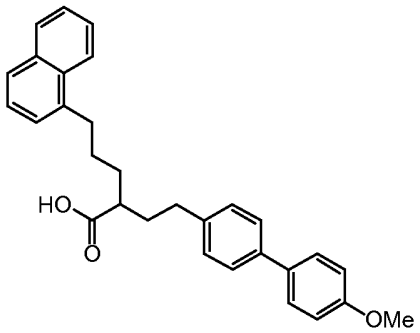
Example 76

Example 76: 5-(1-Naphthyl)-2-{2-[3'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid
The compound was synthesized from methyl 5-(1-naphthyl)-2-{2-[3'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→40% EtOAc/hexanes) to give a colourless oil (yield: 66%).
^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.84-7.48 (m, 3H), 7.34-6.85 (m, 11H), 6.68 (m, 1H), 3.68 (s, 3H), 2.85 (m, 2H), 2.48 (m, 3H), 1.84 (m, 1H), 1.58 (m, 5H). EI MS: *m/z* = 439 (M+1).

Example 77: Methyl 5-(1-naphthyl)-2-{2-[4'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoate

The compound was synthesized from Intermediate B and 4-methoxyphenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to afford a colourless oil (yield: 62%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.84 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.39-6.93 (m, 10 H), 6.80 (d, *J* = 9.0 Hz, 2H), 3.50 (s, 3H), 2.89 (m, 2H), 2.43 (m, 3H), 1.82 (m, 1H), 1.58 (m, 5H).



Example 78

Example 78: 5-(1-Naphthyl)-2-{2-[4'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid

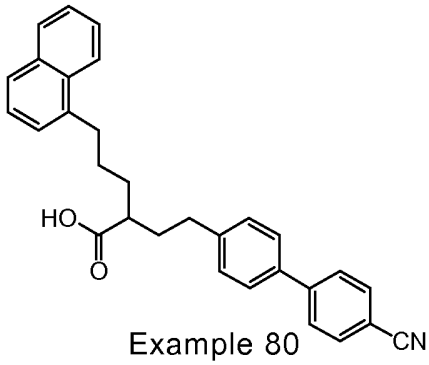
The compound was synthesized from methyl 5-(1-naphthyl)-2-{2-[4'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→50% EtOAc/hexanes) to give a colourless oil (yield: 27%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.79 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.31-6.95 (m, 10 H), 6.74 (d, *J* = 9.0 Hz, 2H), 3.62 (s, 3H), 2.85 (t, 2H), 2.34 (m, 3H), 1.80 (m, 1H), 1.62 (m, 5H). EI MS: *m/z* = 437 (M-1).

Example 79: Methyl 5-(1-naphthyl)-2-{2-[4'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoate

The compound was synthesized from Intermediate B and 4-cyanophenylboronic acid, following the experimental procedure detailed in

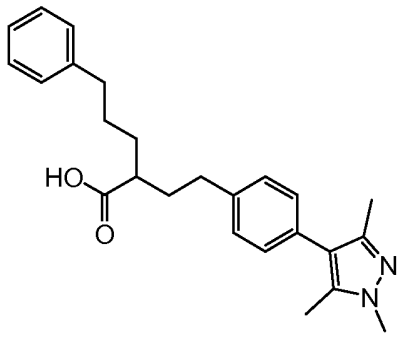
Method F. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to afford a white solid (yield: 52%).
^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.84-7.68 (m, 2H), 7.60-7.03 (m, 13H), 3.50 (s, 3H), 2.88 (m, 2H), 2.40 (m, 3H), 1.77 (m, 1H), 1.56 (m, 5H).



Example 80

Example 80: 5-(1-Naphthyl)-2-{2-[4'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid
The compound was synthesized from methyl 5-(1-naphthyl)-2-{2-[4'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoate following the experimental procedure detailed in Method B. The crude residue was slurred with hexanes, to afford a white solid (yield: 74%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.61-7.54 (m, 2H), 7.33-6.82 (m, 13H), 2.67 (m, 2H), 2.37-2.00 (m, 3H), 1.66 (m, 1H), 1.39 (m, 5H). EI MS: *m/z* = 432 (M-1).

Example 81: Methyl 2-{2-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate
The compound was synthesized from Intermediate A and 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (commercially available from e.g., Boron Molecular ref: BM359) following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (30→80% EtOAc/hexanes) to give a yellow-coloured oil (yield: 70%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 6.96 (m, 9H), 3.61 (s, 3H), 3.49 (m, 3H), 2.43-2.20 (m, 5H), 2.06 (m, 6H), 1.78-1.40 (m, 6H).



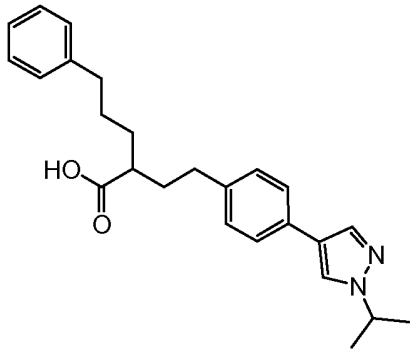
Example 82

Example 82: 2-{2-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid

The compound was synthesized from methyl 2-{2-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→100% EtOAc/hexanes) to give a yellow-coloured oil (yield: 15%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.23 (m, 9H), 3.84 (s, 3H), 2.63 (m, 4H), 2.49 (s, 1H), 2.23 (m, 6H), 2.05 (m, 1H), 1.69 (m, 5H).
EI MS: *m/z* = 391 (M+1).

Example 83: Methyl 2-(2-{[1-isobutyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate

The compound was synthesized from Intermediate A and 1-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (commercially available from e.g., Aldrich ref.: 642614-G) following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→40% EtOAc/hexanes) to give a yellow-coloured oil (yield: 67%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.86 (s, 1H), 7.67 (s,1H), 7.53-7.21 (m, 9H), 4.01 (m, 2H), 3.60 (s, 3H), 2.69 (m, 3H), 2.54 (m, 2H), 2.35 (m, 1H), 2.09 (m, 1H), 1.82 (m, 5H), 1.01 (m, 6H).



