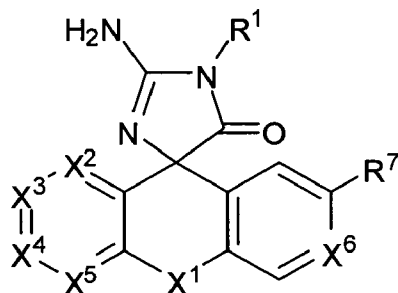




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(54) **Title:** COMPOUNDS FOR TREATING NEURODEGENERATIVE DISEASES



(I)

(57) **Abstract:** The invention provides novel tricyclic compounds of Formula (I) that inhibit B-secretase cleavage of APP and are useful as therapeutic agents for treating neurodegenerative diseases.

COMPOUNDS FOR TREATING NEURODEGENERATIVE DISEASES**[0001] PRIORITY OF INVENTION**

[0002] This application claims priority under 35 U.S.C. 119(e) from United States Provisional Patent Application Number 61/325,096, filed 16 April 2010, the content of which is incorporated herein in its entirety.

BACKGROUND OF THE INVENTION**[0003] FIELD OF THE INVENTION**

[0004] The present invention relates to organic compounds useful for inhibition of β -secretase enzymatic activity and the therapy and/or prophylaxis of neurodegenerative diseases associated therewith. More particularly, certain tricyclic compounds useful in the treatment and prevention of neurodegenerative diseases, such as Alzheimer's disease, are provided herein.

[0005] DESCRIPTION OF THE STATE OF THE ART

[0006] Alzheimer's disease (AD) is a neurological disorder thought to be primarily caused by amyloid plaques, an accumulation of abnormal protein deposits in the brain. It is believed that an increase in the production and accumulation of amyloid beta peptides (also referred to as $A\beta$ or A-beta) in plaques leads to nerve cell death, which contributes to the development and progression of AD. Loss of nerve cells due to amyloid plaques in strategic brain areas, in turn, causes reduction in the neurotransmitters and impairment of memory. The proteins principally responsible for the plaque build up include amyloid precursor protein (APP) and presenilin I and II (PSI and PSII). Mutations in each of these three proteins have been observed to enhance proteolytic processing of APP via an intracellular pathway that produces $A\beta$ peptides ranging from 39 to 43 amino acids. The $A\beta$ 1-42 fragment has a particularly high propensity of forming aggregates due to two very hydrophobic amino acid residues at its C-terminus. Thus, $A\beta$ 1-42 fragment is believed to be mainly responsible for the initiation of neuritic amyloid plaque formation in AD and is therefore actively being pursued as a therapeutic target. Anti- $A\beta$ antibodies have been shown to reverse the histologic and cognitive impairments in mice which overexpress $A\beta$ and are currently being tested in human clinical trials. Effective treatment requires anti- $A\beta$ antibodies to cross the blood-brain barrier (BBB), however, antibodies typically cross the BBB very poorly and accumulate in the brain in low concentration.

[0007] Different forms of APP range in size from 695-770 amino acids, localize to

the cell surface, and have a single C-terminal transmembrane domain. A β is derived from a region of APP adjacent to and containing a portion of the transmembrane domain. Normally, processing of APP by α -secretase cleaves the midregion of the A β sequence adjacent to the membrane and releases a soluble, extracellular domain fragment of APP from the cell surface referred to as APP- α . APP- α is not thought to contribute to AD. On the other hand, pathological processing of APP by the proteases β -secretase (also referred to as "β-site of APP cleaving enzyme" (BACE-1), memapsin-2 and Aspartyl Protease 2 (Asp2)) followed by γ -secretase cleavage, at sites which are located N-terminal and C-terminal to the α -secretase cleavage site, respectively, produces a very different result than processing at the α site, i.e. the release of amyloidogenic A β peptides, in particular, A β 1-42. Processing at the β - and γ -secretase sites can occur in both the endoplasmic reticulum and in the endosomal/lysosomal pathway after reinternalization of cell surface APP. Dysregulation of intracellular pathways for proteolytic processing may be central to the pathophysiology of AD. In the case of amyloid plaque formation, mutations in APP, PS1 or PS2 consistently alter the proteolytic processing of APP so as to enhance A β 1-42 formation.

[0008] The initial processing of APP by β -secretase results in a soluble N-APP which has recently been implicated in neuronal cell death through a pathway independent of amyloid plaque formation. N-APP is involved in normal pruning of neurons in early development in which relatively unused neurons and their nerve-fiber connections (axons) wither and degenerate. Recently, however, it has been shown that N-APP binds to and activates the apoptotic death receptor 6 (DR6) in vitro which is expressed on axons in response to trophic factor (e.g., nerve growth factor) withdrawal resulting in axonal degeneration. The aging process can lead to a reduction in the levels of growth factors in certain areas of the brain and/or the ability to sense growth factors. This in turn would lead to the release of N-APP fragment by cleavage of APP on neuronal surfaces, activating nearby DR6 receptors to initiate the axonal shrinkage and neuronal degeneration of Alzheimer's.

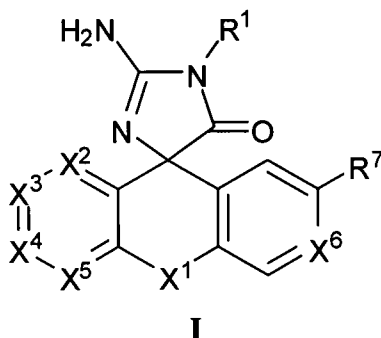
[0009] See also, Rauk, Arvi. "The chemistry of Alzheimer's disease." *Chem. Soc. Rev.* 38 (2009): p. 2698-2715; Vassar, Robert, Dora M. Kovacs, Riqiang Yan and Philip C. Wong. "The γ -Secretase Enzyme BACE in Health and Alzheimer's disease: Regulation, Cell Biology, Function, and Therapeutic Potential. *J. Neurosci.* 29(41) (2009): 12787-12794; and Silvestri, Romano. "Boom in the Development of Non-Peptidic β -Secretase (BACE1) Inhibitors for the Treatment of Alzheimer's Disease." *Medicinal Research Reviews.* Vol. 29, No. 2 (2009): p. 295-338.

[0010] Since β -secretase cleavage of APP is essential for both amyloid plaque

formation and DR6-mediated apoptosis, it is a key target in the search for therapeutic agents for treating AD.

SUMMARY OF THE INVENTION

[0011] In one aspect of the present invention there is provided novel compounds having the general Formula I:



and stereoisomers, diastereomers, enantiomers, tautomers and pharmaceutically acceptable salts thereof, wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , R^1 and R^7 are as defined herein.

[0012] In another aspect of the invention, there are provided pharmaceutical compositions comprising compounds of Formula I, I' or I'' and a carrier, diluent or excipient.

[0013] In another aspect of the invention, there is provided a method of inhibiting cleavage of APP by β -secretase in a mammal comprising administering to said mammal an effective amount of a compound of Formula I, I' or I''.

[0014] In another aspect of the invention, there is provided a method for treating a disease or condition mediated by the cleavage of APP by β -secretase in a mammal, comprising administering to said mammal an effective amount of a compound of Formula I, I' or I''.

[0015] In another aspect of the invention, there is provided a use of a compound of Formula I, I' or I'' in the manufacture of a medicament for the treatment of neurodegenerative diseases, such as Alzheimer's disease.

[0016] In another aspect of the invention, there is provided a use of a compound of Formula I, I' or I'' in the treatment of neurodegenerative diseases, such as Alzheimer's disease.

[0017] Another aspect provides intermediates for preparing compounds of Formula I, I' or I''. Certain compounds of Formula I, I' or I'' may be used as intermediates for other compounds of Formula I, I' or I''.

[0018] Another aspect includes processes for preparing, methods of separation, and methods of purification of the compounds described herein.

DETAILED DESCRIPTION OF THE INVENTION

[0019] DEFINITIONS

[0020] The term “acyl” means a carbonyl containing substituent represented by the formula $-C(O)-R$ in which R is hydrogen, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl, wherein the alkyl, alkoxy, carbocycle and heterocycle are as defined herein. Acyl groups include alkanoyl (e.g., acetyl), aroyl (e.g., benzoyl), and heteroaroyl.

[0021] The term “alkoxycarbonyl” means the group $-C(=O)OR$ in which R is alkyl. A particular alkoxycarbonyl group is C_1-C_6 alkoxycarbonyl, wherein the R group is C_1-C_6 alkyl.

[0022] The term “alkyl” means a branched or unbranched, saturated or unsaturated (i.e., alkenyl, alkynyl) aliphatic hydrocarbon group, having up to 12 carbon atoms unless otherwise specified. When used as part of another term, for example “alkylamino”, the alkyl portion may be a saturated hydrocarbon chain, however also includes unsaturated hydrocarbon carbon chains such as “alkenylamino” and “alkynylamino”. Examples of particular alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 2,2-dimethylbutyl, n-heptyl, 3-heptyl, 2-methylhexyl, and the like. The terms “lower alkyl” “ C_1-C_4 alkyl” and “alkyl of 1 to 4 carbon atoms” are synonymous and used interchangeably to mean methyl, ethyl, 1-propyl, isopropyl, cyclopropyl, 1-butyl, sec-butyl or t-butyl. In other examples, the alkyl group is C_1-C_2 , C_1-C_3 , C_1-C_4 , C_1-C_5 or C_1-C_6 . Unless specified otherwise, substituted alkyl groups contain one, two, three or four substituents which may be the same or different. Alkyl substituents are, unless otherwise specified, halogen, amino, hydroxyl, protected hydroxyl, mercapto, carboxy, alkoxy, nitro, cyano, amidino, guanidino, urea, oxo, sulfonyl, sulfinyl, aminosulfonyl, alkylsulfonylamino, arylsulfonylamino, aminocarbonyl, acylamino, alkoxy, acyl, acyloxy, an optionally substituted carbocycle and an optionally substituted heterocycle. Examples of the above substituted alkyl groups include, but are not limited to; cyanomethyl, nitromethyl, hydroxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, carboxyethyl, carboxypropyl, alkylloxycarbonylmethyl, allyloxycarbonylaminomethyl, carbamoyloxymethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-amino(iso-propyl), 2-carbamoyloxyethyl and the like. The alkyl group may also be substituted with a carbocycle group. Examples include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and

cyclohexylmethyl groups, as well as the corresponding -ethyl, -propyl, -butyl, -pentyl, -hexyl groups, etc. Substituted alkyls include substituted methyls, e.g., a methyl group substituted by the same substituents as the "substituted C_n-C_m alkyl" group. Examples of the substituted methyl group include groups such as hydroxymethyl, protected hydroxymethyl (e.g., tetrahydropyranyloxymethyl), acetoxymethyl, carbamoyloxymethyl, trifluoromethyl, chloromethyl, carboxymethyl, bromomethyl and iodomethyl.

[0023] The terms "alkenyl" and "alkynyl" also include linear or branched-chain radicals of carbon atoms.

[0024] The term "alkoxy" means the group -O(alkyl), wherein the alkyl is linear or branched-chain. The alkyl may be substituted by the same substituents as the "substituted alkyl" group. C₁-C₆ alkoxy means -O(C₁-C₆ alkyl).

[0025] The term "amidine" means the group -C(NH)-NHR in which R is hydrogen, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl wherein the alkyl, alkoxy, carbocycle and heterocycle are as defined herein. A particular amidine is the group -NH-C(NH)-NH₂.

[0026] The term "amino" means primary (i.e., -NH₂), secondary (i.e., -NRH) and tertiary (i.e., -NRR) amines in which R is hydrogen, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl wherein the alkyl, alkoxy, carbocycle and heterocycle are as defined herein. Particular secondary and tertiary amines are alkylamine, dialkylamine, arylamine, diarylamine, aralkylamine and diaralkylamine wherein the alkyl is as herein defined and optionally substituted. Particular secondary and tertiary amines are methylamine, ethylamine, propylamine, isopropylamine, phenylamine, benzylamine dimethylamine, diethylamine, dipropylamine and diisopropylamine.

[0027] The term "amino-protecting group" as used herein refers to a derivative of the groups commonly employed to block or protect an amino group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include carbamates, amides, alkyl and aryl groups, imines, as well as many N-heteroatom derivatives which can be removed to regenerate the desired amine group. Particular amino protecting groups are acetyl, trifluoroacetyl, t-butyloxycarbonyl ("Boc"), benzyloxycarbonyl ("CBz") and 9-fluorenylmethylenoxycarbonyl ("Fmoc"). Further examples of these groups, and other protecting groups, are found in T. W. Greene, et al. Greene's Protective Groups in Organic Synthesis. New York: Wiley Interscience, 2006.

[0028] The term "aryl" when used alone or as part of another term means a carbocyclic aromatic group whether or not fused having the number of carbon atoms

designated or if no number is designated, up to 14 carbon atoms. Particular aryl groups are phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like (see e.g., Dean, J. A. Lange's Handbook of Chemistry. 15th ed. New York: McGraw-Hill Professional, 1998). A particular aryl is phenyl. Substituted phenyl or substituted aryl means a phenyl group or aryl group substituted with one, two, three, four or five substituents, for example 1-2, 1-3 or 1-4 substituents chosen, unless otherwise specified, from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, alkyl (for example C₁-C₆ alkyl), alkoxy (for example C₁-C₆ alkoxy), benzyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, heterocyclysulfonylamino, heterocyclysulfonylaminoalkyl, heterocyclyl, aryl, or other groups specified. One or more methyne (CH) and/or methylene (CH₂) groups in these substituents may in turn be substituted with a similar group as those denoted above. Examples of the term "substituted phenyl" includes but is not limited to a mono- or di(halo)phenyl group such as 2-chlorophenyl, 2-bromophenyl, 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(isopropyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 3,4-dimethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy-phenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4- trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 4-carboxyphenyl; a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino))phenyl; disubstituted phenyl groups such as 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl and 2-hydroxy-4-chlorophenyl; trisubstituted phenyl groups such as 3-methoxy-4-benzyloxy-6-methylsulfonylamino and 3-methoxy-4-

benzyloxy-6-phenylsulfonylamino; tetrasubstituted phenyl groups such as 3-methoxy-4-benzyloxy-5-methyl-6-phenyl sulfonylamino. Particular substituted phenyl groups include the 2-chlorophenyl, 2-aminophenyl, 2-bromophenyl, 3-methoxyphenyl, 3-ethoxy-phenyl, 4-benzyloxyphenyl, 4-methoxyphenyl, 3-ethoxy-4-benzyloxyphenyl, 3,4-diethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy-phenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy -6- methyl sulfonyl aminophenyl groups. Fused aryl rings may also be substituted with any, for example 1, 2 or 3, of the substituents specified herein in the same manner as substituted alkyl groups.

[0029] The terms “carbocyclyl”, “carbocyclic”, “carbocycle” and “carbocyclo” alone and when used as a moiety in a complex group such as a carbocycloalkyl group, refer to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms, for example 3 to 7 carbon atoms or 3 to 6 carbon atoms, which may be saturated or unsaturated, aromatic or non-aromatic. Particular saturated carbocyclic groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. A particular saturated carbocycle is cyclopropyl. Another particular saturated carbocycle is cyclohexyl. Particular unsaturated carbocycles are aromatic, e.g., aryl groups as previously defined, for example phenyl. The terms “substituted carbocyclyl”, “carbocycle” and “carbocyclo” mean these groups substituted by the same substituents as the “substituted alkyl” group.

[0030] The term “carboxy-protecting group” as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, alkyl such as t-butyl or t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, beta-(trimethylsilyl)ethyl, beta-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonyl ethyl, 4-nitrobenzylsulfonyl ethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl, and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the condition of subsequent reaction(s) on other positions of the molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. In particular, it is important not to subject a carboxy-protected molecule to strong nucleophilic bases, such as lithium hydroxide or NaOH, or reductive conditions employing highly

activated metal hydrides such as LiAlH_4 . Such harsh removal conditions are also to be avoided when removing amino-protecting groups and hydroxy-protecting groups, discussed below. Particular carboxylic acid protecting groups are the alkyl (e.g., methyl, ethyl, t-butyl), allyl, benzyl and p-nitrobenzyl groups. The term "protected carboxy" refers to a carboxy group substituted with one of the above carboxy-protecting groups. Further examples are found in Greene's Protective Groups in Organic Synthesis, *supra*.

[0031] The terms "comprise" and "comprising" when used herein are non-limiting in scope, i.e., are intended to specify the presence of the stated features, integers, components, or steps, but do not preclude the presence or addition such features, integers, components, steps, or groups thereof.

[0032] The term "guanidine" means the group -NH-C(NH)-NHR in which R is hydrogen, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl, wherein the alkyl, alkoxy, carbocycle and heterocycle are as defined herein. A particular guanidine is the group -NH-C(NH)-NH_2 .

[0033] The term "hydroxy-protecting group" as used herein refers to a derivative of the hydroxy group commonly employed to block or protect the hydroxy group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include tetrahydropyranyloxy, benzoyl, acetoxy, carbamoyloxy, benzyl, and silylethers (e.g., tert-butyldimethylsilyl ("TBS"), tert-butyldiphenylsilyl ("TBDPS")) groups. Further examples are found in Greene's Protective Groups in Organic Synthesis, *supra*. The term "protected hydroxy" refers to a hydroxy group substituted with one of the above hydroxy-protecting groups.

[0034] The term "heterocyclic group", "heterocyclic", "heterocycle", "heterocyclyl", or "heterocyclo" alone and when used as a moiety in a complex group such as a heterocycloalkyl group, are used interchangeably and refer to any mono-, bi-, or tricyclic, saturated or unsaturated, aromatic (heteroaryl) or non-aromatic ring having the number of atoms designated, generally from 5 to about 14 ring atoms, where the ring atoms are carbon and at least one heteroatom (nitrogen, sulfur or oxygen), for example 1 to 4 heteroatoms. The sulfur heteroatoms may optionally be oxidized (e.g., SO, SO_2), and any nitrogen heteroatom may optionally be quaternized. Typically, a 5-membered ring has 0 to 2 double bonds and 6- or 7-membered ring has 0 to 3 double bonds. In a particular embodiment, heterocyclic groups are four to seven membered cyclic groups containing one, two or three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Particular non-aromatic heterocycles are morpholinyl (morpholino), pyrrolidinyl, oxiranyl, oxetanyl,

tetrahydrofuranyl, 2,3-dihydrofuranyl, 2H-pyranyl, tetrahydropyranyl, thiiranyl, thietanyl, tetrahydrothietanyl, aziridinyl, azetidiny, 1-methyl-2-pyrrolyl, piperazinyl and piperidinyl. A "heterocycloalkyl" group is a heterocycle group as defined above covalently bonded to an alkyl group as defined above. Particular 5-membered heterocycles containing a sulfur or oxygen atom and one to three nitrogen atoms are thiazolyl, in particular thiazol-2-yl and thiazol-2-yl N-oxide, thiadiazolyl, in particular 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl, oxazolyl, for example oxazol-2-yl, and oxadiazolyl, such as 1,3,4-oxadiazol-5-yl, and 1,2,4-oxadiazol-5-yl. Particular 5-membered ring heterocycles containing 2 to 4 nitrogen atoms include imidazolyl, such as imidazol-2-yl; triazolyl, such as 1,3,4-triazol-5-yl; 1,2,3-triazol-5-yl, 1,2,4-triazol-5-yl, and tetrazolyl, such as 1H-tetrazol-5-yl. Particular benzo-fused 5-membered heterocycles are benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl. Particular 6-membered heterocycles contain one to three nitrogen atoms and optionally a sulfur or oxygen atom, for example pyridyl, such as pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl; pyrimidyl, such as pyrimid-2-yl and pyrimid-4-yl; triazinyl, such as 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl; pyridazinyl, in particular pyridazin-3-yl, and pyrazinyl. The pyridine N-oxides and pyridazine N-oxides and the pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyridazinyl and the 1,3,4-triazin-2-yl groups, are a particular group. Substituents for "optionally substituted heterocycles", and further examples of the 5- and 6-membered ring systems discussed above can be found in W. Druckheimer et al., U.S. Patent No. 4,278,793. In a particular embodiment, such optionally substituted heterocycle groups are substituted with hydroxyl, alkyl, alkoxy, acyl, halogen, mercapto, oxo, carboxyl, acyl, halo-substituted alkyl, amino, cyano, nitro, amidino and guanidino.

[0035] The term "heteroaryl" alone and when used as a moiety in a complex group such as a heteroaralkyl group, refers to any mono-, bi-, or tricyclic aromatic ring system having the number of atoms designated where at least one ring is a 5-, 6- or 7-membered ring containing from one to four heteroatoms selected from the group nitrogen, oxygen, and sulfur, and in a particular embodiment at least one heteroatom is nitrogen (see Lange's Handbook of Chemistry, *supra*). In a particular embodiment, the heteroaryl is a 5-membered aromatic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulfur. Included in the definition are any bicyclic groups where any of the above heteroaryl rings are fused to a benzene ring. Particular heteroaryls incorporate a nitrogen or oxygen heteroatom. In a particular embodiment, the heteroaryl is a 5-membered aromatic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulfur. In a particular embodiment, the heteroaryl group is a 6-membered aromatic ring containing one,

two or three heteroatoms selected from nitrogen, oxygen and sulfur. The following are examples of the heteroaryl groups (substituted and unsubstituted): thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, thiazinyl, oxazinyl, triazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, tetrazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, tetrazolo[1,5-b]pyridazinyl and purinyl, as well as benzo-fused derivatives, for example benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl and indolyl. In a particular embodiment the heteroaryl group may be: 1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,2,4-thiadiazol-5-yl, 3-methyl-1,2,4-thiadiazol-5-yl, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 2-hydroxy-1,3,4-triazol-5-yl, 2-carboxy-4-methyl-1,3,4-triazol-5-yl sodium salt, 2-carboxy-4-methyl-1,3,4-triazol-5-yl, 1,3-oxazol-2-yl, 1,3,4-oxadiazol-5-yl, 2-methyl-1,3,4-oxadiazol-5-yl, 2-(hydroxymethyl)-1,3,4-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-thiol-1,3,4-thiadiazol-5-yl, 2-(methylthio)-1,3,4-thiadiazol-5-yl, 2-amino-1,3,4-thiadiazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl sodium salt, 2-methyl-1H-tetrazol-5-yl, 1,2,3-triazol-5-yl, 1-methyl-1,2,3-triazol-5-yl, 2-methyl-1,2,3-triazol-5-yl, 4-methyl-1,2,3-triazol-5-yl, pyrid-2-yl N-oxide, 6-methoxy-2-(n-oxide)-pyridaz-3-yl, 6-hydroxypyridaz-3-yl, 1-methylpyrid-2-yl, 1-methylpyrid-4-yl, 2-hydroxypyrimid-4-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(formylmethyl)-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-astriazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-astriazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-methoxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-2,6-dimethyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl and 8-aminotetrazolo[1,5-b]pyridazin-6-yl. An alternative group of "heteroaryl" includes; 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl sodium salt,

1,2,3-triazol-5-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(2-formylmethyl)-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl, or 8-aminotetrazolo[1,5-b]pyridazin-6-yl. Heteroaryl groups are optionally substituted as described for heterocycles.