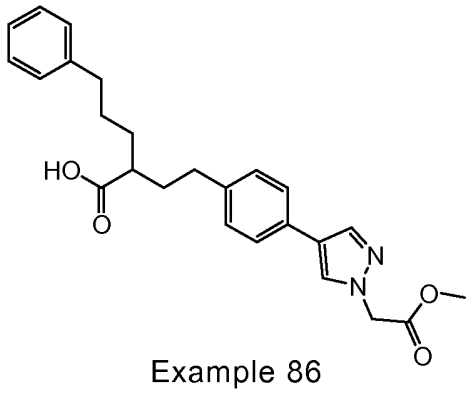
Example 84

Example 84: 2-(2-{[1-Isobutyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid

The compound was synthesized from methyl 2-(2-{[1-isobutyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→30% EtOAc/hexanes) to give a colourless oil (yield: 12%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.86 (s, 1H), 7.67 (s, 1H), 7.53-7.21 (m, 9H), 4.01 (m, 2H), 2.69 (m, 3H), 2.54 (m, 2H), 2.35 (m, 1H), 2.09 (m, 1H), 1.82 (m, 5H), 1.01 (m, 6H). EI MS: *m/z* = 405 (M+1).

Example 85: Methyl 2-(2-{[(2-ethoxy-2-oxoethyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate

The compound was synthesized from Intermediate A and 1-(ethoxycarbonylmethyl)-1H-pyrazole-4-boronic acid pinacol ester (commercial available e.g., Aldrich ref.: 683566-250MG) following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→20% EtOAc/hexanes) to give a yellow-coloured oil (yield: 28%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.35 (m, 2H), 6.81 (m, 9H), 4.49 (s, 2H), 3.83 (m, 2H), 3.26 (s, 3H), 2.14 (m, 4H), 1.34 (m, 7H), 0.89 (m, 3H).



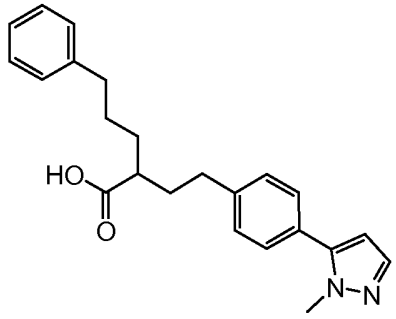
Example 86

Example 86: 2-(2-{[(2-Ethoxy-2-oxoethyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid

The compound was synthesized from methyl 2-(2-{[(2-ethoxy-2-oxoethyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→60% EtOAc/hexanes) to give a colourless oil (yield: 15%). EI MS: *m/z* = 435 (M+1).

Example 87: Methyl 2-(2-{[1-methyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate

The compound was synthesized from Intermediate A and 1-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (commercially available e.g., Aldrich ref.: 698628-5G) following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→50% EtOAc/hexanes) to give a yellow-coloured oil (yield: 43%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.43 (s, 1H), 7.17 (m, 9H), 6.20 (s, 1H), 3.81 (s, 3H), 3.60 (s, 3H), 2.55 (m, 4H), 2.42 (s, 1H), 1.97 (m, 2H), 1.63 (m, 4H).



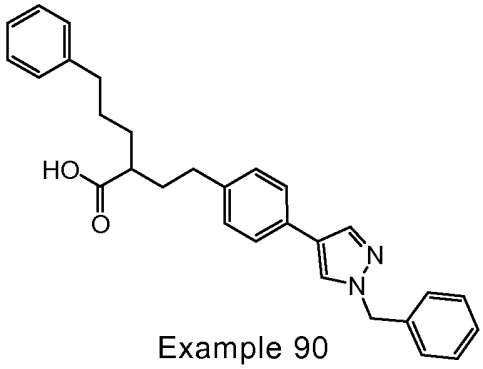
Example 88

Example 88: 2-(2-{[1-Methyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid

The compound was synthesized from methyl 2-(2-{[1-methyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (40→80% EtOAc/hexanes) to give a colourless oil (yield: 11%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.52 (d, *J* = 1.9 Hz, 1H), 1H), 7.36-7.12 (m, 9H), 6.29 (d, *J* = 1.9 Hz, 1H), 3.89 (s, 3H), 2.65 (m, 4H), 2.46 (s, 1H), 2.07-1.56 (m, 6H). EI MS: *m/z* = 363 (M+1).

Example 89: Methyl 2-(2-{[1-benzyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate

The compound was synthesized from Intermediate A and 1-(benzyl)-1H-pyrazole-4-boronic acid pinacol ester (commercially available from e.g., Acros, Apollos, Flurochem or readily prepared by the skilled artisan) following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (5→20% EtOAc/hexanes) to give a yellow-coloured oil (yield: 70%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.84 (s, 1H), 7.59 (s, 1H), 7.27 (m, 14 H), 5.35 (s, 2H), 3.49 (s, 3H), 2.51 (m, 5 H), 2.00 (m, 1H), 1.73 (m, 5H).



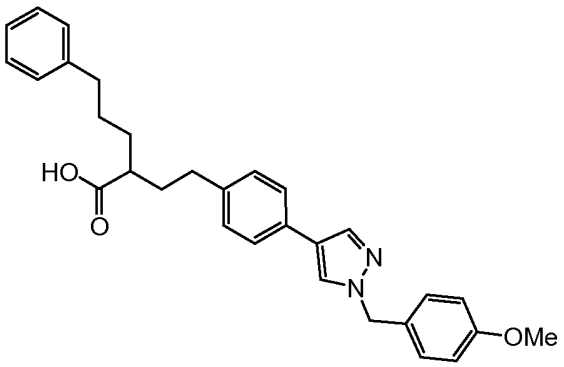
Example 90

Example 90: 2-(2-{[1-Benzyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid

The compound was synthesized from methyl 2-(2-{[1-benzyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10→80% EtOAc/hexanes) to give a yellow-coloured oil (yield: 48%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.84 (s, 1H), 7.59 (s, 1H), 7.27 (m, 14 H), 5.35 (s, 2H), 2.51 (m, 5 H), 2.00 (m, 1H), 1.73 (m, 5H).
EI MS: *m/z* = 439 (M+1).