[0036] The term “inhibitor” means a compound which reduces or prevents the enzymatic cleavage of APP by β -secretase. Alternatively, “inhibitor” means a compound which prevents or slows the formation of beta-amyloid plaques in mammalian brain. Alternatively, “inhibitor” means a compound that prevents or slows the progression of a disease or condition associated with β -secretase enzymatic activity, e.g., cleavage of APP. Alternatively, “inhibitor” means a compound which prevents Alzheimer’s disease. Alternatively, “inhibitor” means a compound which slows the progression of Alzheimer’s disease or its symptoms.

[0037] The term “optionally substituted” unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g. 0, 1, 2, 3 or 4) of the substituents listed for that group in which said substituents may be the same or different. In a particular embodiment, an optionally substituted group has 1 substituent. In another embodiment an optionally substituted group has 2 substituents. In another embodiment an optionally substituted group has 3 substituents.

[0038] The term “pharmaceutically acceptable” indicates that the substance or composition is compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0039] The term “pharmaceutically acceptable salts” include both acid and base addition salts.

[0040] The term “pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-

toluenesulfonic acid, salicylic acid and the like.

[0041] The term “pharmaceutically acceptable base addition salts” include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly base addition salts are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

[0042] The term “sulfanyl” means –S-R group in which R is alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl, wherein the alkyl, alkoxy, carbocycle and heterocycle are as defined herein. Particular sulfanyl groups are alkylsulfanyl (i.e., –SO₂-alkyl), for example methylsulfanyl; arylsulfanyl, for example phenylsulfanyl; aralkylsulfanyl, for example benzylsulfanyl.

[0043] The term “sulfinyl” means –SO-R group in which R is hydrogen, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl, wherein the alkyl, alkoxy, carbocycle and heterocycle are as defined herein. Particular sulfonyl groups are alkylsulfinyl (i.e., –SO-alkyl), for example methylsulfinyl; arylsulfinyl, for example phenylsulfinyl; aralkylsulfinyl, for example benzylsulfinyl.

[0044] The term “sulfonyl” means a –SO₂-R group in which R is hydrogen, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl wherein the alkyl, alkoxy, carbocycle and heterocycle are as defined herein. Particular sulfonyl groups are alkylsulfonyl (i.e., –SO₂-alkyl), for example methylsulfonyl; arylsulfonyl, for example phenylsulfonyl; aralkylsulfonyl, for example benzylsulfonyl.

[0045] The terms “treat” or “treatment” refer to therapeutic, prophylactic, palliative or preventative measures. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable.

"Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder, as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0046] The phrases "therapeutically effective amount" or "effective amount" mean an amount of a compound described herein that, when administered to a mammal in need of such treatment, sufficient to (i) treat or prevent the particular disease, condition, or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) prevent or delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a compound that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art. The "effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit cleavage of APP by β -secretase, for example by 10% or greater in situ. In a particular embodiment an "effective amount" of the compound inhibits cleavage of APP by β -secretase by 25% or greater in situ. In a particular embodiment the effective amount inhibits cleavage of APP by β -secretase by 50% or greater in situ. In a particular embodiment the effective amount inhibits cleavage of APP by β -secretase by 70% or greater in situ. In a particular embodiment the effective amount inhibits cleavage of APP by β -secretase by 80% or greater in situ. In a particular embodiment the effective amount inhibits cleavage of APP by β -secretase by 90% or greater in situ. Such amount may be below the amount that is toxic to normal cells, or the mammal as a whole. Alternatively, an "effective amount" is the amount of compound necessary to reduce A-beta levels in plasma or cerebrospinal fluid of a mammal, for example, by 10% or greater. In a particular embodiment, an "effective amount" is the amount of compound necessary to reduce A-beta levels in plasma or cerebrospinal fluid of a mammal by 25% or greater. In a particular embodiment, an "effective amount" is the amount of compound necessary to reduce A-beta levels in plasma or cerebrospinal fluid of a mammal by 50% or greater. In a particular embodiment, an "effective amount" is the amount of compound necessary to reduce A-beta levels in plasma or cerebrospinal fluid of a mammal by 75% or greater. Alternatively, an "effective amount" of the compound may be the amount of compound necessary to slow the progression of AD or symptoms thereof.

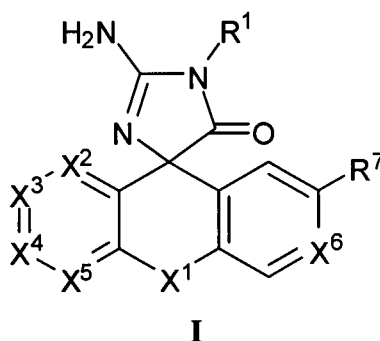
[0047] Abbreviations are sometimes used in conjunction with elemental abbreviations

and chemical structures, for example, methanol ("MeOH"), ethanol ("EtOH") or ethyl acetate ("EtOAc"). Additional abbreviations used throughout the application may include, for example, benzyl ("Bn"), phenyl ("Ph") and acetate ("Ac").

[0048] TRICYCLIC COMPOUNDS

[0049] Provided herein are compounds, and pharmaceutical formulations thereof, that are potentially useful in the treatment of diseases, conditions and/or disorders modulated by BACE-1.

[0050] One embodiment provides compounds of Formula I:



and stereoisomers, diastereomers, enantiomers, tautomers and pharmaceutically acceptable salts thereof, wherein:

X^1 is selected from O, S, S(O), SO₂, NR¹¹ or CHR¹¹;

X^2 is selected from CR² or N;

X^3 is selected from CR³ or N;

X^4 is selected from CR⁴ or N;

X^5 is selected from CR⁵ or N;

X^6 is selected from CR⁶ or N, wherein only one of X^2 , X^3 , X^4 , X^5 or X^6 may be N;

R^1 is selected from hydrogen, alkyl, aralkyl, heteroaryl or heteroaralkyl;

R^2 is selected from hydrogen, halogen and alkyl;

R^3 is selected from hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle;

R^4 is selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl,

sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or heterocycle optionally substituted with hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl and haloalkyl;

R^5 is selected from hydrogen, halogen, alkyl, alkoxy and a carbocycle;

R^6 is selected from hydrogen, halogen and alkyl;

R^7 is selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle, a heterocycle or $-O(\text{heterocycle})$ wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle; and

R^{11} is selected from hydrogen and alkyl.

[0051] In certain embodiments of Formula I:

X^1 is selected from O, S, S(O), SO_2 , NR^{11} or CHR^{11} ;

X^2 is selected from CR^2 or N;

X^3 is selected from CR^3 or N;

X^4 is selected from CR^4 or N;

X^5 is selected from CR^5 or N;

X^6 is selected from CR^6 or N, wherein only one of X^2 , X^3 , X^4 , X^5 or X^6 may be N;

R^1 is selected from hydrogen, alkyl, aralkyl, heteroaryl or heteroaralkyl;

R^2 is selected from hydrogen, halogen and alkyl;

R^3 is selected from hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle;

R^4 is selected from hydrogen, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl,

aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or heterocycle optionally substituted with hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl and haloalkyl;

R^5 is selected from hydrogen, halogen, alkyl, alkoxy and a carbocycle;

R^6 is selected from hydrogen, halogen and alkyl;

R^7 is selected from hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle; and

R^{11} is selected from hydrogen and alkyl.

[0052] In certain embodiments of Formula I:

X^1 is selected from O or S;

X^2 is selected from CR^2 or N;

X^3 is selected from CR^3 or N;

X^4 is selected from CR^4 or N;

X^5 is selected from CR^5 or N;

X^6 is selected from CR^6 or N, wherein only one of X^2 , X^3 , X^4 , X^5 or X^6 may be N;

R^1 is selected from hydrogen, alkyl, aralkyl, heteroaryl or heteroaralkyl;

R^2 is selected from hydrogen, halogen and alkyl;

R^3 is selected from hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle;

R^4 is selected from hydrogen, hydroxy, halogen, cyano, alkyl, alkoxy, a carbocycle or a heterocycle, wherein said alkyl, alkoxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, optionally substituted alkyl, or optionally substituted alkoxy, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or heterocycle optionally substituted with hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl and haloalkyl;

R^5 is selected from hydrogen, halogen, alkyl, alkoxy and a carbocycle;

R^6 is selected from hydrogen, halogen and alkyl; and

R^7 is selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle, a heterocycle or $-O(\text{heterocycle})$ wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle.

[0053] In certain embodiments of Formula I:

X^1 is selected from O or S;

X^2 is selected from CR^2 or N;

X^3 is selected from CR^3 or N;

X^4 is selected from CR^4 or N;

X^5 is selected from CR^5 or N;

X^6 is selected from CR^6 or N, wherein only one of X^2 , X^3 , X^4 , X^5 or X^6 may be N;

R^1 is selected from hydrogen, alkyl, aralkyl, heteroaryl or heteroaralkyl;

R^2 is selected from hydrogen, halogen and alkyl;

R^3 is selected from hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle;

R^4 is selected from hydrogen, halogen, alkyl, or alkoxy, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or heterocycle optionally substituted with hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl and haloalkyl;

R^5 is selected from hydrogen, halogen, alkyl, alkoxy and a carbocycle;

R^6 is selected from hydrogen, halogen and alkyl; and

R^7 is selected from hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl,

acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle.

[0054] In certain embodiments of Formula I:

X¹ is selected from O, S, S(O), SO₂, NR¹¹ or CHR¹¹;

X² is CR²;

X³ is selected from CR³ or N;

X⁴ is selected from CR⁴ or N;

X⁵ is CR⁵;

X⁶ is CR⁶;

R¹ is selected from hydrogen, benzyl or C₁-C₃ alkyl optionally substituted with R^a;

R² is hydrogen;

R³ is selected from hydrogen, halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, a 3 to 6 membered carbocycle, a 3 to 6 membered heterocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C₁-C₆ alkoxy optionally substituted with halogen;

R⁴ is selected from hydrogen, halogen, OH, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen, or

R³ and R⁴ together with the atoms to which they are attached form a 3 to 6 membered carbocycle or 3 to 6 membered heterocycle;

R⁵ is selected from hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy or a 3 to 6 membered carbocycle;

R⁶ is selected from hydrogen, halogen or C₁-C₆ alkyl;

R⁷ is selected from hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, a 3 to 6 membered saturated or partially unsaturated carbocycle, a 3 to 6 membered saturated or partially unsaturated heterocycle, phenyl, 5 to 6 membered heteroaryl, and -O(3 to 6 membered heterocycle), wherein the alkyl, alkenyl, alkynyl, carbocycle, heterocycles, phenyl and heteroaryl are optionally substituted with halogen, CN, C₁-C₆ alkyl or C₁-C₆ alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen;

R¹¹ is selected from hydrogen and C₁-C₆ alkyl; and

each R^a is independently selected from OH, OCH_3 , halogen, a 5 to 6 membered heteroaryl, and a 3-6 membered heterocyclyl optionally substituted with C_1 - C_3 alkyl optionally substituted with oxo.

[0055] In certain embodiments of Formula I:

X^1 is selected from O, S, S(O), SO_2 , NR^{11} or CHR^{11} ;

X^2 is CR^2 ;

X^3 is CR^3 ;

X^4 is selected from CR^4 or N;

X^5 is CR^5 ;

X^6 is CR^6 ;

R^1 is selected from hydrogen, benzyl or C_1 - C_3 alkyl optionally substituted with R^a ;

R^2 is hydrogen;

R^3 is selected from hydrogen, halogen, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen;

R^4 is selected from hydrogen, halogen, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, phenyl, a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or 3 to 6 membered heterocycle;

R^5 is selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or a 3 to 6 membered carbocycle;

R^6 is selected from hydrogen, halogen or C_1 - C_6 alkyl;

R^7 is selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, a 3 to 6 membered carbocycle, a 3 to 6 membered heterocycle, phenyl, 5 to 6 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen;

R^{11} is selected from hydrogen and C_1 - C_6 alkyl; and

each R^a is independently selected from OH, OCH_3 , halogen, a 5 to 6 membered heteroaryl, and a 3-6 membered heterocyclyl optionally substituted with C_1 - C_3 alkyl optionally substituted with oxo.

[0056] In certain embodiments of Formula I:

X^1 is selected from O or S;

X^2 is CR^2 ;

X^3 is selected from CR^3 or N;

X^4 is selected from CR^4 or N;

X^5 is CR^5 ;

X^6 is CR^6 ;

R^1 is selected from hydrogen, benzyl or C_1 - C_3 alkyl optionally substituted with R^a ;

R^2 is hydrogen;

R^3 is selected from hydrogen, halogen, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, a 3 to 6 membered carbocycle, a 3 to 6 membered heterocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C_1 - C_6 alkoxy optionally substituted with halogen;

R^4 is selected from hydrogen, halogen, OH, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or 3 to 6 membered heterocycle;

R^5 is selected from hydrogen, halogen or C_1 - C_6 alkyl;

R^6 is selected from hydrogen, halogen or C_1 - C_6 alkyl;

R^7 is selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, a 3 to 6 membered carbocycle, a 3 to 6 membered saturated or partially unsaturated heterocycle, phenyl, 5 to 6 membered heteroaryl, and $-O(3$ to 6 membered heterocycle), wherein the alkyl, alkenyl, alkynyl, carbocycle, heterocycles, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen;

each R^a is independently selected from OH, OCH_3 , halogen, a 5 to 6 membered heteroaryl, and a 3-6 membered heterocyclyl optionally substituted with C_1 - C_3 alkyl optionally substituted with oxo.

[0057] In certain embodiments of Formula I:

X^1 is selected from O or S;

X^2 is CR^2 ;

X^3 is CR^3 ;

X^4 is selected from CR^4 or N;

X^5 is CR^5 ;

X^6 is CR^6 ;

R^1 is selected from hydrogen, benzyl or C_1 - C_3 alkyl optionally substituted with R^a ;

R^2 is hydrogen;

R^3 is selected from hydrogen, halogen, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen;

R^4 is selected from hydrogen, halogen, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or 3 to 6 membered heterocycle;

R^5 is selected from hydrogen, halogen or C_1 - C_6 alkyl;

R^6 is selected from hydrogen, halogen or C_1 - C_6 alkyl;

R^7 is selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, a 3 to 6 membered carbocycle, a 3 to 6 membered heterocycle, phenyl, 5 to 6 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen;

each R^a is independently selected from OH, OCH_3 , halogen, a 5 to 6 membered heteroaryl, and a 3-6 membered heterocyclyl optionally substituted with C_1 - C_3 alkyl optionally substituted with oxo.

[0058] In certain embodiments of Formula I:

X^1 is selected from O or S;

X^2 is CR^2 ;

X^3 is selected from CR^3 or N;

X^4 is selected from CR^4 or N;

X^5 is CR^5 ;

X^6 is CR^6 ;

R^1 is C_1 - C_3 alkyl;

R^2 is hydrogen;

R^3 is selected from hydrogen, halogen, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, a 3 to 6 membered carbocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C_1 - C_6 alkoxy optionally substituted with halogen;

R^4 is selected from hydrogen, OH, C_1 - C_6 alkyl, C_1 - C_6 alkoxy and a 5 to 6 membered

heteroaryl, wherein the alkyl, alkoxy and heteroaryl are optionally substituted with halogen, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered heterocycle;

R^5 is selected from hydrogen or C_1 - C_6 alkyl;

R^6 is selected from hydrogen or halogen; and

R^7 is selected from halogen, C_1 - C_6 alkyl, a 3 to 6 membered carbocycle, 3 to 6 membered saturated or partially unsaturated heterocycle, phenyl, 5 to 6 membered heteroaryl, and $-O(3$ to 6 membered heterocycle), wherein the alkyl, phenyl, heteroaryl and heterocycle are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen.

[0059] In certain embodiments of Formula I:

X^1 is selected from O or S;

X^2 is CR^2 ;

X^3 is CR^3 ;

X^4 is selected from CR^4 or N;

X^5 is CR^5 ;

X^6 is CR^6 ;

R^1 is C_1 - C_3 alkyl;

R^2 is hydrogen;

R^3 is selected from hydrogen, halogen, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy and heteroaryl are optionally substituted with halogen;

R^4 is selected from hydrogen and C_1 - C_6 alkoxy, wherein the alkoxy is optionally substituted with halogen, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered heterocycle;

R^5 is selected from hydrogen or C_1 - C_6 alkyl;

R^6 is selected from hydrogen or halogen; and

R^7 is selected from halogen, C_1 - C_6 alkyl, a 3 to 6 membered carbocycle, phenyl, 5 to 6 membered heteroaryl, wherein the alkyl, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen.

[0060] In certain embodiments, X^1 is selected from O, S, S(O), SO_2 , NR^{11} or CHR^{11} .

In certain embodiments, R^{11} is selected from hydrogen and alkyl. In certain embodiments, R^{11} is selected from hydrogen and C_1 - C_6 alkyl. In certain embodiments, R^{11} is selected from hydrogen and methyl.

[0061] In certain embodiments, X^1 is selected from O or S. In certain embodiments, X^1 is O. In certain embodiments, X^1 is S.

[0062] In certain embodiments, X^2 is selected from CR^2 or N, X^3 is selected from CR^3 or N, X^4 is selected from CR^4 or N, X^5 is selected from CR^5 or N, X^6 is selected from CR^6 or N. In certain embodiments, X^2 is selected from CR^2 or N, X^3 is selected from CR^3 or N, X^4 is selected from CR^4 or N, X^5 is selected from CR^5 or N, X^6 is selected from CR^6 or N, wherein only one of X^2 , X^3 , X^4 , X^5 or X^6 may be N. In certain embodiments, X^2 is CR^2 , X^3 is CR^3 , X^4 is selected from CR^4 or N, X^5 is CR^5 , and X^6 is CR^6 . In certain embodiments, X^2 is CR^2 , X^3 is CR^3 or N, X^4 is selected from CR^4 or N, X^5 is CR^5 , and X^6 is CR^6 . In certain embodiments, X^2 is CR^2 , X^3 is CR^3 or N, X^4 is selected from CR^4 or N, X^5 is CR^5 , and X^6 is CR^6 , wherein only one of X^3 and X^4 may be N.

[0063] In certain embodiments, X^2 is selected from CR^2 or N, X^3 is selected from CR^3 or N, X^4 is selected from CR^4 or N, X^5 is selected from CR^5 or N, X^6 is selected from CR^6 or N, wherein only one of X^2 , X^3 , X^4 , X^5 or X^6 may be N. In certain embodiments, X^2 is CR^2 , X^3 is CR^3 , X^4 is selected from CR^4 or N, X^5 is CR^5 , and X^6 is CR^6 .

[0064]

[0065] In certain embodiments, R^1 is selected from hydrogen, benzyl or C_1 - C_3 alkyl optionally substituted with R^a . In certain embodiments, each R^a is independently selected from OH, OCH_3 , halogen, a 5 to 6 membered heteroaryl, and a 3-6 membered heterocyclyl optionally substituted with C_1 - C_3 alkyl optionally substituted with oxo. In certain embodiments, R^1 is selected from hydrogen, benzyl, methyl, ethyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2CF_3$, pyridin-2-ylmethyl, pyridin-4-ylmethyl and (1-acetylpiperidin-4-yl)methyl. In certain embodiments, R^1 is selected from benzyl, methyl, ethyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2CF_3$, pyridin-2-ylmethyl, pyridin-4-ylmethyl and (1-acetylpiperidin-4-yl)methyl. In certain embodiment, R^1 is methyl.

[0066] In certain embodiments, R^2 is hydrogen.

[0067] In certain embodiments, R^3 is selected from hydrogen, halogen, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, a 3 to 6 membered carbocycle, a 3 to 6 membered heterocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C_1 -

C₆ alkoxy optionally substituted with halogen. In certain embodiments, R³ is selected from hydrogen, halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, a 3 to 6 membered carbocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C₁-C₆ alkoxy optionally substituted with halogen. In certain embodiments, R³ is selected from hydrogen, halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, a 3 to 6 membered carbocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C₁-C₆ alkoxy optionally substituted with halogen. In certain embodiments, R³ is selected from halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, a 3 to 6 membered carbocycle, a 3 to 6 membered heterocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C₁-C₆ alkoxy optionally substituted with halogen. In certain embodiments, R³ is selected from halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, a 3 to 6 membered carbocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C₁-C₆ alkoxy optionally substituted with halogen. In certain embodiments, R³ is selected from halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, a 3 to 6 membered carbocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C₁-C₆ alkoxy optionally substituted with halogen. In certain embodiments, R³ is selected a 5 to 6 membered heteroaryl, wherein the heteroaryl contains one, two, three or four heteroatoms selected from N, O and S. In certain embodiments, R³ is selected a 5 to 6 membered heteroaryl, wherein the heteroaryl contains one or two nitrogen heteroatoms. In certain embodiments, R³ is selected a 5 to 6 membered heteroaryl, wherein the heteroaryl is optionally substituted with halogen, and wherein the heteroaryl contains one or two nitrogen heteroatoms. In certain embodiments, R³ is selected a 5 to 6 membered heteroaryl, wherein the heteroaryl is selected from pyridinyl and pyrimidinyl. In certain embodiments, R³ is selected a 5 to 6 membered heteroaryl, wherein the heteroaryl is optionally substituted with halogen, and wherein the heteroaryl is selected from pyridinyl and pyrimidinyl. In certain embodiments, R³ is hydrogen, Br, F, CN, propyl, isobutyl, -OCH₃, -OCF₃, cyclopropylmethoxy, -OCH₂CH₃, -OCH₂CHF₂, -OCH(CH₃)₂, -OCH₂CF₃, -OCH₂C(CH₃)₃, cyclopropyl, 3-(difluoromethoxy)phenyl, 5-chloropyridin-3-yl, pyridin-3-yl, 2-fluoropyridin-3-yl, 5-fluoropyridin-3-yl and pyrimidin-5-yl. In certain embodiments, R³ is Br, F, CN, propyl,

isobutyl, -OCH₃, -OCF₃, cyclopropylmethoxy, -OCH₂CH₃, -OCH₂CHF₂, -OCH(CH₃)₂, -OCH₂CF₃, -OCH₂C(CH₃)₃, cyclopropyl, 3-(difluoromethoxy)phenyl, 5-chloropyridin-3-yl, pyridin-3-yl, 2-fluoropyridin-3-yl, 5-fluoropyridin-3-yl and pyrimidin-5-yl.