Example 91: Methyl 2-(2-{[1-(4-methoxybenzyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate

The compound was synthesized from Intermediate A and 1-(4-methoxybenzyl)-1H-pyrazole-4-boronic acid pinacol ester (prepared using standard techniques from the corresponding commercially available boronate) (When necessary, boronates were N-protected as their N-PMB derivatives following known procedures from the literature, as described in Greene's Protective Groups in Organic Synthesis (Wiley-Interscience, John Wiley & Sons, Inc.)) following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (10→50% EtOAc/hexanes) to give a yellow-coloured oil (yield: 38%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.81 (s, 1H), 7.54 (s, 1H), 7.39-7.13 (m, 11H), 6.89 (m, 2H), 5.27 (s, 2H), 3.81 (s, 3H), 3.69 (s, 3H), 2.62-2.39 (m, 5H), 2.00 (s, 1H), 1.80-1.50 (m, 5H).



Example 92

Example 92: 2-(2-{[1-(4-Methoxybenzyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid

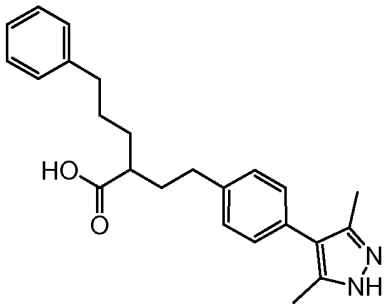
The compound was synthesized from methyl 2-(2-{[1-(4-methoxybenzyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→70% EtOAc/hexanes) to give a colourless oil (yield: 50%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.91 (s, 1H), 7.65 (s, 1H), 7.49-7.17 (m, 11H), 7.02 (m, 2H), 5.36 (s, 2H), 3.88 (s, 3H), 2.82-2.49 (m, 5H), 2.09 (s, 1H), 1.80 (m, 5H). EI MS: *m/z* = 469 (M+1).

Example 93: Methyl 2-{2-(4-[3,5-dimethyl-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)]phenyl)ethyl}-5-phenylpentanoate

The compound was synthesized from Intermediate A and [3,5-dimethyl-1-(4-methoxybenzyl)-1H-pyrazole]-4-boronic acid pinacol ester (prepared using standard procedures from the commercially available corresponding boronate) (When necessary, boronates were N-protected as their N-PMB derivatives following known procedures from the literature, as described in Greene's Protective Groups in Organic Synthesis (Wiley-Interscience, John Wiley & Sons, Inc.)) following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (25→30% EtOAc/hexanes) to give a yellow-coloured oil (yield: 23%).

Example 94: Methyl 2-(2-{[3,5-dimethyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate

The compound was synthesized from methyl 2-{2-(4-[3,5-dimethyl-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)]phenyl)ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method E. at reflux. It was purified by flash chromatography on SiO_2 (50→80% EtOAc/hexanes) to give a colourless oil (yield: 36%). EI MS: *m/z* = 391 (M+1).



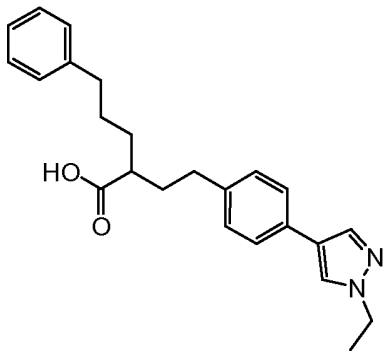
Example 95

Example 95: 2-(2-{[3,5-Dimethyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid

The compound was synthesized from methyl 2-(2-{[3,5-dimethyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10% $MeOH/CH_2Cl_2$) to give a yellow-coloured oil (yield: 54%). ^1H NMR ($CDCl_3$, 250 MHz) δ ppm: 8.88 (bs, 1H), 7.32 (m, 9H), 2.74 (m, 5H), 2.41 (m, 6H), 1.79 (s, 3H), 1.75 (s, 3H). EI MS: *m/z* = 377 (M+1).

Example 96: Ethyl 2-{2-[(1-ethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate

The compound was synthesized from 2-(2-(1H-pyrazol-4-yl)phenyl}ethyl)-5-phenylpentanoic acid and EtI following the experimental procedure detailed in Method A. It was purified by flash chromatography on SiO_2 (5→10% EtOAc/hexanes) to give a yellow-coloured oil (yield: 38%). EI MS: *m/z* = 405 (M+1).



Example 97

Example 97: 2-{2-[(1-Ethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid

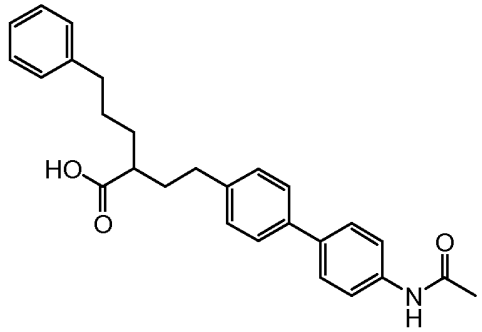
The compound was synthesized from ethyl 2-{2-[(1-ethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (10% $MeOH/CH_2Cl_2$) to give a yellow-coloured oil (yield: 28%).

EI MS: *m/z* = 377 (M+1).

Example 98: Methyl 2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate

The compound was synthesized from Intermediate A and 4-acetamidophenylboronic acid, following the experimental procedure detailed in Method F. It was purified by flash chromatography on SiO_2 (20→70% EtOAc/hexanes) to give a colourless oil (yield: 48%).

^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm: 7.63-7.38 (m, 6H), 7.31-7.09 (m, 7H), 3.71 (s, 3H), 2.60 (m, 4H), 2.44 (m, 1H), 2.21 (s, 3H), 1.99 (m, 1H), 1.86-1.45 (m, 5H).



Example 99

Example 99: 2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid

The compound was synthesized from methyl 2-{2-[4'-(acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate following the experimental procedure detailed in Method B. It was purified by flash chromatography on SiO_2 (20→70% EtOAc/hexanes) to give a white solid (yield: 10%).

^{1}H NMR (MeOD, 250 MHz) δ ppm: 7.74-7.50 (m, 6H), 7.32-7.10 (m, 7H), 2.64 (m, 4H), 2.40 (m, 1H), 2.17 (s, 3H), 1.95 (m, 1H), 1.84-1.49 (m, 5H).

EI MS: *m/z* = 416 (M+1).

Example 100: HDAC Activity Assays

HDAC inhibtion was determined indirectly by measuring the fluorescence generated by deacetylated fluorogenic substrate (KI-104 fluor de Lys™, Biomol®, used at 125 μM) product reacting with a developer solution (KI-105 Fluor de Lys ™ Biomol®). All assays were carried out in the assay buffer: 50 mM Tris/Cl, pH 8.0, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$).

Reactions were carried out in a 96-wells microplate (Corning 96 well Flat Bottom Non-binding surface (black) ref. 3651).

Potential inhibitors were added after five fold serial dilutions in DMSO. Final DMSO concentration in the assay microplate was kept at 2%.

Afterwards, human recombinant HDAC1, HDAC 2, HDAC 6 or HDAC 8 were added up to 125 nM, 33.3 nM, 25 nM and 1850 nM respectively in assay buffer. When necessary, the mixture was incubated at room temperature prior the addition of substrate.

Finally, substrate was added at 125nM. Total reaction volume of 50 µl.

Human recombinant HDACs can be acquired from commercial sources (HDAC1: ref. #50001, BPS Bioscience ™; HDAC 2: ref. # 50002, BPS Bioscience ™; HDAC 6: ref. # 50006, BPS Bioscience ™; HDAC 8: ref. # 50008, BPS Bioscience ™).

Inhibitor-protein incubation, reaction time and reaction temperature are reported in table 1.

Table.1 Main parameters of activity assay with histone deacetylase protein.

Protein	Inhibitor-protein incubation time	Reaction time	Reaction temperature
HDAC8	0 hours	3 hours	*37ºC*
HDAC2	2 hours	1h 30 min	*37ºC*
HDAC1	0 hours	3 hours	*25ºC*
HDAC6	2 hours	3 hours	37ºC

Reactions were stopped with 50 µl Developer (KI-105 Fluor de Lys ™,BIOMOL®) with 2 µmol/L trichostatin A (TSA, final concentration 1µmol/L). After 20 minutes at 37ºC, fluorescence (excitation 360 nm, emission 460 nm) was measured using an Infinite F200 fluorimeter (Tecan). Background was determined in reactions using substrate in the absence of enzyme.

IC_{50} values are defined as the compound concentration at which the deacetylase activity is 50% inhibited and are shown in Table 2 below.

Table 2

Compound Example No.	IC50 on HDAC2
36	570
23	204
9	45
32	124.3
7	104.4
3	26.5
34	40.8
13	350
30	263
38	524
15	129.3
11	111.6
5	117.4
19	55.5
17	30
26	61
42	88
21	41.3
40	37.3
28	37.9
46	172.4
44	64
53	46.3
50	52
25	42.9
54	220
57	39.5
59	35
61	53
66	94
68	48

70	28.6
72	50.5
74	85
76	65
78	60
80	46
82	47
84	42
86	29.8
88	39.6
90	35.8
92	29.8
95	64
97	19.4
99	25

The compounds of the invention also show inhibition of other human HDACs.

Example 101: Anti-proliferative activity

Cell Culture

The human colon cancer cell line HCT116 was from the American Type Culture Collection (ATCC; CCL-247).

The HCT116 cell line was maintained in DMEM GlutaMAX (Invitrogen) supplemented with 10% fetal calf serum. Cells were grown in a humidified incubator at 37ºC in 5% CO_2.

AlamarBlue Assay

Cells were plated in 96-well plates at a density of 6000 cells/well in 100 µl medium 24 h before addition of test compounds. Compounds were then added in triplicate at 8 different concentrations (three fold dilution series). To do so, a drugs-dilution plate at twice the screening concentrations was prepared. The final DMSO concentration was 0.5%. 72 hours later, alamarBlue (Biosource, Invitrogen) viability assay was performed following manufacturer's protocol. In brief, alamarBlue diluted in media was added to cells to have a 5% solution. Cells were incubated at 37ºC, 3 hours and at room temperature, 30 min. Cells without compound and, cells without compoundand lysed with triton X-100 were used as controls. Fluorescence was monitored at 530 nm excitation and 590 nm emission wavelengths. Results were quantified using Infinite F200 Microplate Reader (Tecan Group, Ltd.). EC50 were calculated as the dose of drugs required to inhibit cell growth by 50%.

The EC50 values (µM) obtained for the compounds of the present invention on HCT-116 are summarized in Table 3.

Table 3

Compound Example No.	EC50 on HCT-116
36	A
23	A
9	A
32	A
7	A
3	A
34	A
13	A
30	A
38	A
15	A

11	A
5	A
19	A
17	B
26	A
42	A
21	A
40	A
28	A
44	A
53	A
50	A
25	A
54	A
57	A
59	A
61	A
66	A
70	A
72	A
74	A
76	A
78	A
80	A
82	A
84	A
86	A
88	A
90	A
92	A
99	A

A = in the range of from 1-300 μM; B = in the range of from 300-500 μM.

The compounds of the invention show activity in various models including e.g., Compound Example 3 which had EC50 values below 100 micromolar for various cancer cell lines including colon cancer, lung cancer, and breast cancer cell lines.

Compounds such as valproate and phenylbutyrate were tested in the above-described assays for comparison purposes. Valproate was found to have an IC50 for HDAC2 of about 1300 micromolar and an EC50 in the HCT116 assay of about 2000 micromolar. Phenylbutyrate was found to have an IC50 value of about 1400 micromolar for HDAC2 and an EC50 value of about 3500 micromolar in the HCT116 assay. Thus, the compounds of the invention are surprisingly much more active (generally 1 to 2 orders of magnitude or more) than similar HDAC inhibitors having carboxylic acid zinc chelating groups both in vitro against purified HDAC enzymes and in vivo in cell-based assays.

Regarding the chemical nature of the susbtituents R_1-R_7 and L_1, it has been found that the compounds of the invention have good activity when L_1 is an unsubstituted aliphatic chain (i.e. without substitutions). This finding is surprising because in the light of the teachings of US 5886022, the skilled in the art would have concluded that the linker L_1 should bear a substituent, such as a carbonyl group, (see the activity for instance of examples 44 and 45 which do not have the carbonyl group in the linker as as compared to example 42 which does have the carbonyl group – the compounds without the carbonyl group have much less activity against the target) in order to achieve a compound with potent active against its target. Without being bound to the theory, the fact that L_1 does not need to be substituted in order to achieve an active compound of formula (IIa) or (IIb) is due to the specific nature of the substituents R_1-R_7.