[0068] In certain embodiments, R³ is selected from hydrogen, halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen. In certain embodiments, R³ is selected from hydrogen, halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy and heteroaryl are optionally substituted with halogen. In certain embodiments, R³ is hydrogen, Br, F, CN, propyl, -OCH₃, -OCF₃, or 5-chloropyridin-3-yl.

[0069] In certain embodiments, R⁴ is selected from hydrogen, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle. In certain embodiments, R⁴ is selected from hydrogen, halogen, alkyl, or alkoxy.

[0070] In certain embodiments, R⁴ is selected from hydrogen, halogen, OH, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen. In certain embodiments, R⁴ is selected from hydrogen, halogen, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy and heteroaryl are optionally substituted with halogen. In certain embodiments, R⁴ is selected from hydrogen, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy and a 5 to 6 membered heteroaryl, wherein the alkoxy and heteroaryl are optionally substituted with halogen. In certain embodiments, R⁴ is selected from hydrogen, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy and a 5 to 6 membered heteroaryl, wherein the alkoxy is optionally substituted with halogen. In certain embodiments, R⁴ is selected from halogen, OH, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen. In certain embodiments, R⁴ is selected from halogen, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy and heteroaryl are optionally substituted with halogen. In certain embodiments, R⁴ is selected from OH, C₁-C₆ alkyl, C₁-C₆ alkoxy and a 5 to 6 membered heteroaryl, wherein the alkoxy and heteroaryl are optionally substituted with halogen. In certain embodiments, R⁴ is selected from OH, C₁-C₆ alkyl, C₁-C₆ alkoxy and a 5 to 6 membered heteroaryl, wherein

the alkoxy is optionally substituted with halogen. In certain embodiments, R^4 is a 5 to 6 membered heteroaryl, wherein the heteroaryl contains one, two, three or four heteroatoms selected from N, O and S. In certain embodiments, R^4 is a 5 to 6 membered heteroaryl, wherein the heteroaryl contains one nitrogen heteroatom. In certain embodiments, R^4 is a 5 to 6 membered heteroaryl, wherein the heteroaryl is pyridinyl. In certain embodiments, R^4 is hydrogen, -OH, isobutyl, isopropyl, -OCH₃, -OCF₃ and pyridin-3-yl. In certain embodiments, R^4 is -OH, isobutyl, isopropyl, -OCH₃, -OCF₃ and pyridin-3-yl.

[0071] In certain embodiments, R^4 is selected from hydrogen, halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen. In certain embodiments, R^4 is selected from hydrogen, halogen, C₁-C₆ alkyl, and C₁-C₆ alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen. In certain embodiments, R^4 is selected from hydrogen and C₁-C₆ alkoxy, wherein the alkoxy is optionally substituted with halogen. In certain embodiments, R^4 is hydrogen, -OCH₃, or -OCF₃.

[0072] In certain embodiments, R^4 is selected from hydrogen, hydroxy, halogen, alkyl or alkoxy wherein said alkyl and alkoxy are optionally substituted with halogen. In certain embodiments, R^4 is selected from hydrogen, hydroxy, halogen, alkyl or alkoxy.

[0073] In certain embodiments, R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or 3 to 6 membered heterocycle. In certain embodiments, R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered heterocycle. In certain embodiments, R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered heterocycle, wherein the heterocycle contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur. In certain embodiments, R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered heterocycle, wherein the heterocycle contains one oxygen heteroatom. In certain embodiments, R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered heterocycle, wherein the heterocycle formed is a tetrahydrofuran.

[0074] In certain embodiments, R^5 is selected from hydrogen, halogen, alkyl, alkoxy and a carbocycle. In certain embodiments, R^5 is selected from hydrogen, halogen and alkyl.

[0075] In certain embodiments, R^5 is selected from hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy or a 3 to 6 membered carbocycle. In certain embodiments, R^5 is selected from hydrogen, halogen or C₁-C₆ alkyl. In certain embodiments, R^5 is selected from hydrogen or C₁-C₆ alkyl. In certain embodiments, R^5 is hydrogen or methyl.

[0076] In certain embodiments, R^6 is selected from hydrogen, halogen or C₁-C₆ alkyl.

In certain embodiments, R^6 is selected from hydrogen or halogen. In certain embodiments, R^6 is hydrogen or F.

[0077] In certain embodiments, R^7 is selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, a 3 to 6 membered saturated or partially unsaturated carbocycle, a 3 to 6 membered saturated or partially unsaturated heterocycle, phenyl, 5 to 6 membered heteroaryl, and $-O(3$ to 6 membered heterocycle), wherein the alkyl, alkenyl, alkynyl, carbocycle, heterocycles, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen. In certain embodiments, R^7 is selected from hydrogen, halogen, C_1 - C_6 alkyl, a 3 to 6 membered carbocycle, a 3 to 6 membered partially unsaturated heterocycle, phenyl, 5 to 6 membered heteroaryl, and $-O(3$ to 6 membered heterocycle), wherein the alkyl, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen. In certain embodiments, R^7 is selected from halogen, C_1 - C_6 alkyl, a 3 to 6 membered carbocycle, a 3 to 6 membered partially unsaturated heterocycle, phenyl, 5 to 6 membered heteroaryl, and $-O(3$ to 6 membered heterocycle), wherein the alkyl, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen. In certain embodiments, R^7 is a 5 to 6 membered heteroaryl, wherein the heteroaryl contains one, two, three or four heteroatoms selected from the N, O and S. In certain embodiments, R^7 is a 5 to 6 membered heteroaryl, wherein the heteroaryl contains one or two nitrogen heteroatoms. In certain embodiments, R^7 is a 5 to 6 membered heteroaryl, wherein the heteroaryl is selected from pyridinyl and pyrimidinyl. In certain embodiments, R^7 is a 3 to 6 membered partially unsaturated heterocycle, wherein the heterocycle contains one, two or three heteroatoms selected from N, O and S. In certain embodiments, R^7 is a 3 to 6 membered partially unsaturated heterocycle, wherein the heterocycle contains one oxygen heteroatom. In certain embodiments, R^7 is a 3 to 6 membered partially unsaturated heterocycle, wherein the heterocycle is 3,6-dihydro-2H-pyran. In certain embodiments, R^7 is $-O(3$ to 6 membered heterocycle), wherein the heterocycle contains one, two or three heteroatoms selected from N, O and S. In certain embodiments, R^7 is $-O(3$ to 6 membered heterocycle), wherein the heterocycle contains one oxygen heteroatom. In certain embodiments, R^7 is $-O(3$ to 6 membered heterocycle), wherein the heterocycle is oxetanyl. In certain embodiments, R^7 is Br, isopentyl, propyl, isobutyl, isopropyl, 4-butanenitrile, cyclopropyl, cyclohexyl, 3,6-dihydro-2H-pyran-4-yl, phenyl, 3-(difluoromethoxy)phenyl, 3-methoxyphenyl, 3-chloro-5-methoxyphenyl, 3-

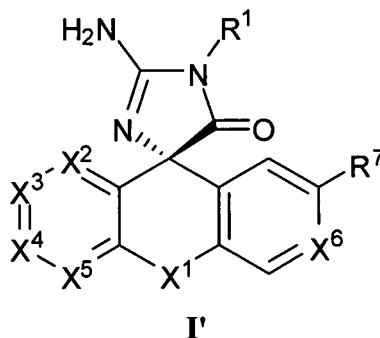
ethoxyphenyl, 3-cyanophenyl (3-benzonitrile), 5-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-chloro-5-fluorophenyl, 3-chlorophenyl, 3-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-2-fluorophenyl, 5-chloro-2-fluorophenyl, pyridin-3-yl, 5-methoxypyridin-3-yl, 2-fluoropyridin-3-yl, 5-cyanopyridin-3-yl (5-nicotinonitrile), 5-chloropyridin-3-yl, 5-fluoropyridin-3-yl, 5-(trifluoromethyl)pyridin-3-yl, 5-chloro-2-fluoropyridin-3-yl, 5-isobutylpyridin-3-yl, pyrimidin-5-yl or oxetan-3-yloxy.

[0078] In certain embodiments, R^7 is selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, a 3 to 6 membered carbocycle, a 3 to 6 membered heterocycle, phenyl, 5 to 6 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen. In certain embodiments, R^7 is selected from hydrogen, halogen, C_1 - C_6 alkyl, a 3 to 6 membered carbocycle, phenyl, 5 to 6 membered heteroaryl, wherein the alkyl, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen. In certain embodiments, R^7 is selected from halogen, C_1 - C_6 alkyl, a 3 to 6 membered carbocycle, phenyl, 5 to 6 membered heteroaryl, wherein the alkyl, phenyl and heteroaryl are optionally substituted with halogen, CN, C_1 - C_6 alkyl or C_1 - C_6 alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen. In certain embodiments, R^7 is Br, isopentyl, 4-butanenitrile, cyclohexyl, phenyl, 3-(difluoromethoxy)phenyl, 3-methoxyphenyl, 3-chloro-5-methoxyphenyl, 3-ethoxyphenyl, 3-cyanophenyl (3-benzonitrile), 5-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-chloro-5-fluorophenyl, 3-chlorophenyl, 3-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-2-fluorophenyl, 5-chloro-2-fluorophenyl, pyridin-3-yl, 5-methoxypyridin-3-yl, 2-fluoropyridin-3-yl, 5-cyanopyridin-3-yl (5-nicotinonitrile), 5-chloropyridin-3-yl, 5-fluoropyridin-3-yl, 5-(trifluoromethyl)pyridin-3-yl, 5-chloro-2-fluoropyridin-3-yl, or pyrimidin-5-yl.

[0079] In certain embodiments, R^7 is selected from hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle, a heterocycle or $-O(\text{heterocycle})$ wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle.

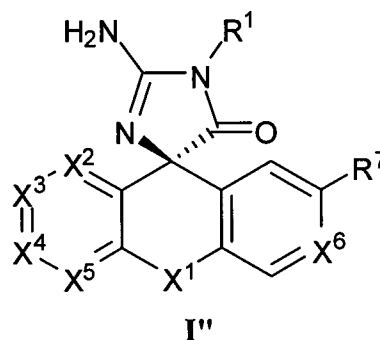
[0080] Compounds of the invention contain one or more asymmetric or chiral centers, e.g., a chiral carbon atom. Accordingly, the compounds may exist as diastereomers,

enantiomers or mixtures thereof. The syntheses of the compounds may employ racemates, diastereomers or enantiomers as starting materials or as intermediates. Diastereomeric compounds may be separated by chromatographic or crystallization methods. Similarly, enantiomeric mixtures may be separated using the same techniques or others known in the art. Each of the asymmetric carbon atoms may be in the R or S configuration and both of these configurations are within the scope of the invention. In a particular embodiment, compounds of the invention have the stereochemical orientation represented by Formula I':



wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , R^1 and R^7 are as defined herein.

[0081] In a particular embodiment, compounds of the invention have the stereochemical orientation represented by Formula I'':



wherein X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , R^1 and R^7 are as defined herein.

[0082] The invention also encompasses prodrugs of the compounds described above. Suitable prodrugs where applicable include known amino-protecting and carboxy-protecting groups which are released, for example hydrolyzed, to yield the parent compound under physiologic conditions. A particular class of prodrugs are compounds in which a nitrogen atom in an amino, amidino, aminoalkyleneamino, iminoalkyleneamino or guanidino group is substituted with a hydroxy (OH) group, an alkylcarbonyl (-CO-R) group, an alkoxycarbonyl (-CO-OR), an acyloxyalkyl-alkoxycarbonyl (-CO-O-R-O-CO-R) group where R is a monovalent or divalent group and as defined above or a group having the formula -C(O)-O-CP1P2-haloalkyl, where P1 and P2 are the same or different and are hydrogen, lower alkyl,

lower alkoxy, cyano, halo lower alkyl or aryl. In a particular embodiment, the nitrogen atom is one of the nitrogen atoms of the amidino group of the compounds of the invention. These prodrug compounds are prepared by reacting the compounds of the invention described above with an activated acyl compound to bond a nitrogen atom in the compound of the invention to the carbonyl of the activated acyl compound. Suitable activated carbonyl compounds contain a good leaving group bonded to the carbonyl carbon and include acyl halides, acyl amines, acyl pyridinium salts, acyl alkoxides, in particular acyl phenoxides such as p-nitrophenoxy acyl, dinitrophenoxy acyl, fluorophenoxy acyl, and difluorophenoxy acyl. The reactions are generally exothermic and are carried out in inert solvents at reduced temperatures such as -78°C to about 50°C . The reactions are usually also carried out in the presence of an inorganic base such as potassium carbonate or sodium bicarbonate, or an organic base such as an amine, including pyridine, triethylamine, etc. One manner of preparing prodrugs is described in PCT publication WO 98/46576, the contents of which are incorporated herein by reference in their entirety.

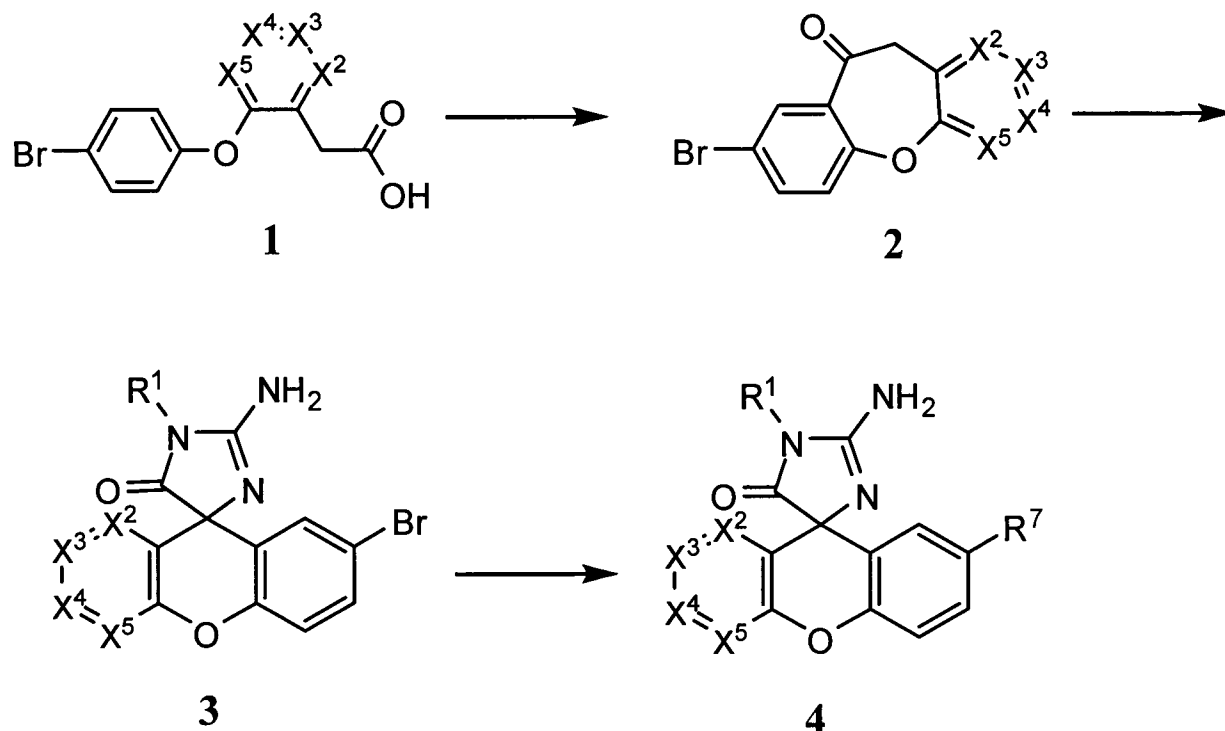
[0083] Compounds of the invention may exist as stereoisomers, e.g., diastereomers and enantiomers, resonance forms, e.g., tautomers, solvates and salts, and all such stereoisomers, resonance forms, solvates and salts are within the scope of the invention herein.

[0084] It will also be appreciated that certain compounds of Formula I may be used as intermediates for further compounds of Formula I.

[0085] SYNTHESIS OF COMPOUNDS

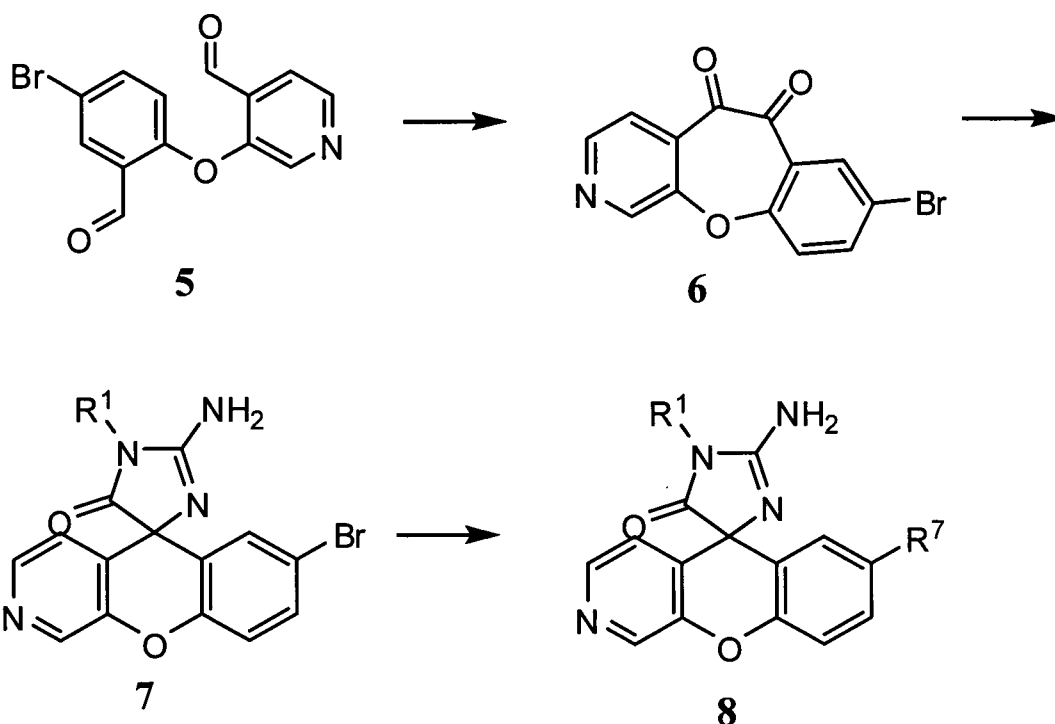
[0086] Compounds of the invention are prepared using standard organic synthetic techniques from starting materials and reagents generally available from commercial sources such as Sigma-Aldrich (St. Louis, MO), Alfa Aesar (Ward Hill, MA), or TCI (Portland, OR), or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Fieser, Louis F., and Mary Fieser, Reagents for Organic Synthesis. v. 1-23, New York: Wiley 1967-2006 ed. (also available via the Wiley InterScience® website), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)). It will be appreciated that synthetic procedures employed in the preparation of compounds of the invention will depend on the particular substituents present in a compound. In preparing compounds of the invention, protection of remote functionalities (e.g., primary or secondary amines, etc.) of intermediates may be necessary but may not be illustrated in the following general Schemes. The need for such protection will vary depending on the nature

of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see Greene's Protective Groups in Organic Synthesis, *supra*.



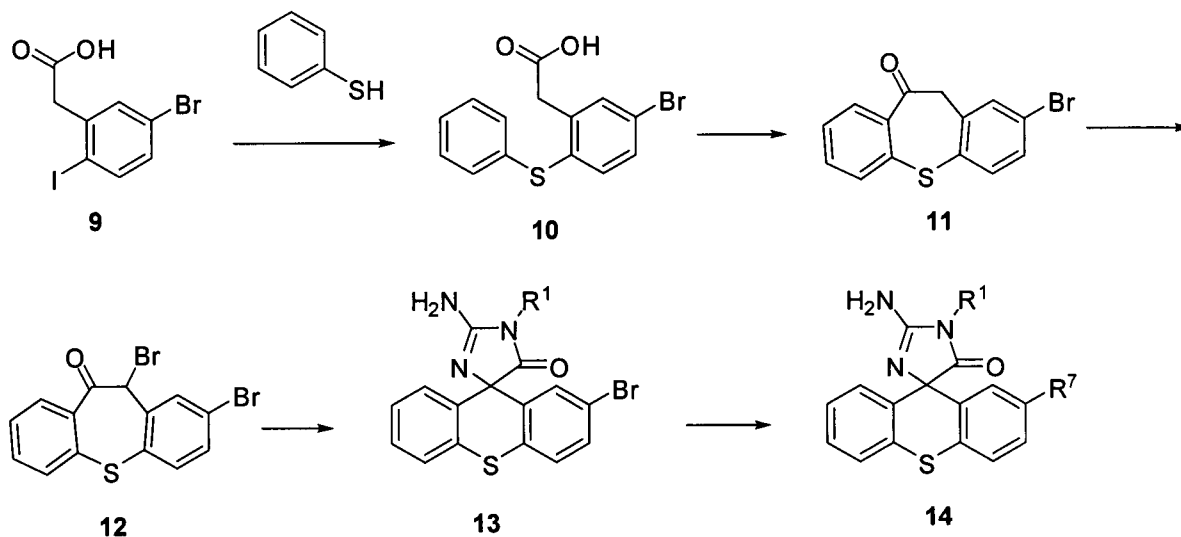
Scheme 1

[0087] Scheme 1 shows a general scheme for the synthesis of compound 4, wherein R^1 and R^7 are as defined herein. Compound 1 may be reacted with a ring closing agent, such as polyphosphoric acid ("PPA"), or SOCl_2 or COCl_2 followed by AlCl_3 , to provide compound 2. Compound 2 may be reacted with an oxidizing agent, such as selenium dioxide, CuBr then dimethylsulfoxide ("DMSO"), or $\text{N}(=\text{O})\text{OR}$ where R is alkyl, followed by 1-methylguanidine to provide compound 3. When R^7 is not bromine, a Suzuki, Negishi or Stille coupling installs the R^7 group and provides compound 4.



Scheme 2

[0088] Scheme 2 shows a general scheme for the synthesis of compound 8, wherein R^1 and R^7 are as defined herein. Compound 5 may be reacted with a ring closing agent, such as KCN under an open air atmosphere, to provide compound 6. Compound 6 may be reacted with an oxidizing agent, such as selenium dioxide, CuBr then DMSO, or $N(=O)OR$ where R is alkyl, followed by 1-methylguanidine to provide compound 7. When R^7 is not bromine, a Suzuki, Negishi or Stille coupling installs the R^7 group and provides compound 8.