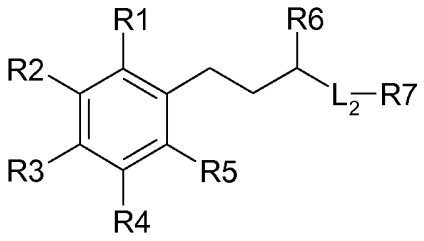
All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent

application was specifically and individually indicated to be incorporated by reference. The mere mentioning of the publications and patent applications does not necessarily constitute an admission that they are prior art to the instant application.

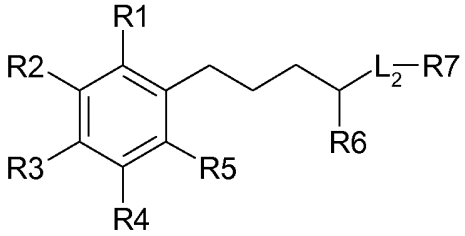
Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims.

CLAIMS

1. A compound of Formula IIa or IIb:

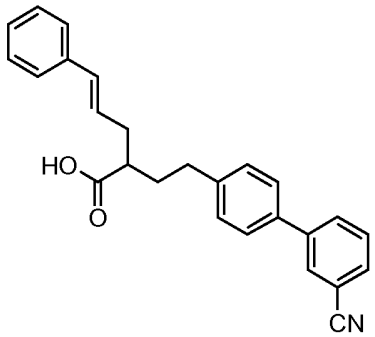


FORMULA IIa



FORMULA IIb

or a compound of formula



wherein

one of R1-R5 is a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocycle, wherein said ring one has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-

carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, N-amido, carbonyl, and C-amido; or said one R1-R5 ring is a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings;

and the others of R1-R5 are independently chosen from -H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

R6 is –C(=O)OH or –C(=O)O(C1-C6 alkyl);

R7 is optionally substituted and is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring, being the optional substituents on R7 independently chosen from halo, alkoxy, aryl, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -C(=O)O(C_{1-6}alkyl), -C(=O)NH_2, -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl; or
R7 can be optionally substituted and is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring, being the optional substituents on R7 independently chosen from -Q-R_{25}, -Q-L_4-Q-R_{25}, and -L_4-$R_{25;}$ wherein each Q is independently chosen from a bond, -CH_2-, -CH_2CH_2-, and -$CH_2CH_2CH_2$-; each L_4 is independently chosen from -N(R_{30})C(=O)-, -C(=O)N(R_{30})-, -N(R_{30})S(=O)$_2$-, -S(=O)$_2$N(R_{30})-, -C(=O)-, -NHC(=O)O-, -S(=O)$_2$-, -OC(=O)NH-, -NHC(=O)NH-, -N(R_{30})-, -O-, and -S-; R_{30} is chosen

from –H, -C1-C4 alkyl optionally substituted with –OH or phenyl, cyclohexyl, and tetrahydropyran-4-yl;

R_{25} is hydrogen; -C1-C8alkyl; or an heterocycle, heteroaryl, aryl, or carbocycle optionally substituted with one or more substituents independently chosen from -Q-heterocycle, -Q-heteroaryl, -Q-aryl, -Q-carbocycle, -C1-C8 alkyl, -OH, -Q-substituted amino, -Q-NH_2, -O-Q-substituted amino, -O-Q-NH_2, -CF_3, -OCF_3, -CN, aryloxy, alkyloxy and halo; and

L and L_2 are independently selected from the group consisting of: -$CH_2CH_2CH_2CH_2$-, –$CH_2CH_2CH_2$-, and –CH_2CH_2-;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1

wherein,
one of R1-R5 is a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocycle, wherein said ring one has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido; or said one R1-R5 ring is a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings;

and the others of R1-R5 are independently chosen from -H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio,

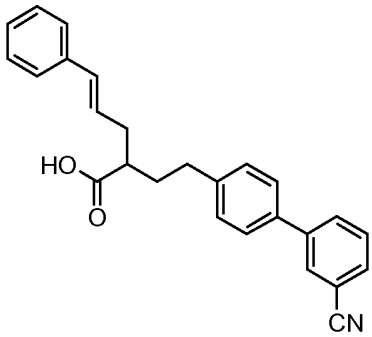
amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

R6 is –C(=O)OH or –C(=O)O(C1-C6 alkyl);

R7 is optionally substituted and is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring; being the optional substituents on R7 independently chosen from -Q-R_{25}, -Q-L_4-Q-R_{25}, and -L_4-$R_{25;}$ wherein each Q is independently chosen from a bond, -CH_2-, -CH_2CH_2-, and -$CH_2CH_2CH_2$-; each L_4 is independently chosen from -N(R_{30})C(=O)-, -C(=O)N(R_{30})-, -N(R_{30})S(=O)$_2$-, -S(=O)$_2$N(R_{30})-, -C(=O)-, -NHC(=O)O-, -S(=O)$_2$-, -OC(=O)NH-, -NHC(=O)NH-, -N(R_{30})-, -O-, and -S-; R_{30} is chosen from –H, -C1-C4 alkyl optionally substituted with –OH or phenyl, cyclohexyl, and tetrahydropyran-4-yl; R_{25} is hydrogen; -C1-C8alkyl; or an heterocycle, heteroaryl, aryl, or carbocycle optionally substituted with one or more substituents independently chosen from -Q-heterocycle, -Q-heteroaryl, -Q-aryl, -Q-carbocycle, -C1-C8 alkyl, -OH, -Q-substituted amino, -Q-NH_2, -O-Q-substituted amino, -O-Q-NH_2, -CF_3, -OCF_3, -CN, aryloxy, alkyloxy and halo; and