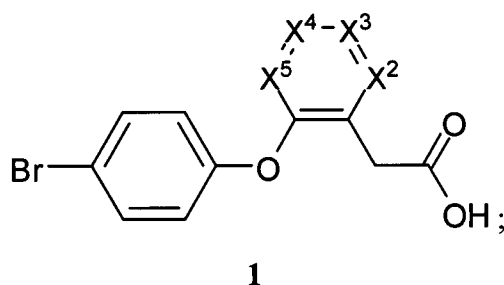
Scheme 3

[0089] Scheme 3 shows a general scheme for the synthesis of compound 14, wherein R^1 and R^7 are as defined herein. Compound 9 may be reacted with benzenethiol to provide

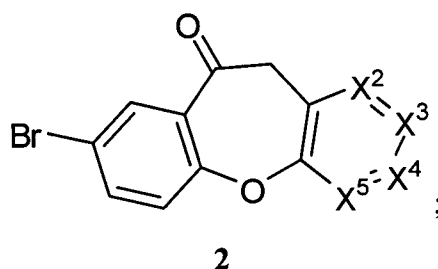
compound 10. Compound 10 may be reacted with a ring closing agent, such as polyphosphoric acid, to provide compound 11. Compound 11 may be brominated to provide compound 12. Compound 12 may be reacted with KI, followed by 1-methylguanidine to provide compound 13. When R^7 is not bromine, a Suzuki, Negishi or Stille coupling installs the R^7 group and provides compound 14.

[0090] In one embodiment, a process for preparing compound of Formula 4 is provided, comprising:

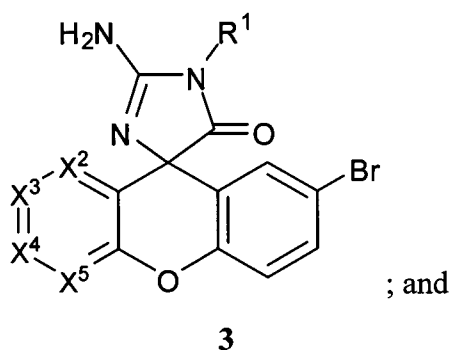
- (a) reacting a compound of Formula 1:



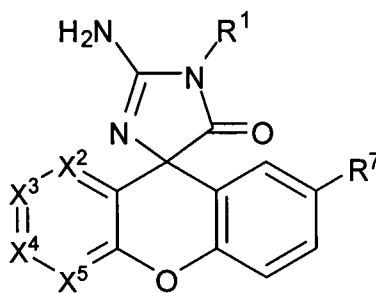
with a ring closing agent to provide a compound of Formula 2:



- (b) reacting a compound of Formula 2 with an oxidizing agent, followed by 1-methylguanidine to provide a compound of Formula 3:



- (c) optionally (when R^7 is not bromine) performing a Suzuki, Negishi or Stille coupling to install the R^7 group provides compound 4:

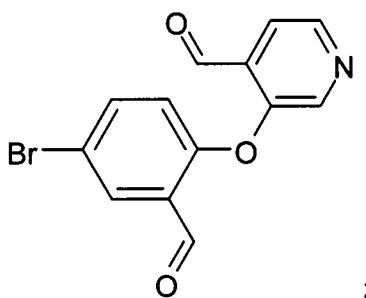


4

In certain embodiments, the ring closing agent is selected from polyphosphoric acid, SOCl_2 followed by AlCl_3 , or COCl_2 followed by AlCl_3 . In certain embodiments, the ring closing agent is polyphosphoric acid. In certain embodiments, the ring closing agent is SOCl_2 followed by AlCl_3 , or COCl_2 followed by AlCl_3 . In certain embodiments, the oxidizing agent is selected from selenium dioxide, CuBr followed by DMSO, or N(=O)OR wherein the R is alkyl. In certain embodiments, the oxidizing agent is selected from selenium dioxide, CuBr followed by DMSO, or N(=O)OR wherein the R is $\text{C}_1\text{-C}_6$ alkyl. In certain embodiments, the oxidizing agent is selenium dioxide. In certain embodiments, the oxidizing agent is CuBr followed by DMSO, or N(=O)OR wherein the R is $\text{C}_1\text{-C}_6$ alkyl. In certain embodiments, the optional Step C is a Suzuki coupling. In certain embodiments, the ring closing agent is polyphosphoric acid, the oxidizing agent is selenium dioxide, and the optional Step C is a Suzuki coupling.

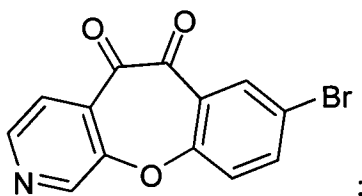
[0091] In one embodiment, a process for preparing compound of Formula 8 is provided, comprising:

- (a) reacting a compound of Formula 5:



5

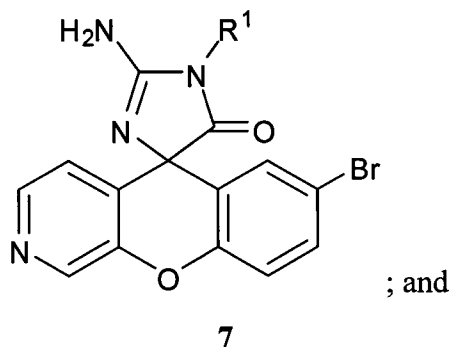
with a ring closing agent to provide a compound of Formula 6:



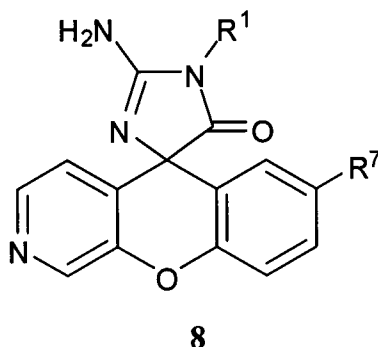
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6

(b) reacting a compound of Formula 6 with an oxidizing agent, followed by 1-methylguanidine to provide a compound of Formula 7:



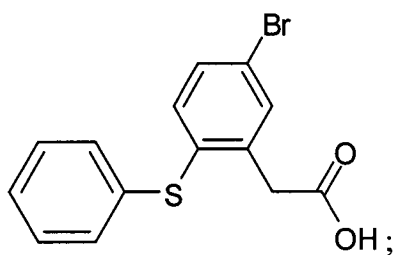
(c) optionally (when R⁷ is not bromine) performing a Suzuki, Negishi or Stille coupling to install the R⁷ group provides compound 8:



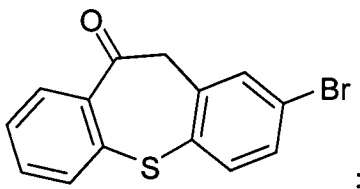
In certain embodiments, the ring closing agent is KCN under an open air atmosphere. In certain embodiments, the oxidizing agent is selected from selenium dioxide, CuBr followed by DMSO, or N(=O)OR wherein the R is alkyl. In certain embodiments, the oxidizing agent is selected from selenium dioxide, CuBr followed by DMSO, or N(=O)OR wherein the R is C₁-C₆ alkyl. In certain embodiments, the oxidizing agent is selenium dioxide. In certain embodiments, the oxidizing agent is CuBr followed by DMSO, or N(=O)OR wherein the R is C₁-C₆ alkyl. In certain embodiments, the optional Step C is a Suzuki coupling. In certain embodiments, the ring closing agent is KCN under an open air atmosphere, the oxidizing agent is selenium dioxide, and the optional Step C is a Suzuki coupling.

[0092] In one embodiment, a process for preparing compound of Formula 14 is provided, comprising:

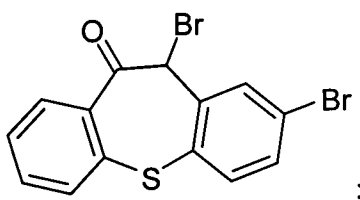
(a) reacting a compound of Formula 10:

**10**

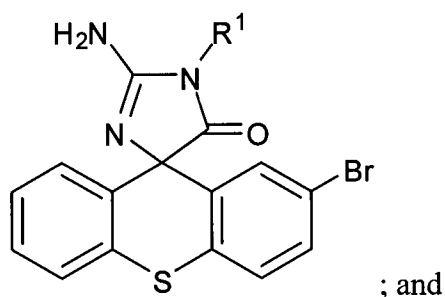
with a ring closing agent to provide a compound of Formula 11:

**11**

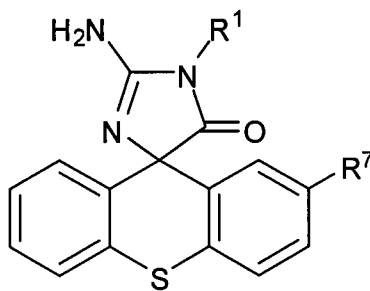
(b) brominating Formula 11 to provide a compound of Formula 12:

**12**

(c) reacting a compound of Formula 12 with KI, followed by 1-methylguanidine to provide a compound of Formula 13:

**13**

(d) optionally (when R^7 is not bromine) performing a Suzuki, Negishi or Stille coupling to install the R^7 group provides compound 14:



14

In certain embodiments, the ring closing agent is polyphosphoric acid. In certain embodiments, the bromination in Step B is performed with a brominating agent. In certain embodiments, the bromination in Step B is performed with a brominating agent, wherein the brominating agent is CuBr₂. In certain embodiments, the optional Step C is a Suzuki coupling. In certain embodiments, the ring closing agent is polyphosphoric acid, the brominating agent is CuBr₂, and the optional Step C is a Suzuki coupling.

[0093] It may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art will apply techniques most likely to achieve the desired separation.

[0094] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[0095] A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as

formation of diastereomers using optically active resolving agents (Eliel, E. and S. Wilen. Stereochemistry of Organic Compounds. New York: John Wiley & Sons, Inc., 1994; Lochmuller, C. H., et al. "Chromatographic resolution of enantiomers: Selective review." J. Chromatogr., 113(3) (1975): pp. 283-302). Racemic mixtures of chiral compounds described herein may be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: Wainer, Irving W., ed. Drug Stereochemistry: Analytical Methods and Pharmacology. New York: Marcel Dekker, Inc., 1993.

[0096] Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α -methyl- β -phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid, can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E., and S. Wilen. Stereochemistry of Organic Compounds. New York: John Wiley & Sons, Inc., 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α -methoxy- α -(trifluoromethyl)phenyl acetate (Jacob III, Peyton. "Resolution of ($\pm$)-5-Bromonornicotine. Synthesis of (R)- and (S)-Nornicotine of High Enantiomeric Purity." J. Org. Chem. Vol. 47, No. 21 (1982): pp. 4165-4167), of the racemic mixture, and analyzing the ^1H NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Lough, W.J., ed. Chiral Liquid

Chromatography. New York: Chapman and Hall, 1989; Okamoto, Yoshio, et al. "Optical resolution of dihydropyridine enantiomers by high-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase." J. of Chromatogr. Vol. 513 (1990): pp. 375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

[0097] INDICATIONS

[0098] The compounds of the invention inhibit the cleavage of amyloid precursor protein by β -secretase which is implicated in diseases, in particular, neurodegenerative diseases such as Alzheimer's disease. In AD, processing of APP by β -secretase produces soluble N-APP which activates extrinsic apoptotic pathways by binding to death receptor 6. Furthermore, APP that is processed by β -secretase is subsequently cleaved by γ -secretase thereby producing amyloid beta peptides such as A β 1-42 that form amyloid plaques which contribute to nerve cell death. Compounds of the invention inhibit enzymatic cleavage of APP by β -secretase.

[0099] Accordingly, in an aspect of the invention, there is provided a method of inhibiting cleavage of APP by β -secretase in a mammal comprising administering to said mammal an effective amount of a compound of Formula I.

[00100] In another aspect of the invention, there is provided a method for treating a disease or condition mediated by the cleavage of APP by β -secretase in a mammal, comprising administering to said mammal an effective amount of a compound of Formula I.

[00101] In another aspect, there is provided the use of a compound of Formula I in the manufacture of a medicament for the treatment of a neurodegenerative disease. In one embodiment, the neurodegenerative disease is Alzheimer's disease.

[00102] In another aspect of the invention, there is provided a use of a compound of Formula I in the treatment of neurodegenerative diseases. In one embodiment, the neurodegenerative disease is Alzheimer's disease.

[00103] Compounds of the invention may be administered prior to, concomitantly with, or following administration of other therapeutic compounds. Sequential administration of each agent may be close in time or remote in time. The other therapeutic agents may be anti-neurodegenerative with a mechanism of action that is the same as compounds of the invention, i.e., inhibit beta-secretase cleavage of APP, or a different mechanism of action, e.g., anti-A β antibodies. The compounds may be administered together in a unitary pharmaceutical composition or separately and, when administered separately this may occur

simultaneously or sequentially in any order. Such sequential administration may be close in time or remote in time.

[00104] The invention also includes compositions containing the compounds of the invention and a carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions. In a particular embodiment, there is provided a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier, diluent or excipient.

[00105] Typically, the compounds of the invention used in the methods of the invention are formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but may range anywhere from about 3 to about 8. Formulation in an acetate buffer at pH 5 is a suitable embodiment. In an embodiment, formulations comprising compounds of the invention are sterile. The compounds ordinarily will be stored as a solid composition, although lyophilized formulations or aqueous solutions are acceptable.

[00106] Compositions comprising compounds of the invention will be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of administration, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

[00107] The compounds may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. If parenteral administration is desired, the compositions will be sterile and in a solution or suspension form suitable for injection or infusion.

[00108] Generally, the initial pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg/day, for example about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. Oral unit dosage forms, such as tablets and capsules, may contain from about 25 to about 1000 mg of the compound

of the invention.

[00109] The compound of the invention may be administered by any suitable means, including oral, sublingual, buccal, topical, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. An example of a suitable oral dosage form is a tablet containing about 25 mg, 50 mg, 100 mg, 250 mg, or 500 mg of the compound of the invention compounded with about 90-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30 mg polyvinylpyrrolidone ("PVP") K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An aerosol formulation can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g., a salt such sodium chloride, if desired. The solution is typically filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

[00110] Another formulation may be prepared by mixing a compound described herein and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound described herein or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

EXAMPLES

[00111] The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. For example, the synthesis of non-exemplified compounds may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering

groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds described herein. The identity and purity of compounds were checked by LCMS and ^1H NMR analysis.

[00112] Column chromatography was done on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel column or on a silica SepPak cartridge (Waters) (unless otherwise stated). ^1H NMR spectra were recorded on a Varian instrument operating at 400 MHz. ^1H -NMR spectra were obtained as CDCl_3 , CD_3OD , D_2O , $(\text{CD}_3)_2\text{SO}$, $(\text{CD}_3)_2\text{CO}$, C_6D_6 , CD_3CN solutions (reported in ppm), using tetramethylsilane (0.00 ppm) or residual solvent (CDCl_3 : 7.26 ppm; CD_3OD : 3.31 ppm; D_2O : 4.79 ppm; $(\text{CD}_3)_2\text{SO}$: 2.50 ppm; $(\text{CD}_3)_2\text{CO}$: 2.05 ppm; C_6D_6 : 7.16 ppm; CD_3CN : 1.94 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[00113] In the Examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Sigma-Aldrich, Alfa Aesar, or TCI, and were used without further purification unless otherwise indicated.

[00114] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

Biological Example

Cellular BACE1 Inhibition Assay

[00115] The BACE inhibition properties of the compounds of the invention may be determined by the following in vitro cellular Amyloid β 1-40 production assay.

[00116] Inhibition of Amyloid β 1-40 production was determined by incubating cells with compound for 48 hours and quantifying the level of Amyloid β 1-40 using an homogeneous time-resolved fluorescence ("HTRF") immunoassay.

[00117] Materials and Methods: HEK-293 cells stably transfected with a DNA construct containing the coding sequence for the wild type APP695 sequence were grown in Dulbecco's Modified Eagle Medium ("DMEM") supplemented with 10% fetal bovine serum, penicillin/streptomycin and 150 $\mu\text{g/mL}$ G418. Cells were plated in 96-well plates at 35,000

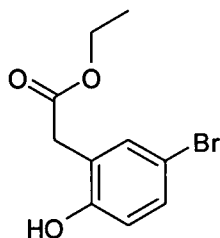
cells/well and allowed to attach for 8-12 hours. Media was changed to DMEM supplemented with 10% fetal bovine serum, penicillin/streptomycin 15 minutes prior to compound addition. Diluted compounds were then added at a final concentration of 0.5% DMSO. After 48 hours, 4 μ L of media from each well was added to a corresponding well of a 384 well plate (Perkin Elmer Cat#6008280) containing the HTRF reagents. HTRF reagents were obtained from the CisBio Amyloid β 1-40 peptide assay kit (Cat# 62B40PEC) and were prepared as follows anti-peptide β (1-40)-Cryptate and anti-peptide β (1-40)-XL655 were stored in 2 plate aliquots at -80°C. Diluent and Reconstitution buffer were stored at 4°C. Aliquots of the two antibodies were diluted 1:100 with Reconstitution buffer, and this mixture was diluted 1:2 with Diluent. 12 μ L of the reagent mixture was added to the required wells of the 384 well assay plate. The assay plate was incubated at 4°C for 17 hours and then analyzed for fluorescence at 665 and 620 nm.

[00118] The following compounds were tested in the above assay:

Example #	IC ₅₀ (nM)
Example 2	23.7
Example 2A	33.4
Example 2B	9
Example 5	46.1
Example 6	37.9
Example 7	44.6
Example 9	44.6
Example 11	93.2
Example 14	118.5
Example 18	54
Example 21	84
Example 22	130
Example 24	138.4
Example 25	6.2
Example 26	7.4
Example 27	16.6
Example 30	15.3
Example 32	13.6

Example #	IC ₅₀ (nM)
Example 33	37.8
Example 45	141.5
Example 46	102.8
Example 47	139.5
Example 50	60.5
Example 53	137.5
Example 59	65.3
Example 64	22.8
Example 67	126.2
Example 76	54.5
Example 103	0.3
Example 109	6.4
Example 110	9.5
Example 115	13.9
Example 120	2.1
Example 122	3.8
Example 123	7.7
Example 124	13.7

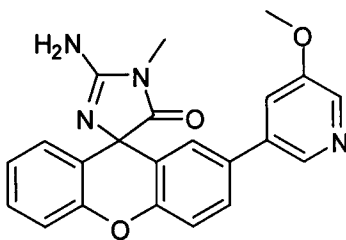
Example A



ethyl 2-(5-bromo-2-hydroxyphenyl)acetate

[00119] A solution of 2-(2-hydroxyphenyl)acetic acid (40.00 g, 262.9 mmol) and phenyltrimethylammonium bromide (98.83 g, 262.9 mmol) in ethanol (1315 mL, 262.9 mmol) was stirred at room temperature overnight. The mixture was evaporated then partitioned between ether and 1N HCl. The organic layer was washed with sodium bisulfate (aq), water, brine, dried and concentrated to give a residue that was purified by flash chromatography, eluting with a hexanes/ethyl acetate gradient. The resulting residue was triturated with hexanes to crystallize product (32.5 g, 125 mmol, 48%).

Example 1



2-amino-2'-(5-methoxypyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00120] Step A: Ethyl 2-(2-hydroxyphenyl)acetate (5.0 g, 28 mmol), 1-fluoro-4-nitrobenzene (3.6 mL, 33 mmol) and K_2CO_3 (5.8 g, 42 mmol) were diluted with dimethylformamide ("DMF") (100 mL). The reaction was heated to 70°C and stirred for 12 hours. The reaction was allowed to cool, diluted with ethyl acetate and washed with water then brine. The organics were dried over $MgSO_4$, filtered and concentrated. The material was purified on silica gel eluting with 10% ethyl acetate/hexanes to yield ethyl 2-(2-(4-nitrophenoxy)phenyl)acetate (5.6 g, 19 mmol, 67% yield).

[00121] Step B: Ethyl 2-(2-(4-nitrophenoxy)phenyl)acetate (5.6 g, 19 mmol) was diluted with methanol (50 mL), followed by the addition of palladium 10 wt. % (dry basis), activated carbon, wet, Degussa (0.20 g, 1.9 mmol). The reaction was purged three times with a hydrogen balloon and was left to stir for 12 hours. The reaction was filtered through glass microfibre filter ("GF/F") paper and concentrated to yield ethyl 2-(2-(4-aminophenoxy)phenyl)acetate (5.0 g, 18 mmol, 99% yield).

[00122] Step C: A mixture of $tBuNO_2$ (2.43 mL, 18.4 mmol) and $CuBr_2$ (3.29 g, 14.7

mmol) in acetonitrile (100 mL) were stirred at 0°C for 30 minutes. Ethyl 2-(2-(4-aminophenoxy)phenyl)acetate (5.0 g, 18.4 mmol; in 2 mL of acetonitrile ("ACN")) was slowly added. This was stirred for 2 hours and then allowed to warm to ambient temperature. The reaction was quenched with HCl (1N) and the organics were extracted with dichloromethane ("DCM"). The combined organics were washed with brine and dried with MgSO₄. This was purified on silica gel eluting with 10-50% ethyl acetate/hexanes to yield ethyl 2-(2-(4-bromophenoxy)phenyl)acetate (4.34 g, 12.9 mmol, 70.3% yield).

[00123] Step D: Ethyl 2-(2-(4-bromophenoxy)phenyl)acetate (4.34 g, 12.9 mmol) was diluted with ethanol (50 mL) followed by the addition of NaOH (32.4 mL, 64.7 mmol). After stirring for 12 hours, the reaction was diluted with ethyl acetate and 2N HCl. The layers were separated, and the organic was dried over MgSO₄, filtered and concentrated to yield 2-(2-(4-bromophenoxy)phenyl)acetic acid (3.7 g, 12.0 mmol, 93.0% yield).

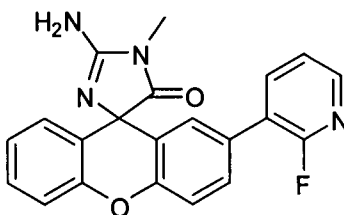
[00124] Step E: 2-(2-(4-Bromophenoxy)phenyl)acetic acid (3.7 g, 12 mmol) was added to a stirring 80°C solution of PPA. After stirring for 12 hours, the reaction was allowed to cool and poured into ice water. The material was extracted twice with DCM. The DCM was combined, dried over MgSO₄, filtered and concentrated. The material was purified on silica gel eluting with 10-50% ethyl acetate/hexanes to yield 8-bromodibenzo[b,f]oxepin-10(11H)-one (3.3 g, 11 mmol, 95% yield).

[00125] Step F: 8-Bromodibenzo[b,f]oxepin-10(11H)-one (3.3 g, 11 mmol) was diluted with dioxane (30 mL) and water (600 uL) followed by the addition of selenium dioxide (2.8 g, 25 mmol). The reaction was heated to reflux and stirred for 12 hours. The reaction was cooled and then filtered. 1-Methylguanidine hydrochloride (5.0 g, 46 mmol) and ethanol (30 mL) were added followed by the addition of Na₂CO₃ (23 mL, 46 mmol). The reaction was heated to 80°C and stirred for 12 hours. The reaction was allowed to cool, diluted with ethyl acetate and water. The layers were separated, and the organics were dried over MgSO₄, filtered and concentrated. The material was purified on silica gel eluting with 1-10% methanol/DCM (with 1% NH₄OH) to afford 2-amino-2'-bromo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (2.4 g, 6.7 mmol, 59% yield).