L and L_2 are independently selected from the group consisting of: -$CH_2CH_2CH_2CH_2$-, –$CH_2CH_2CH_2$-, and –CH_2CH_2-;

or the compound



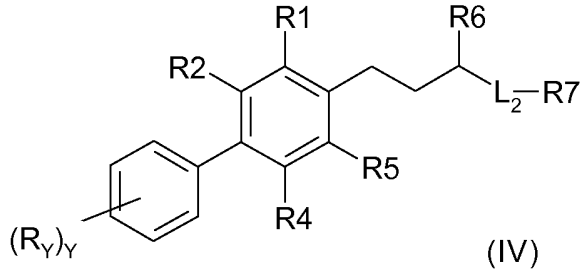
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein

R3 is chosen from a monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocycle, wherein said ring has from 1-5 substituents; or R3 is chosen from a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings;

R7 is chosen from a carbocyclic, heteroaryl, heterocyclic, and aryl ring each of which being optionally substituted with 1-5 independently chosen optional substituents selected from the group consisting of: hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, -S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl

4. The compound of any one of the claims 1-2, which has the Formula (IV):



(IV)

wherein

R1-R4 are independently chosen from –H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl,

thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

at least one R_Y is chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

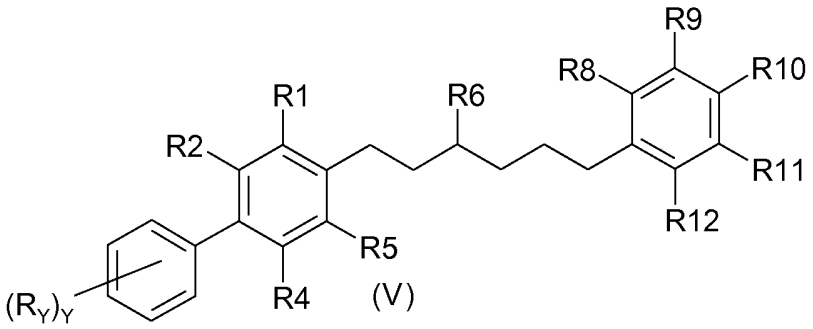
and the other R_Y are chosen from –H, -halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido; and

y is chosen from 1, 2, 3, 4, 5;

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of the preceding claims, wherein R7 is an optionally substituted phenyl or napthyl group.

6. The compound of any one of the claims 1-2, which has the Formula (V):



wherein R1, R2, R4, R5, and R8-R12 are each independently chosen from –H, halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;

each R_Y is chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido, wherein at least one R_Y is not hydro; or two R_Y can be taken together to form an optionally substituted heterocyclic, aryl, or heteroaryl ring system having two or more fused rings;

y is chosen from 1, 2, 3, 4, 5; and

each L is independently selected from the group consisting of: $-CH_2CH_2CH_2CH_2-$, $–CH_2CH_2CH_2-$, and $–CH_2CH_2-$;

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 6, wherein y is chosen from 1 or 2.

8. The compound of any one of the claims 4-7, wherein R1 and R5 are -H.

9. The compound of any one of the claims 4-8, wherein each R_Y is independently chosen from hydroxyl, halo, alkyl, alkoxy, haloalkyl, haloalkoxy, -N(C_{1-3} alkyl)$_2$, -NH(C_{1-3} alkyl), -NHC(=O)(C_{1-3} alkyl), -C(=O)OH, -C(=O)O(C_{1-6}alkyl), -C(=O)(C_{1-3} alkyl), -C(=O)NH_2, -C(=O)NH(C_{1-3} alkyl), -C(=O)NH(cycloalkyl), -C(=O)N(C_{1-3} alkyl)$_2$, -S(=O)$_2$(C_{1-3}alkyl), -S(=O)$_2NH_2$, -S(=O)$_2$N(C_{1-3} alkyl)$_2$, - S(=O)$_2$NH(C_{1-3} alkyl), -CHF_2, -OCF_3, -$OCHF_2$, -SCF_3, -CF_3, -CN, -NH_2, -NO_2, and tetrazolyl.

10. The compound of any one of the claims 1-9, wherein R1, R2, R4, R5 are each hydro.

11. The compound of any one of the preceding claims, which is selected from the group consisting of: 5-(1-Naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid; 2-{2-[3'-(Aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-Trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-Cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-Acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(4'-Fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(4'-Methoxy, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate; Methyl 2-{2-[(4'-fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate; 2-{2-[2'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; Methyl 2-{2-[2'-fluoro-1,1'-biphenyl-4-

yl]ethyl}-5-phenylpentanoate; 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; Methyl 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate; 2-{2-[(1-Methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid; 2-{2-[(2'-Methoxypyridinyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[2'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[2'-Trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-Chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-([3'-Cyano-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoic acid; 2-{2-[4-(1H-tetrazol-5-yl)phenyl]ethyl}-5-phenyl-pentanoic acid; 2-{2-[3'-hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-([2'-cyano-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoic acid; 2-{2-[3'-hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-(tert-butoxycarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-(Aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[3'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(2'-Fluoro, 5'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(2'-Fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 2-{2-[(2'-Chloro, 5'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; 5-[4-(benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid; 5-[(1,1'-biphenyl-4-yl)]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid; 4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(1,1'-biphenyl-4-yl)butanoic acid; 2-(4-Bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoic acid; 2-(1,1'-Biphenyl-4-ylmethyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoic acid; 2-[2-(6-Benzyloxy-1,1'-biphenyl-3-yl)ethyl]-5-phenylpentanoic acid; 5-(1-Naphthyl)-2-[2-(4'-trifluoro-1,1'-biphenyl-4-yl)ethyl]-pentanoic acid; 5-(1-Naphthyl)-2-{2-[3'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid; 5-(1-Naphthyl)-2-{2-[4'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid; 5-(1-Naphthyl)-2-{2-[4'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid; 2-{2-[4-(1,3,5-trimethyl-1H-pyrazol-4-

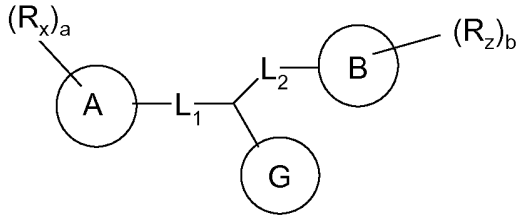
yl)phenyl]ethyl}-5-phenylpentanoic acid; 2-(2-{[1-Isobutyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid; 2-(2-{[(2-Ethoxy-2-oxoethyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid; 2-(2-{[1-Methyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid; 2-(2-{[1-Benzyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid; 2-(2-{[1-(4-Methoxybenzyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid; 95: 2-(2-{[3,5-Dimethyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid; 2-{2-[(1-Ethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid; and 2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid; or an ester thereof;

or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound of any one of claims 1-11 and a pharmaceutically acceptable carrier.

13. The compound as defined in any one of the claims 1-11 or the pharmaceutical composition of claim 12 for the treatment of a disease chosen from cancer and/or a neurodegenerative disorder or disease chosen from Alzheimer's disease, Parkinson's disease, and Huntington Disease.

14. A method for identifying an inhibitor of HDAC comprising providing a compound of Formula I



Formula I

and assaying for the ability of said compound of Formula I to inhibit one or more HDACs targets, wherein

A is an optionally substituted ring system chosen from an aryl and heteroaryl ring;
B is an optionally substituted ring system chosen from an aryl, carbocyclic, heterocyclic, and heteroaryl ring;
G is –C(=O)R_w wherein R_w is chosen from –OH, -O(C1-C6 alkyl), -OC($R_{w1}R_{w2}$)C(=O)R_{w3}, and -NHR_{w4} wherein R_{w1} and R_{w2} are independently chosen from –H, C1-C6 alkyl, C2-C6 alkenyl, and halo, and R_{w3} and R_{w4} are independently chosen –H, C1-C6 alkyl, and C2-C6 alkenyl;
each R_x is independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;
each R_z is independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-carbocycle, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, and C-amido;
wherein the A-ring is substituted with a ring chosen from monocyclic aryl, monocyclic heteroaryl, and monocyclic heterocyclic, wherein said monocyclic ring substituting the A-ring has from 1-5 substituents independently chosen from halo, alkyl, alkynyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, -L-aryl, -L-heteroaryl, -L-heterocycle, -L-carbocycle, acylamino, acyloxy, alkylthio, amino, substituted amino, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkoxy, aryloxy, arylthio, cyano, cyanato, haloaryl, hydroxyl, heteroaryloxy, heteroarylalkoxy, isocyanato, isothiocyanato, nitro, sulfinyl, sulfonyl, sulfonamide, thiocarbonyl, thiocyanato, trihalomethanesulfonamido, O-carbamyl, N-carbamyl, O-

thiocarbamyl, N-thiocarbamyl, and C-amido; or said ring substituting said A-ring is a heteroaryl, heterocyclic, or aryl ring system having two or more fused rings which may be substituted with 1-5 optional substituents;
"a" represents the number of substituents on the A-ring and is chosen from 1, 2, 3, 4, 5 or 6;
"b" represents the number of substituents on the B-ring and is chosen from 0, 1, 2, 3, 4, 5, or 6;
each L, L_1, and L_2 can be saturated, partially saturated, or unsaturated, and is independently chosen from $-(CH_2)_n-(CH_2)_n-$, $-(CH_2)_nNH(CH_2)_n-$, $-(CH_2)_nO(CH_2)_n-$, and $-(CH_2)_nS(CH_2)_n-$, and where each n is independently chosen from 0, 1 , 2, 3, and 4, and wherein each carbon and/or nitrogen can be optionally substituted with one or more substituents independently chosen from hydroxyl, halo, alkoxy, alkyl, and amino; and pharmaceutically acceptable salts thereof.

15.The method of claim 14, wherein said HDAC is one or more HDACs chosen from HDAC1, HDAC2, HDAC3, HDAC4, HDAC5, HDAC6, HDAC7, HDAC8 and HDAC9.

16. A compound identified by the method of claims 14 or 15, wherein said compound of Formula I has an HDAC IC50 value of 1000 uM or less.

17. A compound identified by the method of claims 14 or 15 wherein said compound of Formula I has an HDAC IC50 value of 750 uM or less.

18. A compound identified by the method of claims 14 or 15 wherein said compound of Formula I has an HDAC IC50 value of 500 uM or less.

19. A compound identified by the method of claims 14 or 15 wherein said compound of Formula I has an HDAC IC50 value of 250 uM or less.

20. A compound identified by the method of claims 14 or 15 wherein said compound of Formula I has an HDAC IC50 value of 100 uM or less.

21. A pharmaceutical composition comprising a compound of any one of claims 16-20.

22. The pharmaceutical composition of claim 21 for treating Huntington disease.

23. The pharmaceutical composition of claim 21 for treating cancer.

24. A compound or a pharmaceutically acceptable salt thereof chosen from 2-{2-([3'-Cyano-1,1'-biphenyl-4-yl])ethyl}-5-phenylpentanoic acid;
2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[4'-Chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[2'-Trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[2'-Methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[(2'-Methoxypyridinyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[(1-Methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenyl pentanoic acid;
2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[2'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[(4'-Methoxy, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[(4'-Fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-Acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[4'-Fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[4'-Cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-Trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[4'-(Trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-(Aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
5-(1-Naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl- 4-yl)]ethyl}pentanoic acid;

2-{2-[4-(1-Oxidopyridin-3-yl)phenyl]ethyl}-5-phenylpentanoic acid;
2-{2-[3'-nitrile-1,1'-biphenyl-4-yl]ethyl}-5-phenylpent-4-enoic acid;
5-[3-(4-methylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid;
4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(4-benzyloxybenzyl)butanoic acid.;
5-[4-(Anilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid;
2-{2-[3'-Hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid;
5-[4-(Benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid;
5-(1,1'-Biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoic acid;
2-(4-Bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoic acid;
2-(1,1'-Biphenyl-4-ylmethyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoic acid;
2-[2-(6-Benzyloxy-1,1'-biphenyl-3-yl)ethyl]-5-phenylpentanoic acid;
5-(1-Naphthyl)-2-[2-(4'-trifluoro-1,1'-biphenyl-4-yl)ethyl]-pentanoic acid;
5-(1-Naphthyl)-2-{2-[3'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid;
5-(1-Naphthyl)-2-{2-[4'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid;
5-(1-Naphthyl)-2-{2-[4'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoic acid;
2-{2-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid;
2-(2-{[1-Isobutyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[(2-Ethoxy-2-oxoethyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[1-Methyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[1-Benzyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[1-(4-Methoxybenzyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-(2-{[3,5-Dimethyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoic acid;
2-{2-[(1-Ethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoic acid;and
2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoic acid.