[00126] Step G: 2-Amino-2'-bromo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (30 mg, 0.084 mmol) and 5-methoxypyridin-3-ylboronic acid (15 mg, 0.10 mmol) were diluted with dioxane (1 mL) followed by the addition of Pd(PPh₃)₄ (4.8 mg, 0.0042 mmol) and Na₂CO₃ (126 µL, 0.25 mmol). The reaction was sealed, heated to 85°C and stirred for 12 hours. The reaction was loaded directly onto silica gel and eluted with 1-10% methanol/DCM (1% NH₄OH) to afford 2-amino-2'-(5-methoxypyridin-3-yl)-1-

methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (20 mg, 0.052 mmol, 62% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.39 (d, 1H), 8.29 (d, 1H), 7.55 (m, 1H), 7.20-7.40 (m, 7H), 7.15 (t, 1H), 3.92 (s, 3H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 387.2$.

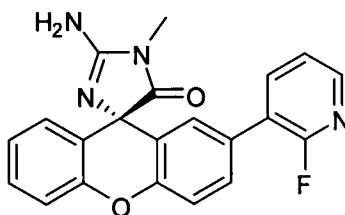
Example 2



2-amino-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00127] Prepared according to Example 1, substituting 2-fluoropyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, 1H), 7.80 (t, 1H), 7.55 (d, 1H), 7.20-7.40 (m, 7H), 7.10 (t, 1H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 375.1$.

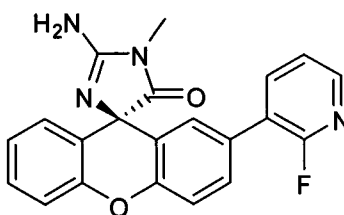
Example 2A



(S)-2-amino-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00128] Example 2 was separated on a Berger SFC MGII system using a Chiralpak IB (200 x 21.2 mm, 5u) chiral column eluting at 50 mL/minute with 30% methanol (0.1% DEA). Separation was done at 40°C to afford (S)-2-amino-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, 1H), 7.80 (t, 1H), 7.55 (d, 1H), 7.20-7.40 (m, 7H), 7.10 (t, 1H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 375.1$.

Example 2B

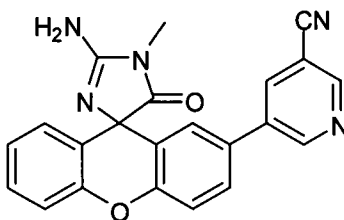


(R)-2-amino-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00129] Example 2 was separated on a Berger SFC MGII system using a Chiralpak IB (200 x 21.2 mm, 5u) chiral column eluting at 50 mL/minute with 30% methanol (0.1% DEA).

Separation was done at 40°C to afford (R)-2-amino-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one. m/z (APCI-pos) $M+1 = 375.1$.

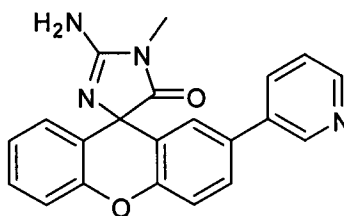
Example 3



5-(2-amino-1-methyl-5-oxo-1,5-dihydrospiro[imidazole-4,9'-xanthen]-2'-yl)nicotinonitrile

[00130] Prepared according to Example 1, substituting 5-cyanopyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.99 (d, 1H), 8.82 (d, 1H), 8.10 (t, 1H), 7.55 (m, 1H), 7.20-7.40 (m, 6H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 382.2$.

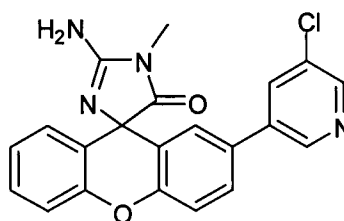
Example 4



2-amino-1-methyl-2'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

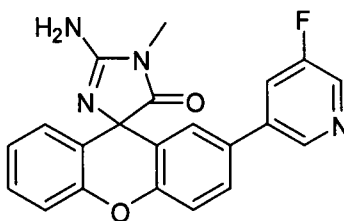
[00131] Prepared according to Example 1, substituting pyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.79 (d, 1H), 8.59 (d, 1H), 7.80 (m, 1H), 7.55 (m, 1H), 7.20-7.40 (m, 5H), 7.11 (t, 1H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 357.1$.

Example 5

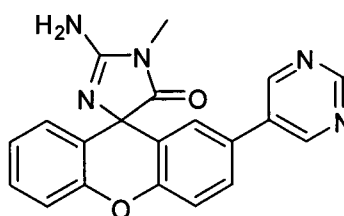


2-amino-2'-(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

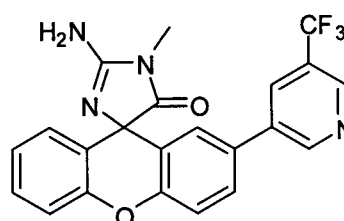
[00132] Prepared according to Example 1, substituting 5-chloropyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.85 (d, 1H), 8.59 (d, 1H), 8.15 (m, 1H), 7.65 (m, 1H), 7.20-7.50 (m, 6H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 391.1$.

Example 62-amino-2'-(5-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00133] Prepared according to Example 1, substituting 5-fluoropyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.65 (d, 1H), 8.45 (d, 1H), 7.10-7.60 (m, 8H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 375.1$.

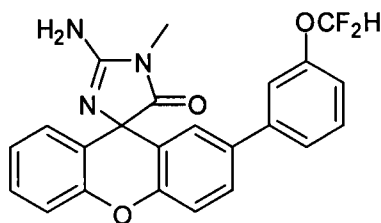
Example 72-amino-1-methyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00134] Prepared according to Example 1, substituting 5-fluoropyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 9.18 (s, 1H), 8.90 (s, 2H), 7.55 (d, 1H), 7.10-7.40 (m, 6H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 358.2$.

Example 82-amino-1-methyl-2'-(5-(trifluoromethyl)pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

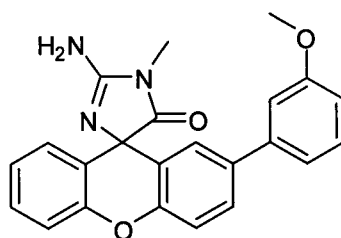
[00135] Prepared according to Example 1, substituting 5-(trifluoromethyl)pyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.95 (s, 1H), 8.85 (s, 1H), 8.00 (s, 1H), 7.55 (m, 1H), 7.20-7.40 (m, 5H), 7.10 (t, 1H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 425.2$.

Example 9



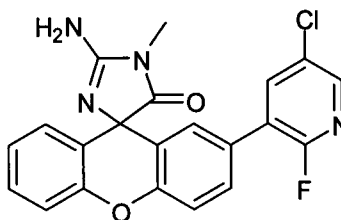
2-amino-2'-(3-(difluoromethoxy)phenyl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one
[00136] Prepared according to Example 1, substituting 5-(trifluoromethyl)pyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 422.1$.

Example 10



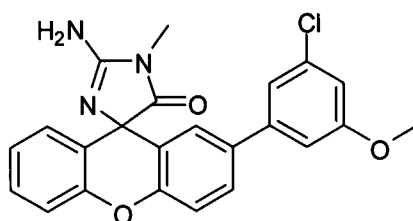
2-amino-2'-(3-methoxyphenyl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one
[00137] Prepared according to Example 1, substituting 3-methoxyphenylboronic acid for 5-methoxypyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 386.2$.

Example 11

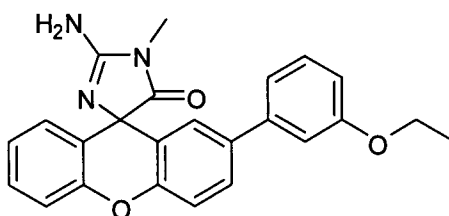


2-amino-2'-(5-chloro-2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one
[00138] Prepared according to Example 1, substituting 5-chloro-2-fluoropyridin-3-ylboronic acid for 5-methoxypyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 409.1$.

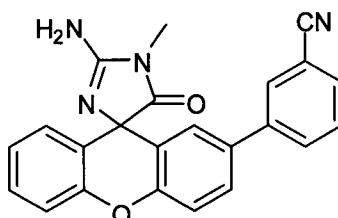
Example 12



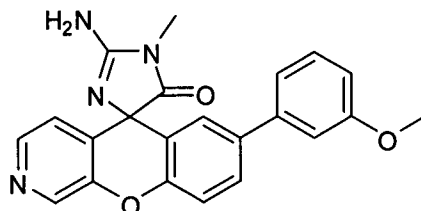
2-amino-2'-(3-chloro-5-methoxyphenyl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one
[00139] Prepared according to Example 1, substituting 3-chloro-5-methoxyphenylboronic acid for 5-methoxypyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 420.1$.

Example 132-amino-2'-(3-ethoxyphenyl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00140] Prepared according to Example 1, substituting 3-ethoxyphenylboronic acid for 5-methoxypyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 400.2$.

Example 143-(2-amino-1-methyl-5-oxo-1,5-dihydrospiro[imidazole-4,9'-xanthene]-2'-yl)benzonitrile

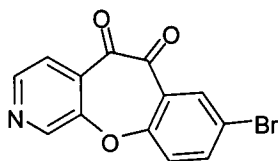
[00141] Prepared according to Example 1, substituting 3-cyanophenylboronic acid for 5-methoxypyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 381.2$.

Example 152'-amino-7-(3-methoxyphenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one

[00142] Step A: 3-Fluoroisonicotinaldehyde (9.7 g, 78 mmol), 5-bromosalicylaldehyde (13 g, 65 mmol) and K_2CO_3 (9.8 g, 71 mmol) were diluted with DMSO (125 mL). The reaction was heated to 70°C and stirred for 12 hours. The reaction was allowed to cool, diluted with ethyl acetate and water. The layers were separated, and the organics were dried over $MgSO_4$, filtered and concentrated. The material was purified on silica gel eluting with 5-50% ethyl acetate/hexanes to yield 3-(4-bromo-2-formylphenoxy)isonicotinaldehyde (7 g, 23 mmol, 35% yield).

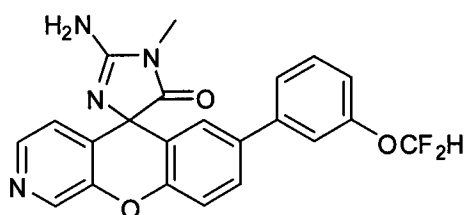
[00143] Step B: 3-(4-Bromo-2-formylphenoxy)isonicotinaldehyde (5.8 g, 19 mmol) was diluted with DMSO (15 mL) followed by the addition of KCN (0.99 g, 15 mmol). The reaction was stirred at ambient temperature for 12 hours. The reaction was diluted with ethyl

acetate and saturated sodium bicarbonate. The layers were separated, and the organic was dried over MgSO_4 , filtered and concentrated. The material was purified on silica gel eluting with 20-90% ethyl acetate/hexanes to yield the compound 15B (2.2 g, 7.2 mmol, 38% yield).

**15B**

[00144] Step C: Compound 15B (2.2 g, 7.2 mmol) was diluted with dioxane (20 mL) and water (200 μL) followed by the addition of selenium dioxide (1.6 g, 14 mmol). The reaction was heated to reflux and stirred for 12 hours. The reaction was cooled and then filtered. 1-Methylguanidine hydrochloride (3.1 g, 29 mmol) and ethanol (30 mL) were added, followed by the addition of Na_2CO_3 (14 mL, 29 mmol). The reaction was heated to 80°C and stirred for 12 hours. The reaction was allowed to cool, diluted with ethyl acetate and water. The layers were separated, and the organics were dried over MgSO_4 , filtered and concentrated. The material was triturated with diethyl ether to afford 2'-amino-7-bromo-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1H)-one (1.6 g, 4.5 mmol, 62% yield) as a solid.

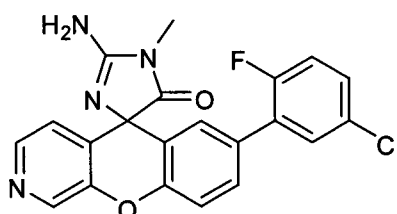
[00145] Step D: 2'-Amino-7-bromo-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1H)-one (30 mg, 0.0835 mmol) and 3-methoxyphenylboronic acid (13.3 mg, 0.0877 mmol) were diluted with dioxane (1 mL) followed by the addition of $\text{Pd}(\text{PPh}_3)_4$ (4.83 mg, 0.00418 mmol) and Na_2CO_3 (125 μL , 0.251 mmol). The reaction was sealed, heated to 85°C and stirred for 12 hours. The reaction was loaded directly onto silica gel and eluted with 1-10% methanol/DCM (1% NH_4OH) to afford 2'-amino-7-(3-methoxyphenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1H)-one (9 mg, 0.0233 mmol, 27.9% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.62 (s, 1H), 8.35 (d, 1H), 7.55 (m, 1H), 7.30-7.40 (m, 3H), 7.05-7.20 (m, 3H), 6.90 (m, 1H), 3.85 (s, 3H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 387.1$.

Example 16

2'-amino-7-(3-(difluoromethoxy)phenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-

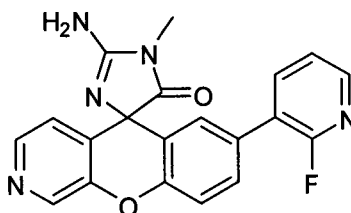
imidazol]-5'-(1'H)-one

[00146] Prepared according to Example 15, substituting 3-(difluoromethoxy) phenylboronic acid for 3-methoxyphenylboronic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.62 (s, 1H), 8.35 (d, 1H), 7.55 (m, 1H), 7.30-7.45 (m, 5H), 7.05-7.20 (m, 2H), 6.55 (t, 1H), 3.15 (s, 3H); *m/z* (APCI-pos) *M*+1 = 423.1.

Example 17

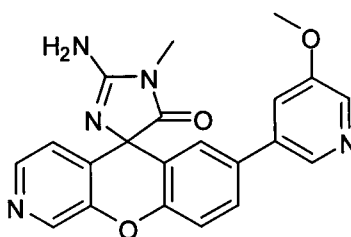
2'-amino-7-(5-chloro-2-fluorophenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-
imidazol]-5'-(1'H)-one

[00147] Prepared according to Example 15, substituting 5-chloro-2-fluorophenylboronic acid for 3-methoxyphenylboronic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.62 (s, 1H), 8.35 (d, 1H), 7.55 (m, 1H), 7.00-7.40 (m, 6H), 3.15 (s, 3H); *m/z* (APCI-pos) *M*+1 = 409.0.

Example 18

2'-amino-7-(2-fluoropyridin-3-yl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-
5'-(1'H)-one

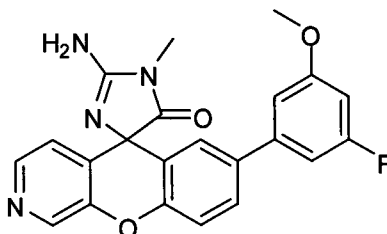
[00148] Prepared according to Example 15, substituting 2-fluoropyridin-3-ylboronic acid for 3-methoxyphenylboronic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.62 (d, 1H), 8.55 (d, 1H), 7.75 (m, 1H), 7.50 (m, 1H), 7.40 (m, 1H), 7.30 (m, 3H), 7.10 (d, 1H), 3.15 (s, 3H); *m/z* (APCI-pos) *M*+1 = 376.1.

Example 19

2'-amino-7-(5-methoxypyridin-3-yl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one

[00149] Prepared according to Example 15, substituting 5-methoxypyridin-3-ylboronic acid for 3-methoxyphenylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.62 (s, 1H), 8.40 (d, 1H), 8.35 (d, 1H), 8.30 (d, 1H), 7.55 (d, 1H), 7.38 (d, 1H), 7.32 (m, 2H), 7.15 (d, 1H), 3.92 (s, 3H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 388.1$.

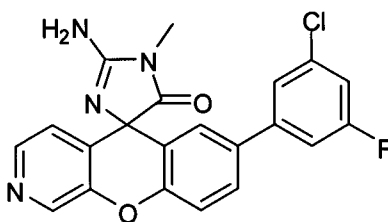
Example 20



2'-amino-7-(3-fluoro-5-methoxyphenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one

[00150] Prepared according to Example 15, substituting 3-fluoro-5-methoxyphenylboronic acid for 3-methoxyphenylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.62 (s, 1H), 8.35 (d, 1H), 7.55 (d, 1H), 7.35 (m, 2H), 7.13 (d, 1H), 6.8 (m, 2H), 6.60 (m, 1H), 3.82 (s, 3H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 405.1$.

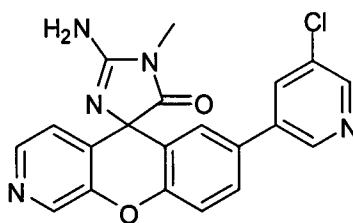
Example 21



2'-amino-7-(3-chloro-5-fluorophenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one

[00151] Prepared according to Example 15, substituting 3-chloro-5-fluorophenylboronic acid for 3-methoxyphenylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.62 (s, 1H), 8.35 (d, 1H), 7.55 (d, 1H), 7.35 (d, 1H), 7.30 (m, 2H), 7.05-7.15 (m, 3H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 409.1$.

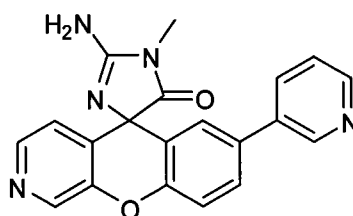
Example 22



2'-amino-7-(5-chloropyridin-3-yl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1H)-one

[00152] Prepared according to Example 15, substituting 5-chloropyridin-3-ylboronic acid for 3-methoxyphenylboronic acid. m/z (APCI-pos) $M+1 = 392.1$.

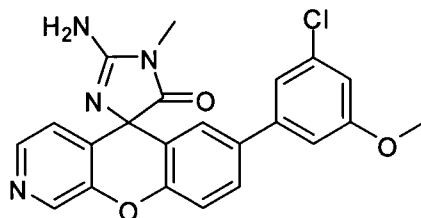
Example 23



2-amino-1'-methyl-7-(pyridin-3-yl)spiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1H)-one

[00153] Prepared according to Example 15, substituting pyridin-3-ylboronic acid for 3-methoxyphenylboronic acid. m/z (APCI-pos) $M+1 = 358.1$.

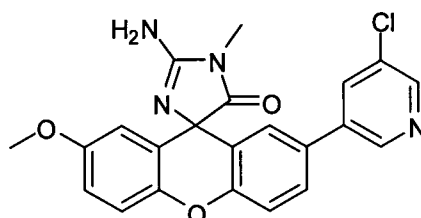
Example 24



2'-amino-7-(3-chloro-5-methoxyphenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1H)-one

[00154] Prepared according to Example 15, substituting 3-chloro-5-methoxyphenylboronic acid for 3-methoxyphenylboronic acid. m/z (APCI-pos) $M+1 = 421.1$.

Example 25



2-amino-2'-(5-chloropyridin-3-yl)-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

one

[00155] Step A: A mixture of methyl 2-(2-fluoro-5-nitrophenyl)acetate (1.0 g, 4.69 mmol), 4-methoxyphenol (0.611 g, 4.93 mmol) and Cs_2CO_3 (2.29 g, 7.04 mmol) in DMF (0.343 g, 4.69 mmol) was heated to 90°C overnight. The mixture was then partitioned between ethyl acetate and water. The organics were extracted with ethyl acetate twice, washed with brine and dried with Na_2SO_4 . This was then concentrated down and purified on a column using ethyl acetate and hexanes to give methyl 2-(2-(4-methoxyphenoxy)-5-nitrophenyl)acetate (1.30 g, 4.10 mmol, 87.3% yield) as an oil.

[00156] Step B: Methyl 2-(2-(4-methoxyphenoxy)-5-nitrophenyl)acetate (1.30 g, 4.10 mmol) and Pd/C (0.436 g, 4.10 mmol) in MeOH (0.166 mL, 4.10 mmol; d 0.791) under H_2 in a balloon was stirred to completion at room temperature. The mixture was then filtered through GF/F paper. The filtrate was concentrated down to give methyl 2-(5-amino-2-(4-methoxyphenoxy)phenyl)acetate (1.11 g, 3.86 mmol, 94.3% yield).

[00157] Step C: A solution of CuBr_2 (0.690 g, 3.09 mmol) and $t\text{BuNO}_2$ (0.510 mL, 3.86 mmol) in acetonitrile (30 mL, 574 mmol; p = 0.786) was stirred at 0°C for 30 minutes. Methyl 2-(5-amino-2-(4-methoxyphenoxy)phenyl)acetate (1.11 g, 3.86 mmol) in acetonitrile (5 mL) was added, and the mixture was stirred overnight at room temperature. The mixture was then partitioned between ethyl acetate and water. The organics were extracted with ethyl acetate twice, washed with brine and dried with Na_2SO_4 . This was then purified on a column using ethyl acetate and hexanes to give methyl 2-(5-bromo-2-(4-methoxyphenoxy)phenyl)acetate (0.628 g, 1.79 mmol, 46.3% yield).

[00158] Step D: NaOH (4.47 mL, 8.94 mmol) was added to a mixture of methyl 2-(5-bromo-2-(4-methoxyphenoxy)phenyl)acetate (0.628 g, 1.79 mmol) in ethanol (15 mL, 1.79 mmol) at room temperature. This was stirred overnight to completion. The mixture was partitioned between ethyl acetate and 2N HCl. The organics were extracted with ethyl acetate, washed with brine and dried with Na_2SO_4 . This was then concentrated down to give 2-(5-bromo-2-(4-methoxyphenoxy)phenyl)acetic acid (0.60 g, 1.78 mmol, 99.5% yield).

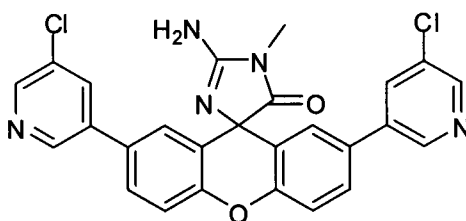
[00159] Step E: A mixture of 2-(5-bromo-2-(4-methoxyphenoxy)phenyl)acetic acid (0.600 g, 1.78 mmol) in PPA (0.174 g, 1.78 mmol) was heated to 90°C overnight. The mixture was then partitioned between DCM and water. The organics were extracted with DCM twice, washed with brine and dried with Na_2SO_4 . This was then concentrated down and purified on a column using ethyl acetate and hexanes to give 2-bromo-8-methoxydibenzo[b,f]oxepin-10(11H)-one (0.480 g, 1.50 mmol, 84.5% yield).

[00160] Step F: A mixture of 2-bromo-8-methoxydibenzo[b,f]oxepin-10(11H)-one

(0.480 g, 1.50 mmol) and SeO_2 (0.367 g, 3.31 mmol) in dioxane (15 mL, 1.50 mmol) and water (0.5 mL, 1.50 mmol) was refluxed overnight. The mixture was then filtered through GF/F paper, and the filtrate was put in a round bottom flask. Ethanol (15 mL, 1.50 mmol) was added, followed by 1-methylguanidine hydrochloride (0.741 g, 6.77 mmol). This was stirred into solution. Na_2CO_3 (3.38 mL, 6.77 mmol) was then added, and the mixture was heated to 90°C for 30 minutes. The mixture was partitioned between DCM and water. The organics were extracted with DCM twice, washed with brine and dried with Na_2SO_4 . This was concentrated down and purified on a column using DCM:MeOH: NH_4OH (90:10:1) to give 2-amino-2'-bromo-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.413 g, 1.06 mmol, 70.7% yield) as a solid.

[00161] Step G: A mixture of 2-amino-2'-bromo-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.040 g, 0.103 mmol), 5-chloropyridin-3-ylboronic acid (0.0195 g, 0.124 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.0119 g, 0.0103 mmol) and Na_2CO_3 (0.0273 g, 0.258 mmol) and dioxane (1 mL, 0.103 mmol) was heated to 90°C overnight. The mixture was purified on a column using DCM:MeOH: NH_4OH (90:10:1) to give 2-amino-2'-(5-chloropyridin-3-yl)-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.0133 g, 0.0316 mmol, 30.7% yield) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.63 (1H), 8.52 (1H), 7.77 (1H), 7.50 (1H), 7.33 (1H), 7.28 (1H), 7.16 (1H), 6.90 (1H), 6.70 (1H), 3.76 (3H), 3.14 (3H); m/z (APCI-pos) $M+1 = 421.1$.

Example 26



2-amino-2',7'-bis(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00162] Step A: A mixture of methyl 2-(5-bromo-2-hydroxyphenyl)acetate (2.0 g, 8.16 mmol), 1-bromo-4-iodobenzene (6.93 g, 24.5 mmol), 2-(dimethylamino)acetic acid hydrochloride (0.683 g, 4.90 mmol), Cs_2CO_3 (6.65 g, 20.4 mmol) and Cu(I)Cl (0.485 g, 4.90 mmol) in dioxane (20.4 mL, 8.16 mmol) was purged with argon for 10 minutes. The mixture was then refluxed for 4 hours. HPLC showed that the reaction was complete. The mixture was then filtered through GF/F paper. The filtrate was partitioned between ethyl acetate and water. The organics were extracted with ethyl acetate twice, washed with brine and dried with Na_2SO_4 . This was then concentrated down and purified on a column using ethyl acetate

and hexanes to give methyl 2-(5-bromo-2-(4-bromophenoxy)phenyl)acetate (0.721 g, 1.80 mmol, 22.1% yield).

[00163] Step B: A mixture of methyl 2-(5-bromo-2-(4-bromophenoxy)phenyl)acetate (0.721 g, 1.80 mmol) and sodium hydroxide (5.41 mL, 10.8 mmol) in ethanol (10 mL, 1.80 mmol) was stirred at room temperature for 4 hours. The mixture was then partitioned between ethyl acetate and 2N HCl. The organics were extracted with ethyl acetate twice, washed with brine and dried with Na₂SO₄. This was then concentrated down to give 2-(5-bromo-2-(4-bromophenoxy)phenyl)acetic acid (0.689 g, 1.78 mmol, 99.0% yield).

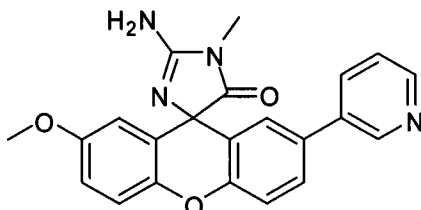
[00164] Step C: Oxalyl chloride in 2M DCM (0.389 mL, 0.777 mmol) was added to 2-(5-bromo-2-(4-bromophenoxy)phenyl)acetic acid (0.250 g, 0.648 mmol) in DCM (10 mL, 0.648 mmol) at 0°C. A few drops of DMF were added, and this was stirred at room temperature for 15 minutes. This was then concentrated down to give an oil. 1,2-Dichloroethane ("DCE") (10 mL) was added to the oil, and this was chilled to 0°C. AlCl₃ (0.259 g, 1.94 mmol) in DCE (5 mL) was added, and this was stirred at room temperature for 1 hour. The mixture was then partitioned between DCM and water. The organics were extracted with DCM twice, washed with brine and dried with Na₂SO₄. This was then concentrated down and purified on a column using ethyl acetate and hexanes to give 2,8-dibromodibenzo[b,f]oxepin-10(11H)-one (0.200 g, 0.543 mmol, 83.9% yield).

[00165] Step D: A mixture of 2,8-dibromodibenzo[b,f]oxepin-10(11H)-one (0.20 g, 0.543 mmol) and selenium dioxide (0.151 g, 1.36 mmol) in dioxane (0.0479 g, 0.543 mmol) was heated to 90°C overnight. The mixture was then filtered through GF/F paper. Ethanol (0.0250 g, 0.543 mmol) was added to the filtrate, followed by the addition of 1-methylguanidine hydrochloride (0.268 g, 2.45 mmol). Na₂CO₃ (1.22 mL, 2.45 mmol) was added, and this was heated to 90°C for 30 minutes. The mixture was then partitioned between DCM and water. The organics were extracted twice with DCM, washed with brine and dried with Na₂SO₄. The mixture was purified on a column using DCM:MeOH:NH₄OH (90:10:1) to give 2-amino-2',7'-dibromo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.152 g, 0.348 mmol, 64.0% yield) as a solid.

[00166] Step E: A mixture of 2-amino-2',7'-dibromo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.030 g, 0.069 mmol), 5-chloropyridin-3-ylboronic acid (0.024 g, 0.15 mmol), Pd(PPh₃)₄ (0.0079 g, 0.0069 mmol) and Na₂CO₃ (0.12 mL, 0.24 mmol) in dioxane (2 mL, 0.069 mmol) was heated to 90°C overnight. The mixture was then partitioned between DCM and water. The organics were extracted with DCM twice, washed with brine and dried with Na₂SO₄. The mixture was then concentrated down to be purified on preparative HPLC

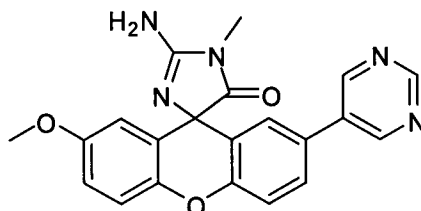
to give 2-amino-2',7'-bis(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.0033 g, 0.0066 mmol, 9.6% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.82 (2H), 8.62 (2H), 8.18 (3H), 7.80 (2H), 7.48 (2H), 7.41 (2H), 3.01 (3H); m/z (APCI-pos) $M+1 = 502.1$.

Example 27



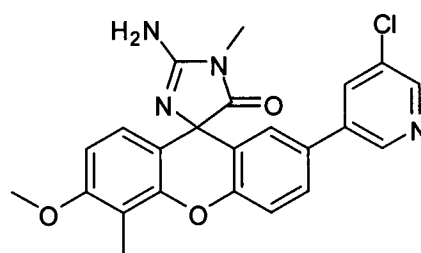
2-amino-2'-methoxy-1-methyl-7'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one
[00167] 2-Amino-2'-methoxy-1-methyl-7'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedures of Example 25, substituting pyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.73 (1H), 8.54 (1H), 7.76 (1H), 7.48 (1H), 7.31 (2H), 7.23 (1H), 7.12 (1H), 6.86 (1H), 6.67 (1H), 3.72 (3H), 3.11 (3H); m/z (APCI-pos) $M+1 = 387.1$.

Example 28



2-amino-2'-methoxy-1-methyl-7'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one
[00168] 2-Amino-2'-methoxy-1-methyl-7'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedures of Example 25, substituting pyrimidin-5-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 9.16 (1H), 8.84 (2H), 7.49 (1H), 7.30 (2H), 7.12 (1H), 6.86 (1H), 6.66 (1H), 3.73 (3H), 3.12 (3H); m/z (APCI-pos) $M+1 = 388.1$.

Example 29



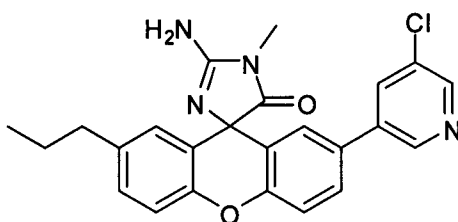
2-amino-2'-(5-chloropyridin-3-yl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00169] Steps A-D: 2-(5-Bromo-2-(3-methoxy-2-methylphenoxy)phenyl)acetic acid was made according to the procedures in Example 1, Steps A through D, substituting 3-methoxy-2-methylphenol for 4-methoxyphenol.

[00170] Step E: Oxalyl chloride in 2M DCM (3.55 mL, 7.10 mmol) was added to a mixture of 2-(5-bromo-2-(3-methoxy-2-methylphenoxy)phenyl)acetic acid (2.08 g, 5.92 mmol) in DCM (12 mL, 5.92 mmol) at 0°C. A few drops of DMF were added, and the mixture was stirred at room temperature for 4 hours. The mixture was then concentrated down to give an oil. The oil was taken up in DCE (0.586 g, 5.92 mmol; bp83) and AlCl₃ (2.37 g, 17.8 mmol) was added at 0°C. The mixture was stirred at room temperature overnight. The mixture was then partitioned between ethyl acetate and water. The organics were extracted with ethyl acetate twice, washed with brine and dried with Na₂SO₄. This was concentrated down to give 2-bromo-7-methoxy-6-methyldibenzo[b,f]oxepin-10(11H)-one (1.90 g, 5.70 mmol, 96.4% yield).

[00171] Step F: A mixture of 2-bromo-7-methoxy-6-methyldibenzo[b,f]oxepin-10(11H)-one (1.90 g, 5.70 mmol) and selenium dioxide (0.949 g, 8.55 mmol) in dioxane (14 mL, 5.70 mmol) was heated to 90°C overnight. The mixture was then filtered through GF/F paper. Ethanol (0.263 g, 5.70 mmol) was added to the filtrate, followed by the addition of 1-methylguanidine hydrochloride (2.81 g, 25.7 mmol). Na₂CO₃ (12.8 mL, 25.7 mmol) was added, and this was heated to 90°C for 30 minutes. The mixture was then partitioned between DCM and water. The organics were extracted twice with DCM, washed with brine and dried with Na₂SO₄. The mixture was purified on a column using DCM:MeOH:NH₄OH (90:10:1) to give 2-amino-2'-bromo-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.984 g, 2.45 mmol, 42.9% yield) as a solid.

[00172] Step G: A mixture of 2-amino-2'-bromo-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.050 g, 0.124 mmol), 5-chloropyridin-3-ylboronic acid (0.0215 g, 0.137 mmol), Pd(PPh₃)₄ (0.0144 g, 0.0124 mmol) and Na₂CO₃ (0.155 mL, 0.311 mmol) in dioxane (2 mL, 0.124 mmol) was heated to 90°C overnight. The mixture was then partitioned between DCM and water. The organics were extracted with DCM twice, washed with brine and dried with Na₂SO₄. The mixture was then concentrated down to be purified on preparative HPLC to give 2-amino-2'-(5-chloropyridin-3-yl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.0201 g, 0.0462 mmol, 37.2% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.60 (1H), 8.50 (1H), 7.73 (1H), 7.46 (1H), 7.31 (1H), 7.28 (1H), 6.95 (1H), 6.54 (1H), 3.79 (3H), 3.11 (3H), 2.26 (3H); *m/z* (APCI-pos) *M*+1 = 435.1.

Example 30

2-amino-2'-(5-chloropyridin-3-yl)-1-methyl-7'-propylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00173] Step A: A solution of 2-(2-hydroxyphenyl)acetic acid (40.00 g, 262.9 mmol) and phenyltrimethylammonium bromide (98.83 g, 262.9 mmol) in ethanol (1315 mL, 262.9 mmol) was stirred at room temperature overnight. The mixture was evaporated then partitioned between ether and 1N HCl. The organic layer was washed with sodium bisulfate (aq), water, brine, dried and concentrated to give a residue that was purified by flash chromatography, eluting with a hexanes/ethyl acetate gradient. The resulting residue was triturated with hexanes to crystallize ethyl 2-(5-bromo-2-hydroxyphenyl)acetate (32.5 g, 125 mmol, 48%).

[00174] Step B: A mixture of ethyl 2-(5-bromo-2-hydroxyphenyl)acetate (6.0 g, 23.2 mmol), 5-chloropyridin-3-ylboronic acid (4.37 g, 27.8 mmol), Pd(PPh₃)₄ (0.535 g, 0.463 mmol) and Na₂CO₃ (28.9 mL, 57.9 mmol) in dioxane (60 mL, 23.2 mmol) was heated to 90°C overnight. The mixture was filtered through GF/F paper. The filtrate was then partitioned between ethyl acetate and 2N HCl. The organics were extracted with ethyl acetate twice, washed with brine and dried with Na₂SO₄. This was then concentrated down and purified on a column using ethyl acetate hexanes to give 2-(5-(5-chloropyridin-3-yl)-2-hydroxyphenyl)acetic acid (5.24 g, 19.9 mmol, 85.8% yield).

[00175] Step C: A few drops of H₂SO₄ (2.08 g, 21.2 mmol) were added to a mixture of 2-(5-(5-chloropyridin-3-yl)-2-hydroxyphenyl)acetic acid (5.6 g, 21.2 mmol) in MeOH (0.860 mL, 21.2 mmol; d 0.791). The mixture was refluxed overnight. The mixture was then partitioned between ethyl acetate and water. The organics were extracted twice with ethyl acetate, washed with brine and dried with Na₂SO₄. The mixture was then concentrated down and purified on a column using ethyl acetate hexanes to give methyl 2-(5-(5-chloropyridin-3-yl)-2-hydroxyphenyl)acetate (2.87 g, 10.3 mmol, 48.7% yield).

[00176] Step D: A mixture of methyl 2-(5-(5-chloropyridin-3-yl)-2-hydroxyphenyl)acetate (2.87 g, 10.3 mmol), 1-bromo-4-iodobenzene (11.7 g, 41.3 mmol), 2-(dimethylamino)acetic acid hydrochloride (0.866 g, 6.20 mmol), Cu(I)Cl (0.614 g, 6.20

mmol) and Cs_2CO_3 (8.42 g, 25.8 mmol) in dioxane (35 mL, 10.3 mmol) was purged with argon for 5 minutes. This was then heated to reflux for 2 hours under N_2 . The mixture was then filtered through Celite® and then partitioned between ethyl acetate and water. The organics were extracted with ethyl acetate twice, washed with brine and dried with Na_2SO_4 . This was then concentrated down to be purified on a column using ethyl acetate hexanes to give methyl 2-(2-(4-bromophenoxy)-5-(5-chloropyridin-3-yl)phenyl)acetate (1.21 g, 2.80 mmol, 27.1% yield).

[00177] Step E: A mixture of methyl 2-(2-(4-bromophenoxy)-5-(5-chloropyridin-3-yl)phenyl)acetate (1.21 g, 2.80 mmol) and NaOH (8.39 mL, 16.8 mmol) was stirred in ethanol (20 mL, 2.80 mmol) for 4 hours. The mixture was then partitioned between ethyl acetate and 1N HCl . The organics were extracted with ethyl acetate twice, washed with brine and dried with Na_2SO_4 . The mixture was then concentrated down to give 2-(2-(4-bromophenoxy)-5-(5-chloropyridin-3-yl)phenyl)acetic acid (1.17 g, 2.79 mmol, 99.9% yield).

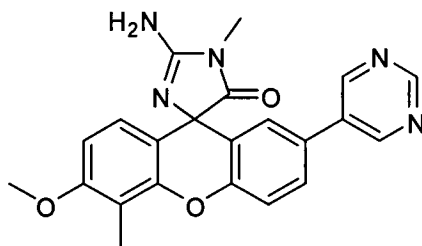
[00178] Step F: Oxalyl dichloride (0.287 mL, 0.573 mmol) was added to a mixture of 2-(2-(4-bromophenoxy)-5-(5-chloropyridin-3-yl)phenyl)acetic acid (0.200 g, 0.478 mmol) in DCM (4 mL, 0.478 mmol) at 0°C . A few drops of DMF were added, and the mixture was stirred at room temperature for 15 minutes. The mixture was then concentrated down to give an oil. The oil was taken up in DCE (4 mL, 0.478 mmol; bp83) and cooled to 0°C . AlCl_3 (0.191 g, 1.43 mmol) was added, and the mixture was refluxed for 2 hours. The mixture was then partitioned between ethyl acetate and water. The organics were extracted with ethyl acetate twice, washed with brine and dried with Na_2SO_4 . This was then concentrated down to be purified on a column using ethyl acetate and hexanes to give 8-bromo-2-(5-chloropyridin-3-yl)dibenzo[b,f]oxepin-10(11H)-one (0.061 g, 0.152 mmol, 31.9% yield).

[00179] Step G: A mixture of 8-bromo-2-(5-chloropyridin-3-yl)dibenzo[b,f]oxepin-10(11H)-one (0.061 g, 0.15 mmol) and selenium dioxide (0.037 g, 0.33 mmol) in dioxane (2 mL, 0.15 mmol) was heated to 90°C overnight. The mixture was then filtered through GF/F paper. Ethanol (2 mL, 0.15 mmol) was added to the filtrate, followed by the addition of 1-methylguanidine hydrochloride (0.075 g, 0.69 mmol). Na_2CO_3 (0.34 mL, 0.69 mmol) was added, and this was heated to 90°C for 30 minutes. The mixture was then partitioned between DCM and water. The organics were extracted twice with DCM, washed with brine and dried with Na_2SO_4 . The mixture was purified on a column using DCM:MeOH: NH_4OH (90:10:1) to give 2-amino-2'-bromo-7'-(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.022 g, 0.047 mmol, 31% yield) as a solid.

[00180] Step H: A mixture of 2-amino-2'-bromo-7'-(5-chloropyridin-3-yl)-1-

methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.015 g, 0.032 mmol), propylzinc(II) bromide (0.20 mL, 0.10 mmol) and Bis(tri-*t*-butylphosphine)palladium (0) (0.0016 g, 0.0032 mmol) in THF (1 mL, 0.032 mmol) was heated to 90°C for 4 hours. The mixture was filtered through some Celite®. The filtrate was concentrated down and purified on preparative HPLC to give 2-amino-2'-(5-chloropyridin-3-yl)-1-methyl-7'-propylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.0029 g, 0.0067 mmol, 21% yield) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 7.86 (1H), 7.61 (1H), 7.39 (1H), 7.34 (1H), 7.27 (2H), 7.22 (2H), 6.94 (1H), 3.30 (3H), 2.59 (2H), 1.61 (2H), 0.94 (3H); *m/z* (APCI-pos) *M*+1 = 433.1.

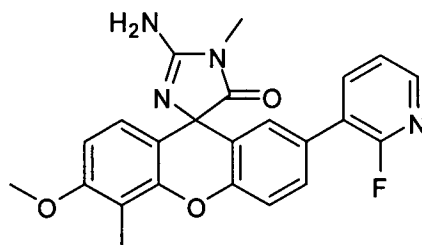
Example 31



2-amino-6'-methoxy-1,5'-dimethyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

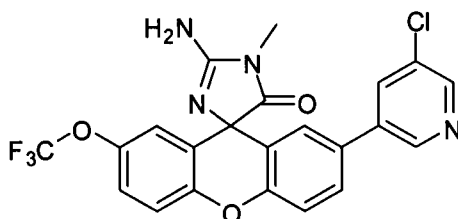
[00181] 2-Amino-6'-methoxy-1,5'-dimethyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedures of Example 29, substituting pyrimidin-5-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ¹H NMR (400 MHz, CDCl₃) δ 9.15 (1H), 8.81 (2H), 7.45 (1H), 7.29 (2H), 6.92 (1H), 6.51 (1H), 3.77 (3H), 3.10 (3H), 2.25 (3H); *m/z* (APCI-pos) *M*+1 = 402.1.

Example 32



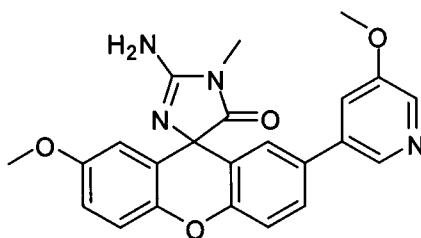
2-amino-2'-(2-fluoropyridin-3-yl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00182] 2-Amino-2'-(2-fluoropyridin-3-yl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according the procedures of Example 29, substituting 2-fluoropyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (1H), 7.81 (1H), 7.52 (1H), 7.41 (1H), 7.32 (1H), 7.24 (1H), 7.02 (1H), 6.62 (1H), 3.83 (3H), 3.11 (3H), 2.30 (3H); *m/z* (APCI-pos) *M*+1 = 419.1.

Example 33

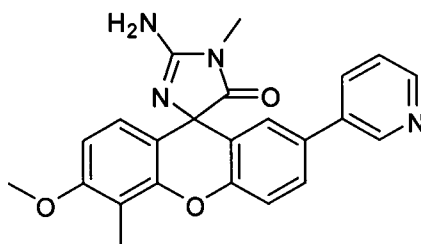
2-amino-2'-(5-chloropyridin-3-yl)-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00183] 2-Amino-2'-(5-chloropyridin-3-yl)-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedures of Example 25, substituting 4-(trifluoromethoxy)phenol for 4-methoxyphenol. ¹H NMR (400 MHz, CDCl₃) δ 8.65 (1H), 8.54 (1H), 7.79 (1H), 7.53 (1H), 7.34 (1H), 7.27 (1H), 7.22 (1H), 7.05 (1H), 3.13 (3H); *m/z* (APCI-pos) *M*+1 = 475.1.

Example 34

2-amino-2'-methoxy-7'-(5-methoxypyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00184] 2-Amino-2'-methoxy-7'-(5-methoxypyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to Example 25, substituting 5-methoxypyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.36 (1H), 8.25 (1H), 7.49 (1H), 7.33 (1H), 7.25 (1H), 7.14 (1H), 6.88 (1H), 6.69 (1H), 3.90 (3H), 3.74 (3H), 3.12 (3H); *m/z* (APCI-pos) *M*+1 = 417.1.