25. A compound or a salt thereof chosen from
Methyl 2-{2-[3'-cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;

Methyl 2-{2-[4'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-chloro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[2'-trifluoromethyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[2'-methoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[(2'-methoxypyridinyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[(1-methyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[(3'-*N*-cyclopropylamide)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[2'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[(4'-fluoro, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
2-{2-[(4'-Methoxy, 3'-cyano)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-acetyl-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-fluoro-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-cyano-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-trifluoromethoxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-(acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 2-{2-[3'-(aminocarbonyl)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 5-(1-naphthyl)-2-{2-[3'-cyano-1,1'-biphenyl-4-yl)]ethyl}-pentanoate;
Methyl 2-{2-[4-(1-oxidopyridin-3-yl)phenyl]ethyl}-5-phenylpentanoate;
Methyl 4-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)butanoate;
Methyl 2-{2-[3'-nitrile-1,1'-biphenyl-4-yl]ethyl}-5-phenylpent-4-enoate;
Methyl 5-[3-(tert-butoxycarbonyl-4-methylanilinosulfonyl) phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-ynoate;

Methyl 5-[3-(tert-butoxycarbonyl-4-methylanilinosulfonyl) phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate;
Methyl 5-[4-(tert-butoxycarbonylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-ynoate;
Methyl 4-(3'-cyano-1,1'-biphenyl-4-yl)-2-(4-benzyloxybenzyl)butanoate;
Methyl 5-[4-(tert-butoxycarbonylanilinosulfonyl)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate;
Methyl 2-{2-[3'-hydroxy-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate;
Methyl 5-[4-(benzyloxy)phenyl]-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate;
Methyl (4E)-5-(4-bromophenyl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-enoate;
Methyl (4E)-5-(1,1'-biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pent-4-enoate;
Methyl 5-(1,1'-biphenyl-4-yl)-2-[2-(3'-cyano-1,1'-biphenyl-4-yl)ethyl]pentanoate;
Methyl 2-(4-bromobenzyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate;
Methyl 2-(1,1'-biphenyl-4-ylmethyl)-4-(3'-cyano-1,1'-biphenyl-4-yl)butanoate;
Methyl 2-[2-(6-benzyloxy-1,1'-biphenyl-3-yl)ethyl]-5-phenylpentanoate;
Methyl 5-(1-naphthyl)-2-[2-(4'-trifluoro-1,1'-biphenyl-4-yl)ethyl]-pentanoate;
Methyl 5-(1-naphthyl)-2-{2-[3'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoate;
Methyl 5-(1-naphthyl)-2-{2-[4'-methoxy-1,1'-biphenyl-4-yl)]ethyl}pentanoate;
Methyl 5-(1-naphthyl)-2-{2-[4'-cyano-1,1'-biphenyl-4-yl)]ethyl}pentanoate;
Methyl 2-{2-[4-(1,3,5-trimethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate;
Methyl 2-(2-{[1-isobutyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-(2-{[(2-ethoxy-2-oxoethyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-(2-{[1-methyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-(2-{[1-benzyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;

Methyl 2-(2-{[1-(4-methoxybenzyl)-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Methyl 2-{2-(4-[3,5-dimethyl-1-(4-methoxybenzyl)-1H-pyrazol-4-yl)]phenyl)ethyl}-5-phenylpentanoate;
Methyl 2-(2-{[3,5-dimethyl-1H-pyrazol-4-yl]phenyl}ethyl)-5-phenylpentanoate;
Ethyl 2-{2-[(1-ethyl-1H-pyrazol-4-yl)phenyl]ethyl}-5-phenylpentanoate; and
Methyl 2-{2-[4'-(Acetylamino)-1,1'-biphenyl-4-yl]ethyl}-5-phenylpentanoate.

26. A pharmaceutical composition comprising a compound of claim 24 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

27. The compound of claim 24 or the pharmaceutical composition of claim 26 for the treatment of a disease chosen from cancer and/or a neurodegenerative disorder or disease chosen from Alzheimer's disease, Parkinson's disease, and Huntington Disease.

28. The compound of claims 1-10, 24 or the pharmaceutical composition of claim 11 or 26 for treating Huntington disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/067466

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C57/30 C07C57/38 C07C57/58 C07C59/64 C07C69/65
C07C69/734 C07C233/07 C07C233/65 C07C255/57 C07C311/29
C07D213/89 C07D213/64 C07D231/12 A61P35/00 A61K31/192

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)
C07C C07D A61K

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 practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FINKE ET AL: BIOORGANIC&MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 18, 2001, pages 2469-2473, XP002527778 cited in the application	14-15
A	compound 11a, scheme 2;	1-13, 24-28

A	US 5 886 022 A (KLUENDER HAROLD CLINTON EUGENE [US] ET AL) 23 March 1999 (1999-03-23) cited in the application column 5, line 49; claims 13,14; examples 44,45; compound (I)	1-13, 24-28

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[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 document 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
23 March 2010	28/04/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Breimaier, Waltraud

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/067466

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 789 434 A (KLUENDER HAROLD CLINTON EUGENE [US] ET AL) 4 August 1998 (1998-08-04) cited in the application column 6, line 15; claim 10; examples 44,45; compound (I)	1-13, 24-28
A	US 5 684 152 A (PONPIPOM MITREE M [US] ET AL) 4 November 1997 (1997-11-04) cited in the application example 19	1-13, 24-28
A	WO 2005/105764 A (MERCK PATENT GMBH [DE]; ZEILLER JEAN JACQUES [FR]; DUMAS HERVE [FR]; G) 10 November 2005 (2005-11-10) the whole document	1-13, 24-28
A	WO 2004/063148 A (MERCK PATENT GMBH [DE]; ADJE NATHALIE [FR]; BRUNET MICHEL [FR]; ROCHE) 29 July 2004 (2004-07-29) claims 1,14-16; compound 164	1-13, 24-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/067466

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