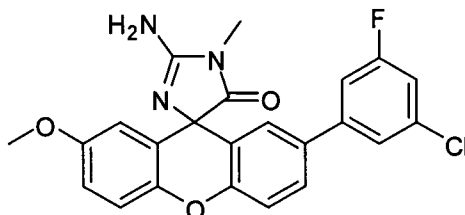
Example 35

2-amino-6'-methoxy-1,5'-dimethyl-2'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00185] 2-Amino-6'-methoxy-1,5'-dimethyl-2'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedures of Example 29, substituting

pyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.75 (1H), 8.56 (1H), 7.77 (1H), 7.50 (1H), 7.36 (1H), 7.32 (2H), 6.99 (1H), 6.58 (1H), 3.80 (3H), 3.12 (3H), 2.28 (3H); m/z (APCI-pos) $M+1 = 401.1$.

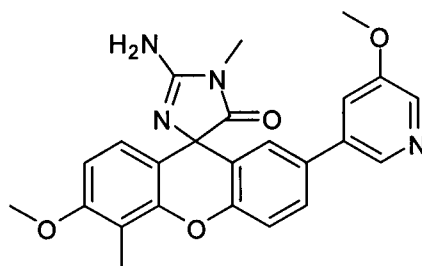
Example 36



2-amino-2'-(3-chloro-5-fluorophenyl)-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00186] 2-Amino-2'-(3-chloro-5-fluorophenyl)-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedures of Example 25, substituting 3-chloro-5-fluorophenylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 7.46 (1H), 7.28 (1H), 7.23 (1H), 7.14 (1H), 7.05 (2H), 6.88 (1H), 6.69 (1H), 3.76 (3H), 3.13 (3H); m/z (APCI-pos) $M+1 = 438.1$.

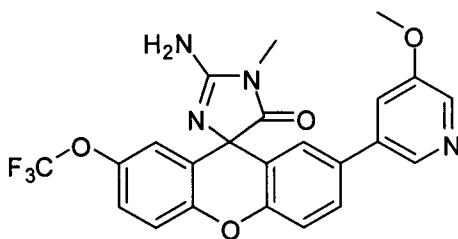
Example 37



2-amino-6'-methoxy-2'-(5-methoxypyridin-3-yl)-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00187] 2-Amino-6'-methoxy-2'-(5-methoxypyridin-3-yl)-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared using the procedures of Example 29, substituting 5-methoxypyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.35 (1H), 8.24 (1H), 7.47 (1H), 7.34 (1H), 7.27 (1H), 7.25 (1H), 6.95 (1H), 6.54 (1H), 3.90 (3H), 3.79 (3H), 3.10 (3H), 2.27 (3H); m/z (APCI-pos) $M+1 = 431.1$.

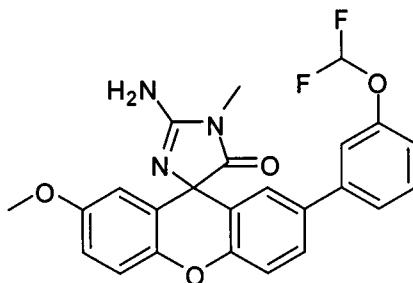
Example 38



2-amino-2'-(5-methoxypyridin-3-yl)-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00188] 2-Amino-2'-(5-methoxypyridin-3-yl)-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to the procedures of Example 33, substituting 5-methoxypyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.68 (1H), 8.49 (1H), 8.20 (1H), 7.94 (1H), 7.83 (1H), 7.53 (1H), 7.50 (3H), 4.06 (3H), 3.32 (3H); m/z (APCI-pos) $M+1 = 471.1$.

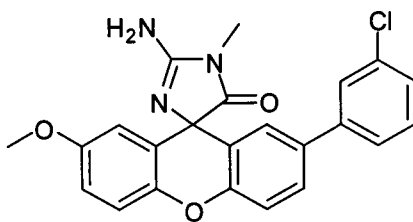
Example 39



2-amino-2'-(3-(difluoromethoxy)phenyl)-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00189] 2-Amino-2'-(3-(difluoromethoxy)phenyl)-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to the procedures of Example 25, substituting 3-(difluoromethoxy)phenylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 7.49 (1H), 7.38 (1H), 7.32 (1H), 7.22 (1H), 7.13 (1H), 7.06 (1H), 6.88 (1H), 6.69 (1H), 6.54 (1H), 3.74 (3H), 3.11 (3H); m/z (APCI-pos) $M+1 = 452.1$.

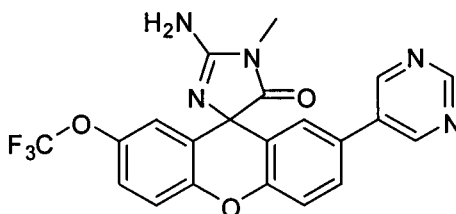
Example 40



2-amino-2'-(3-chlorophenyl)-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00190] 2-Amino-2'-(3-chlorophenyl)-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to the procedure of Example 25, substituting 3-chlorophenylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 7.47 (1H), 7.45 (1H), 7.32 (3H), 7.29 (1H), 7.21 (1H), 7.12 (1H), 6.88 (1H), 6.69 (1H), 3.74 (3H), 3.15(3H); m/z (APCI-pos) $M+1 = 420.1$.

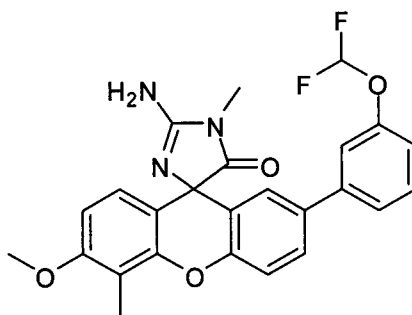
Example 41



2-amino-1-methyl-2'-(pyrimidin-5-yl)-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00191] 2-Amino-1-methyl-2'-(pyrimidin-5-yl)-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according the procedures of Example 33, substituting pyrimidin-5-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 9.16 (1H), 9.08 (1H), 7.90 (1H), 7.82 (1H), 7.51 (4H), 3.31 (3H); m/z (APCI-pos) $M+1 = 442.1$.

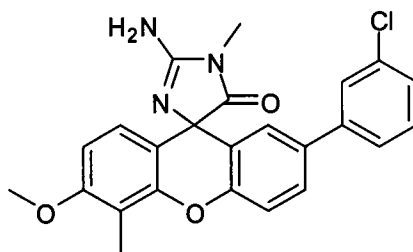
Example 42



2-amino-2'-(3-(difluoromethoxy)phenyl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00192] 2-Amino-2'-(3-(difluoromethoxy)phenyl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared using the procedure of Example 29, substituting 3-(difluoromethoxy)phenylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 7.45 (1H), 7.36 (1H), 7.30 (2H), 7.24 (1H), 7.21 (1H), 7.05 (1H), 6.93 (1H), 6.53 (1H), 6.48 (1H), 3.76 (3H), 3.06 (3H), 2.25 (3H); m/z (APCI-pos) $M+1 = 466.2$.

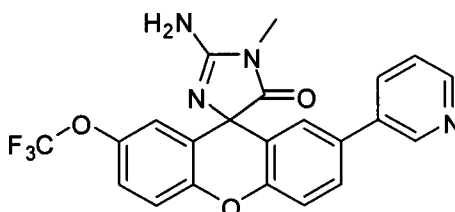
Example 43



2-amino-2'-(3-chlorophenyl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00193] 2-Amino-2'-(3-chlorophenyl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared using the procedure of Example 29, substituting 3-chlorophenylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 7.48 (2H), 7.34 (3H), 7.28 (2H), 7.25 (1H), 6.98 (1H), 6.57 (1H), 3.80 (3H), 3.11 (3H), 2.27 (3H); m/z (APCI-pos) $M+1 = 434.1$.

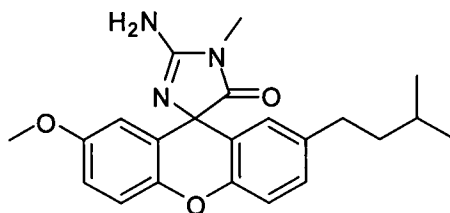
Example 44



2-amino-1-methyl-2'-(pyridin-3-yl)-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00194] 2-Amino-1-methyl-2'-(pyridin-3-yl)-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according the procedures of Example 33, substituting pyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.89 (1H), 8.65 (1H), 8.43 (1H), 7.85 (1H), 7.80 (2H), 7.46 (4H), 3.25 (3H); m/z (APCI-pos) $M+1 = 441.1$.

Example 45

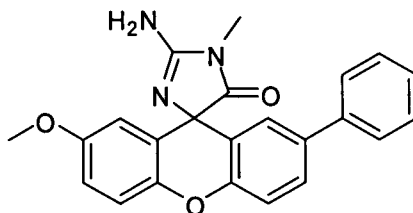


2-amino-2'-isopentyl-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00195] A mixture of 2-amino-2'-bromo-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.040 g, 0.103 mmol) and isopentylzinc(II) bromide (0.515 mL, 0.258 mmol) and Bis(tri-*t*-butylphosphine)palladium (0) (0.00527 g, 0.0103 mmol) was heated to

90°C overnight. The mixture was then purified on a column using DCM:MeOH:NH₄OH (90:10:1) to give 2-amino-2'-isopentyl-7'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.0172 g, 0.0453 mmol, 44.0% yield) as a solid. *m/z* (APCI-pos) *M*+1 = 380.2.

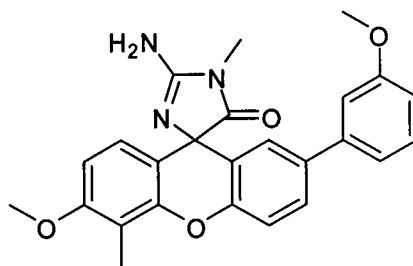
Example 46



2-amino-2'-methoxy-1-methyl-7'-phenylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00196] 2-Amino-2'-methoxy-1-methyl-7'-phenylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to the procedure of Example 25, substituting phenylboronic acid for 5-chloropyridin-3-ylboronic acid. *m/z* (APCI-pos) *M*+1 = 386.1.

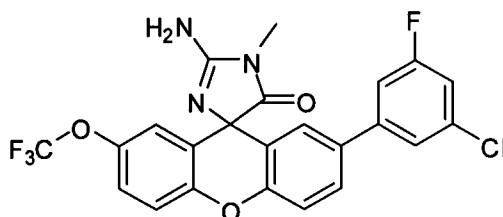
Example 47



2-amino-6'-methoxy-2'-(3-methoxyphenyl)-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00197] 2-Amino-6'-methoxy-2'-(3-methoxyphenyl)-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared using the procedure of Example 29, substituting 3-methoxyphenylboronic acid for 5-chloropyridin-3-ylboronic acid. *m/z* (APCI-pos) *M*+1 = 430.2.

Example 48

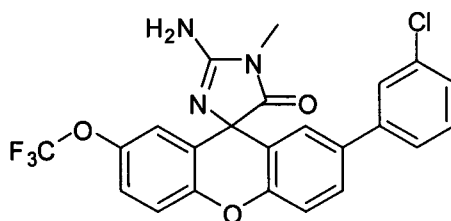


2-amino-2'-(3-chloro-5-fluorophenyl)-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00198] 2-Amino-2'-(3-chloro-5-fluorophenyl)-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according the

procedures of Example 33, substituting 3-chloro-5-fluorophenylboronic acid for 5-chloropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 492.1$.

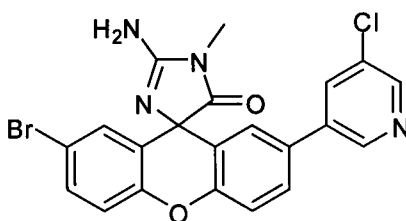
Example 49



2-amino-2'-(3-chlorophenyl)-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00199] 2-Amino-2'-(3-chlorophenyl)-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according the procedures of Example 33, substituting 3-chlorophenylboronic acid for 5-chloropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 474.1$.

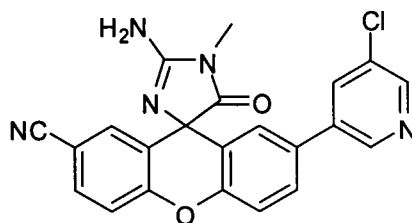
Example 50



2-amino-2'-bromo-7'-(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00200] 2-Amino-2',7'-dibromo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (54 mg, 0.12 mmol; Example 26, Step D) and 5-chloropyridin-3-ylboronic acid (19 mg, 0.12 mmol) were diluted with dioxane (1 mL) followed by the addition of $\text{Pd(PPh}_3)_4$ (7.1 mg, 0.0062 mmol) and Na_2CO_3 (185 μL , 0.37 mmol). The reaction was sealed, heated to 85°C and stirred for 12 hours. The reaction was loaded directly onto silica gel and eluted with 1-10% Methanol/DCM (1% NH_4OH) to afford 2-amino-2'-bromo-7'-(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (15 mg, 0.032 mmol, 26% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.62 (d, 1H), 8.52 (d, 1H), 7.75 (m, 1H), 7.50 (dd, 1H), 7.40 (dd, 1H), 7.25-7.35 (m, 3H), 7.10 (d, 1H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 471.0$.

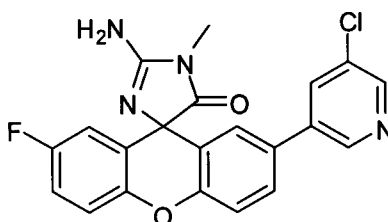
Example 51



2-amino-2'-(5-chloropyridin-3-yl)-1-methyl-5-oxo-1,5-dihydrospiro[imidazole-4,9'-xanthene]-7'-carbonitrile

[00201] 2-Amino-2'-bromo-7'-(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (30 mg, 0.064 mmol; Example 50), $\text{Zn}(\text{CN})_2$ (16 mg, 0.14 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (3.7 mg, 0.0032 mmol) were diluted with DMF (500 μL). The reaction was heated to 110°C and stirred for 30 minutes in the microwave. The reaction was allowed to cool, diluted with ethyl acetate and water. The organics were dried over MgSO_4 , filtered and concentrated. The residue was purified on silica gel eluting with 1-10% methanol/DCM (1% NH_4OH) to afford 2-amino-2'-(5-chloropyridin-3-yl)-1-methyl-5-oxo-1,5-dihydrospiro[imidazole-4,9'-xanthene]-7'-carbonitrile (3.0 mg, 0.0072 mmol, 11% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.65 (d, 1H), 8.55 (d, 1H), 7.82 (m, 1H), 7.50-7.70 (m, 3H), 7.30-7.40 (m, 3H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 416.1$.

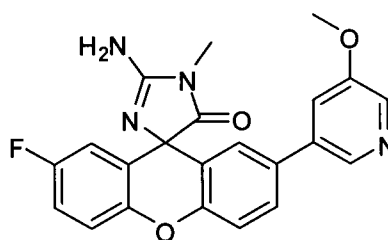
Example 52



2-amino-2'-(5-chloropyridin-3-yl)-7'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00202] Prepared according to the procedure of Example 25, substituting 4-fluorophenol for 4-methoxyphenol. m/z (APCI-pos) $M+1 = 409.1$.

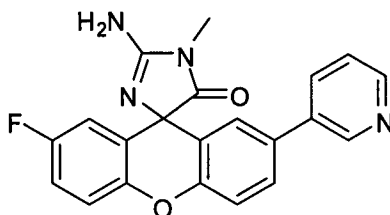
Example 53



2-amino-2'-fluoro-7'-(5-methoxypyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00203] Prepared according to the procedure of Example 52, substituting 5-methoxypyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 405.1$.

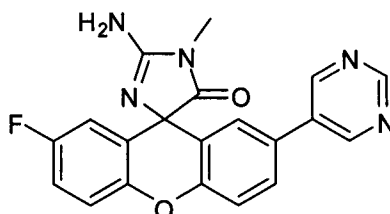
Example 54



2-amino-2'-fluoro-1-methyl-7'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00204] Prepared according to the procedure of Example 52, substituting pyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 375.1$.

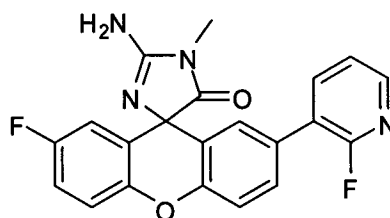
Example 55



2-amino-2'-fluoro-1-methyl-7'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00205] Prepared according to the procedure of Example 52, substituting pyrimidin-5-ylboronic acid for 5-chloropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 376.1$.

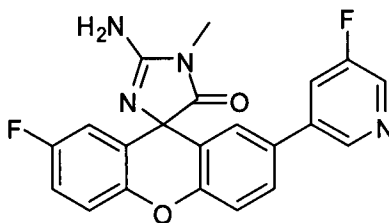
Example 56



2-amino-2'-fluoro-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00206] Prepared according to the procedure of Example 52, substituting 2-fluoropyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (m, 1H), 7.85 (m, 1H), 7.55 (m, 1H), 7.20-7.40 (m, 4H), 7.10 (m, 1H), 6.95 (m, 1H), 3.15 (s, 3H); m/z (APCI-pos) $M+1 = 393.1$.

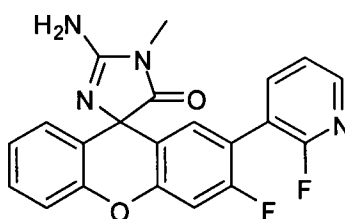
Example 57



2-amino-2'-fluoro-7'-(5-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00207] Prepared according to the procedure of Example 52, substituting 5-fluoropyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 393.1$.

Example 58



2-amino-3'-fluoro-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00208] Step A: A slurry of ethyl 2-(2-hydroxyphenyl)acetate (2.10 g, 11.7 mmol), 4-bromo-3-fluorophenylboronic acid (5.10 g, 23.3 mmol), diacetoxycopper (2.12 g, 11.7 mmol), and triethylamine (3.25 mL, 23.3 mmol) in CH_2Cl_2 (117 mL) was stirred at room temperature for 24 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried and concentrated, and the residue was by flash chromatography eluting with an ethyl acetate/hexanes gradient to afford ethyl 2-(2-(4-bromo-3-fluorophenoxy)phenyl)acetate (1.70g, 4.81 mmol, 41%).

[00209] Step B: A solution of ethyl 2-(2-(4-bromo-3-fluorophenoxy)phenyl)acetate (1.70 g, 4.81 mmol) and LiOH hydrate (0.61 g, 14.4 mmol) in MeOH (12 mL) and water (4.81 ml) was stirred at room temperature overnight. The mixture was acidified with 2N HCl then extracted with ethyl acetate (3 X). The organic layers were dried and concentrated to give 2-(2-(4-bromo-3-fluorophenoxy)phenyl)acetic acid (1.56 g, 4.80 mmol, 99%), which was used without purification.

[00210] Step C: Oxalyl chloride (0.90 mL, 9.84 mmol) was added to a solution of 2-(2-(4-bromo-3-fluorophenoxy)phenyl)acetic acid (1.56 g, 4.80 mmol) in CH_2Cl_2 (25 mL), followed by 3 drops of DMF. The solution was stirred at room temperature for 1 hour and then concentrated to give 2-(2-(4-bromo-3-fluorophenoxy)phenyl)acetyl chloride (1.68 g, 4.80 mmol, 99%), which was used without purification.

[00211] Step D: AlCl_3 (1.31 g, 9.84 mmol) was added to a solution of 2-(2-(4-bromo-

3-fluorophenoxy)phenyl)acetyl chloride (1.68 g, 4.80 mmol) in 1,2-dichloroethane (25 mL, 4.92 mmol), and the resulting solution was stirred at room temperature for 1 hour. The reaction was quenched with water and extracted with ether (3 X). The combined organic layers were dried and concentrated to give a residue that was purified by flash chromatography, eluting with an ethyl acetate/hexanes gradient to afford 8-bromo-7-fluorodibenzo[b,f]oxepin-10(11H)-one (0.775 g, 2.52 mmol, 53%).

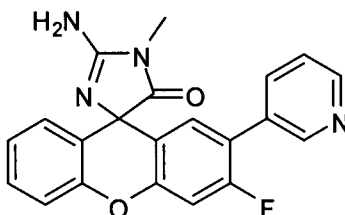
[00212] Step E: A nitrogen-degassed solution 8-bromo-7-fluorodibenzo[b,f]oxepin-10(11H)-one (0.775 g, 2.52 mmol) in ethyl acetate (5.05 mL, 2.52 mmol) and CHCl_3 (5.05 mL, 2.52 mmol) was heated to 80°C. The sparging was continued as CuBr_2 (1.13 g, 5.05 mmol) was slowly added. Sparging was discontinued, and the reaction mixture was heated at 80°C for 1 day under nitrogen. The reaction mixture was filtered, and the filter cake was thoroughly washed with CH_2Cl_2 . The filtrate was concentrated. The residue was dissolved in ether, washed with water, NaHCO_3 , brine, dried and concentrated to afford 8,11-dibromo-7-fluorodibenzo[b,f]oxepin-10(11H)-one (0.974 g, 2.52 mmol, 99%), which was used without purification.

[00213] Step F: DMSO (9 mL) was added to a flask containing 8,11-dibromo-7-fluorodibenzo[b,f]oxepin-10(11H)-one (0.97 g, 2.52 mmol), and then KI (0.419 g, 2.52 mmol) and Na_2CO_3 (0.267 g, 2.52 mmol) were added. The resulting mixture was stirred at room temperature for 30 minutes. Upon completion as determined by LCMS and TLC, 1-methylguanidine hydrochloride (0.83 g, 7.57 mmol) was added, followed by aqueous Na_2CO_3 (2.50 mL, 5.05 mmol). The mixture was heated to 80°C for 1 hour. The mixture was diluted with ethyl acetate and water. The aqueous layer was separated and extracted with EtOAc (2 X). The combined organic layers were washed with brine (3 X), dried and concentrated to give a residue that was purified by flash chromatography, eluting with a $\text{CH}_2\text{Cl}_2/\text{MeOH}$ gradient to give 2-amino-2'-bromo-3'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.240 g, 0.638 mmol, 25% yield).

[00214] Step G: A biphasic mixture of 2-amino-2'-bromo-3'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (15.0 mg, 0.04 mmol), 2-fluoropyridin-3-ylboronic acid (7.02 mg, 0.050 mmol), $\text{Pd}(\text{PPh}_3)_4$ (4.61 mg, 0.004 mmol) and Na_2CO_3 (2M, 59.8 μL) in dioxane (199 μL , 0.040 mmol) in a pressure vial was degassed for 5 minutes with nitrogen and then capped and stirred at 100°C overnight. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by reversed-phase HPLC to afford 2-amino-3'-fluoro-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (6.1 mg, 0.016 mmol, 39%). ^1H NMR (400 MHz, CD_3OD) δ 8.27 (d, $J=3.9$ Hz,

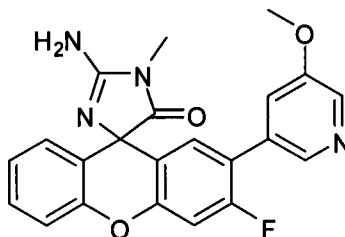
1H), 7.99 (t, J=7.0 Hz, 1H), 7.67 (d, J=7.8 Hz, 1H), 7.55 (t, J=7.8 Hz, 1H), 7.42 (m, 2H), 7.37 (d, J=7.8 Hz, 1H), 7.28 (m, 2H), N-Me under solvent reference. m/z (APCI-pos) $M+1 = 393.1$.

Example 59



2-amino-3'-fluoro-1-methyl-2'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one
[00215] 2-Amino-3'-fluoro-1-methyl-2'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one (13.2 mg, 0.035 mmol, 88%) was prepared according to the procedure of Example 58, substituting pyridin-3-ylboronic acid (6.13 mg, 0.050 mmol) for 2-fluoropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 375.1$.

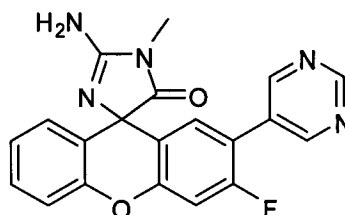
Example 60



2-amino-3'-fluoro-2'-(5-methoxypyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00216] 2-Amino-3'-fluoro-2'-(5-methoxypyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (10.6 mg, 0.026 mmol, 66%) was prepared according to the procedure of Example 58, substituting 5-methoxypyridin-3-ylboronic acid (7.62 mg, 0.0498 mmol) for 2-fluoropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 405.1$.

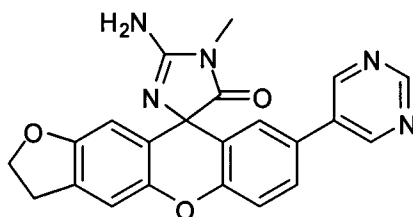
Example 61



2-amino-3'-fluoro-1-methyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one
[00217] 2-Amino-3'-fluoro-1-methyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one (11.4 mg, 0.030 mmol, 76%) was prepared according to the procedure of Example

58, substituting pyrimidin-5-ylboronic acid (6.18 mg, 0.050 mmol) for 2-fluoropyridin-3-ylboronic acid. m/z (APCI-pos) $M+1 = 376.1$.

Example 62



2'-amino-1'-methyl-8-(pyrimidin-5-yl)-2,3-dihydrospiro[furo[2,3-b]xanthene-10,4'-imidazol]-5'-(1'H)-one

[00218] Step A: The same procedure was followed as in Example 58, Step A, substituting 2,3-dihydrobenzofuran-5-ylboronic acid (1.70 g, 10.4 mmol) for 4-bromo-3-fluorophenylboronic acid to afford ethyl 2-(5-bromo-2-(2,3-dihydrobenzofuran-5-yloxy)phenyl)acetate (0.600 g, 1.59 mmol, 31%).

[00219] Step B: The same procedure was followed as in Example 58, Step B, substituting ethyl 2-(5-bromo-2-(2,3-dihydrobenzofuran-5-yloxy)phenyl)acetate (600 mg, 1.59 mmol) for ethyl 2-(2-(4-bromo-3-fluorophenoxy)phenyl)acetate to afford 2-(5-bromo-2-(2,3-dihydrobenzofuran-5-yloxy)phenyl)acetic acid (0.555 g, 1.59 mmol, 99%).

[00220] Step C: The same procedure was followed as in Example 58, Step C, substituting 2-(5-bromo-2-(2,3-dihydrobenzofuran-5-yloxy)phenyl)acetic acid (0.555 g, 1.59 mmol) for 2-(2-(4-bromo-3-fluorophenoxy)phenyl)acetic acid to afford 2-(5-bromo-2-(2,3-dihydrobenzofuran-5-yloxy)phenyl)acetyl chloride (0.584 g, 1.59 mmol, 99%).

[00221] Step D: The same procedure was followed as in Example 58, Step D, substituting 2-(5-bromo-2-(2,3-dihydrobenzofuran-5-yloxy)phenyl)acetyl chloride (0.584 g, 1.59 mmol) for 2-(2-(4-bromo-3-fluorophenoxy)phenyl)acetyl chloride to afford 8-bromo-2,3-dihydrobenzo[b]benzofuro[6,5-f]oxepin-11(10H)-one (0.12 g, 0.36 mmol, 23%).

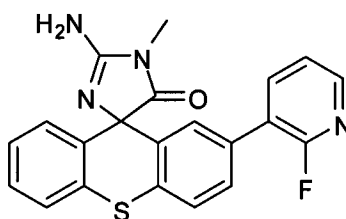
[00222] Step E: The same procedure was followed as in Example 58, Step E, substituting 8-bromo-2,3-dihydrobenzo[f]benzofuro[5,6-b]oxepin-11(10H)-one (114 mg, 0.344 mmol) for 8-bromo-7-fluorodibenzo[b,f]oxepin-10(11H)-one to afford 8,10-dibromo-2,3-dihydrobenzo[f]benzofuro[5,6-b]oxepin-11(10H)-one (141 mg, 0.344 mmol, 99%).

[00223] Step F: The same procedure was followed as in Example 58, Step F, substituting 8,11-dibromo-2,3-dihydrobenzo[f]benzofuro[5,6-b]oxepin-10(11H)-one (141 mg, 0.344 mmol) for 8,11-dibromo-7-fluorodibenzo[b,f]oxepin-10(11H)-one to afford 2'-amino-8-bromo-1'-methyl-2,3-dihydrospiro[furo[2,3-b]xanthene-10,4'-imidazol]-5'-(1'H)-one

(17 mg, 0.043 mmol, 12%).

[00224] Step G: The same procedure was followed as in Example 58, Step G, substituting 2'-amino-8-bromo-1'-methyl-2,3-dihydrospiro[furo[2,3-b]xanthene-10,4'-imidazol]-5'(1H)-one (15 mg, 0.0375 mmol) for 2-amino-2'-bromo-3'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one to afford 2'-amino-1'-methyl-8-(pyrimidin-5-yl)-2,3-dihydrospiro[furo[2,3-b]xanthene-10,4'-imidazol]-5'(1H)-one (8.3 mg, 0.021 mmol, 55%).

Example 63



2-amino-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one

[00225] Step A: A mixture of 1-bromo-4-nitrobenzene (25.0 g, 124 mmol) and tert-butyl 2-chloroacetate (19.42 mL, 136.1 mmol) in DMF (250 mL) was slowly added to a solution of KOtBu (1M in THF, 309 mL) in DMF (500 mL) at 0°C. The reaction was stirred at 0°C for 3 hours, then quenched with 5% KHSO₄ and extracted with ethyl acetate (3 X). The combined organic layers were washed with water and brine, dried and concentrated to give a residue, which was purified by flash chromatography, eluting with 20:1 hexane/ethyl acetate to afford tert-butyl 2-(5-bromo-2-nitrophenyl)acetate (28.2 g, 89.2 mmol, 72%). HPLC Rt = 3.17 minutes.

[00226] Step B: Raney nickel (0.380 g, 4.44 mmol) was added to a solution of tert-butyl 2-(5-bromo-2-nitrophenyl)acetate (28.1 g, 88.7 mmol) in ethanol (444 mL), and the mixture was evacuated and purged with nitrogen and then introduced to 50 psi hydrogen for 24 hours in a Parr reactor. The reaction mixture was filtered through GF/F paper, and the filtrate was evaporated to give a residue that was purified by flash chromatography eluting with 15% ethyl acetate/hexane to afford tert-butyl 2-(2-amino-5-bromophenyl)acetate (22.4 g, 78.3 mmol, 88%). HPLC Rt = 2.99 min.

[00227] Step C: tert-Butyl 2-(2-amino-5-bromophenyl)acetate (5.00 g, 17.5 mmol) was added to sulfuric acid (concentrated, 87 mL) at 0°C, and the mixture was heated to 50°C until dissolved. The solution was cooled to 0°C, and NaNO₂ (2.65 g, 38.4 mmol) dissolved in a minimal amount of water was slowly added to this solution. The resulting mixture was stirred at 0°C for 10 minutes. Nitrogen was bubbled through the reaction mixture for 5

minutes. The reaction was poured into flask containing KI (17.4 g, 105 mmol) in water (25 mL) at 0°C. The resulting tar was dissolved with DCM, and 25% NaHSO₃ (aq) was added to this mixture. The layers were separated, and the aqueous layer was extracted with DCM (3 X). The combined organics were washed with NaHSO₃ (2 X), brine, dried, and concentrated. The residue was purified by flash chromatography eluting with hexane/ethyl acetate +1% AcOH gradient to afford 2-(5-bromo-2-iodophenyl)acetic acid (3.20 g, 9.39 mmol, 54%). HPLC Rt = 2.55 minutes.

[00228] Step D: A pressure vial was charged with K₂CO₃ (134 mg, 0.968 mmol), 2-(5-bromo-2-iodophenyl)acetic acid (300 mg, 0.880 mmol), benzenethiol (126 mg, 1.14 mmol), Cu(I)I (4.19 mg, 0.0220 mmol) and N-methylpyrrolidone ("NMP") (170 µL, 1.76 mmol). The vial was sealed and stirred on a preheated block for 1day at 100°C. The reaction mixture was filtered, and the filter cake was washed with ether. The filtrate was concentrated, and the residue was purified by flash chromatography, eluting with hexanes/ethyl acetate +1% AcOH to afford 2-(5-bromo-2-(phenylthio)phenyl)acetic acid (277 mg, 0.857 mmol, 97%). HPLC Rt = 2.96 minutes.

[00229] Step E: Water (2.02 g, 112 mmol) was added to a flask containing polyphosphoric acid (20.0 g, 204 mmol), followed by 2-(5-bromo-2-(phenylthio)phenyl)acetic acid (.220 g, 0.681 mmol). A reflux condenser was added to the flask, and the mixture was stirred at 140°C for 1day, adding DCM dropwise through the condenser to facilitate stirring when necessary. The mixture was quenched with ice and extracted with DCM (3 X). The combined organic layers were dried and concentrated to afford 2-bromodibenzo[b,f]thiepin-10(11H)-one (166 mg, 0.544 mmol, 80%). HPLC Rt = 3.41 minutes.

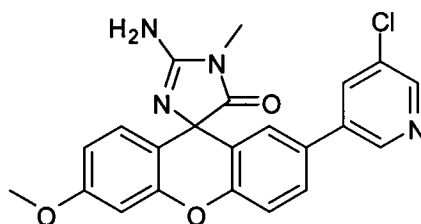
[00230] Step F: A solution of 2-bromodibenzo[b,f]thiepin-10(11H)-one (149 mg, 0.488 mmol) in ethyl acetate (1.00 mL) and CHCl₃ (1.00 mL) was degassed with nitrogen sparging. The mixture was heated to 80°C. The sparging was continued as CuBr₂ (0.218 g, 0.976 mmol) was slowly added. The reaction mixture turned green with addition and the color was allowed to disappear before adding the next portion of CuBr₂. After addition, the reaction mixture was stirred for 2 hours and then filtered through GF/F paper. The solid was washed with CHCl₃, and the filtrate was concentrated. The residue was dissolved in ether, washed with water, NaHCO₃, then brine, dried and concentrated to afford 2,11-dibromodibenzo[b,f]thiepin-10(11H)-one (185 mg, 0.49 mmol, 99%). HPLC Rt = 3.59 minutes.

[00231] Step G: 2,11-Dibromodibenzo[b,f]thiepin-10(11H)-one (185 mg, 0.49 mmol)

was added to a solution of KI (81 mg, 0.49 mmol), Na₂CO₃ (52 mg, 0.49 mmol) in DMSO (1.60 mL), and the resulting solution was stirred at ambient temperature for 15 minutes. Na₂CO₃ (2.0M in water, 1 mL) and 1-methylguanidine hydrochloride (215 mg, 1.96 mmol) were added to this mixture, and the mixture was heated at 80°C for 1 hour. The reaction mixture was cooled to room temperature, then diluted with ethyl acetate and washed with brine (3 X). The organic layer was concentrated to give a residue that was purified by flash chromatography eluting with a DCM/MeOH gradient to afford 2-amino-2'-bromo-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one (80 mg, 0.214 mmol, 44%). *m/z* (APCI-pos) *M*+1 = 374.0, 376.0.

[00232] Step H: The same procedure was followed as in Example 58, Step G, substituting 2-fluoropyridin-3-ylboronic acid (4.71 mg, 0.033 mmol) to afford 2-amino-2'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one (4.0 mg, 0.010 mmol, 38 %). *m/z* (APCI-pos) *M*+1 = 391.4.

Example 64



2-amino-2'-(5-chloropyridin-3-yl)-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00233] Step A: Potassium carbonate (0.7132 g, 5.160 mmol) was added to a solution of 3-methoxyphenol (0.5595 mL, 5.160 mmol) and methyl 2-(2-fluoro-5-nitrophenyl)acetate (1.00 g, 4.691 mmol) in DMSO (6 mL) degassed with argon, and the reaction was heated to 80°C overnight. It was diluted with EtOAc and washed with 10% citric acid, bicarbonate, and brine. It was dried over Na₂SO₄, filtered, and concentrated. It was purified on silica gel to yield methyl 2-(2-(3-methoxyphenoxy)-5-nitrophenyl)acetate (0.929 g, 2.928 mmol, 62.4% yield).

[00234] Step B: Palladium on carbon (0.312 g, 0.146 mmol) was added to a solution of methyl 2-(2-(3-methoxyphenoxy)-5-nitrophenyl)acetate (0.929 g, 2.93 mmol) in MeOH (15 mL), and the reaction was put under 1 atmosphere of H₂. It was stirred vigorously overnight. It was flushed with argon, filtered, and concentrated to yield methyl 2-(5-amino-2-(3-methoxyphenoxy)phenyl)acetate (0.841 g, 2.93 mmol, 100.0% yield). It was taken onto the next reaction without further purification.

[00235] Step C: *tert*-Butyl nitrite (0.425 mL, 3.22 mmol) was added to a suspension of copper(II) bromide (0.719 g, 3.22 mmol) in MeCN (15 mL) at 0°C, and the reaction was allowed to stir for 30 minutes at this temperature. Methyl 2-(5-amino-2-(3-methoxyphenoxy)phenyl)acetate (.841 g, 2.93 mmol) in MeCN (~5 mL) was added dropwise to the reaction mixture, and the reaction was stirred at 0°C for 1 hour. It was warmed to room temperature, partitioned between EtOAc and water, and the organic layer was collected. This layer was washed with saturated NH₄Cl with 1M NH₄OH and brine, dried over Na₂SO₄, filtered, and concentrated. It was purified on silica gel to yield methyl 2-(5-bromo-2-(3-methoxyphenoxy)phenyl)acetate (0.664 g, 1.89 mmol, 64.6% yield).

[00236] Step D: Sodium hydroxide (0.756 mL, 3.78 mmol) was added to a solution of methyl 2-(5-bromo-2-(3-methoxyphenoxy)phenyl)acetate (0.664 g, 1.89 mmol) in 2:1 MeOH/water (10 mL), and the reaction was allowed to stir overnight. It was diluted with water and acidified with 5M HCl until a pH of about 1 was reached. It was extracted twice with DCM, and the extracts were dried over Na₂SO₄, filtered, and concentrated to yield 2-(5-bromo-2-(3-methoxyphenoxy)phenyl)acetic acid (0.581 g, 1.72 mmol, 91.1% yield).

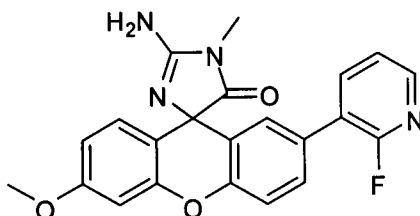
[00237] Step E: A suspension of 2-(5-bromo-2-(3-methoxyphenoxy)phenyl)acetic acid (0.591 g, 1.75 mmol) in polyphosphoric acid (5.15 g, 52.6 mmol) was heated to 100°C with stirring overnight. It was poured onto water, and the solids were collected via filtration. They were then purified on silica gel to yield 2-bromo-7-methoxydibenzo[b,f]oxepin-10(11H)-one (0.447 g, 1.40 mmol, 79.9% yield).

[00238] Step F: Selenium dioxide (0.326 g, 2.94 mmol) was added to a solution of 2-bromo-7-methoxydibenzo[b,f]oxepin-10(11H)-one (0.447 g, 1.40 mmol) in dioxane (7 mL) with about 10 drops of water, and the reaction was heated to reflux overnight. It was cooled to room temperature and filtered, and the filtrate was concentrated to yield 2-bromo-7-methoxydibenzo[b,f]oxepine-10,11-dione (0.467 g, 1.40 mmol, 100% yield), which was taken onto the next reaction without further purification.

[00239] Step G: Sodium carbonate (0.669 g, 6.31 mmol) and 1-methylguanidine hydrochloride (0.691 g, 6.31 mmol) were added to a solution of 2-bromo-7-methoxydibenzo[b,f]oxepine-10,11-dione (0.467 g, 1.40 mmol) in 1:1 EtOH/dioxane (7 mL), and the reaction was heated to reflux for 2 hours. It was cooled to room temperature, diluted with water, and extracted twice with DCM. The extracts were dried over Na₂SO₄, filtered, and concentrated. It was purified on the reverse phase HPLC to yield 2-amino-2'-bromo-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one formate (.089 g, 0.205 mmol, 14.6% yield).

[00240] Step H: Aqueous sodium carbonate (0.19 g, 0.36 mmol) was added to a solution of 2-amino-2'-bromo-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.044 g, 0.10 mmol) and 5-chloropyridin-3-ylboronic acid (0.021 g, 0.13 mmol) in dioxane (1 mL), and the reaction was degassed with argon. Palladium tetrakis (0.0059 g, 0.0051 mmol) was added to the reaction mixture, and the reaction was heated to 100°C overnight. It was purified on silica gel to yield 2-amino-2'-(5-chloropyridin-3-yl)-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.031 g, 0.074 mmol, 73% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.60 (d, 1H), 8.50 (d, 1H), 7.70 (t, 1H), 7.48 (dd, 1H), 7.30 (d, 1H), 7.22 (d, 1H), 7.05 (d, 1H), 6.65 (d, 1H), 6.60 (dd, 1H), 3.80 (s, 3H), 3.15 (s, 3H); *m/z* (APCI-pos) *M*+1 = 421.1.

Example 65



2-amino-2'-(2-fluoropyridin-3-yl)-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

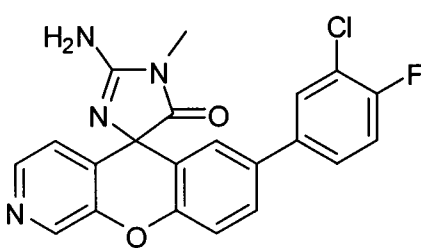
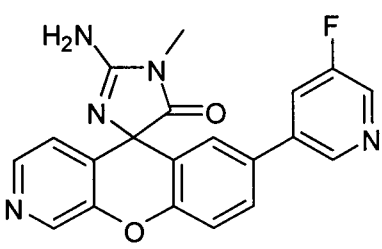
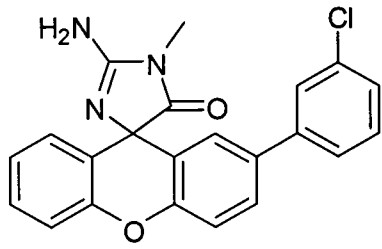
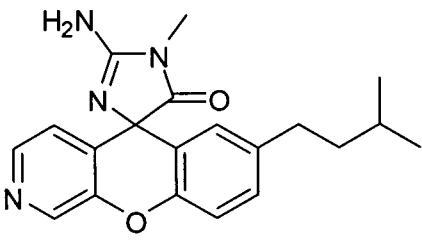
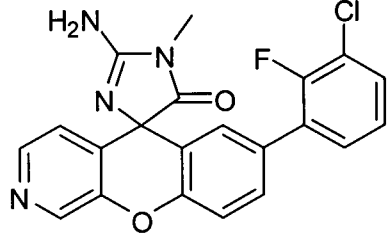
[00241] 2-Amino-2'-(2-fluoropyridin-3-yl)-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 64, substituting 2-fluoropyridin-3-ylboronic acid for 5-chloropyridin-3-ylboronic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, 1H), 7.79 (m, 1H), 7.50 (m, 1H), 7.35 (m, 1H), 7.25 (m, 2H), 7.05 (d, 1H), 6.68 (d, 1H), 6.60 (dd, 1H), 3.80 (s, 3H), 3.15 (s, 3H); *m/z* (APCI-pos) *M*+1 = 405.1.

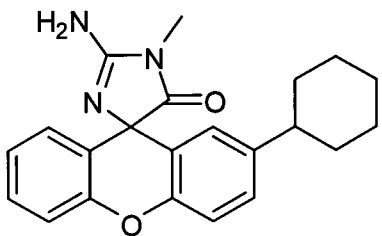
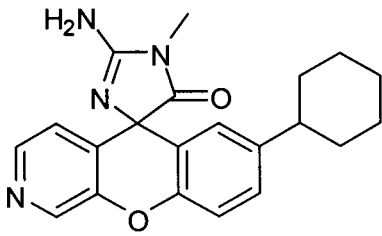
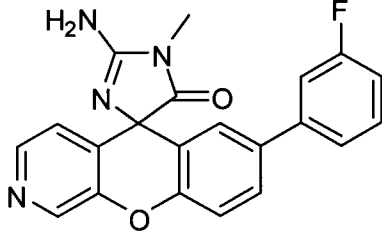
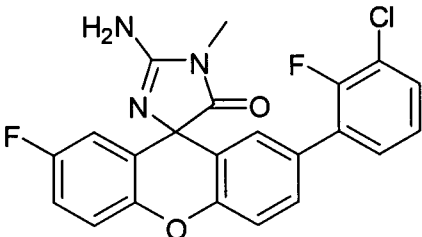
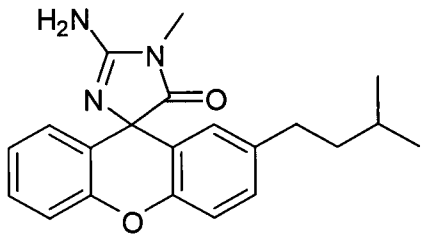
[00242] The following compounds in Table 1 were prepared according to the above procedures using appropriate intermediates.

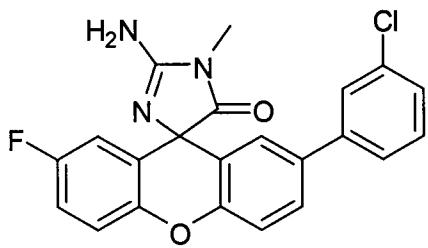
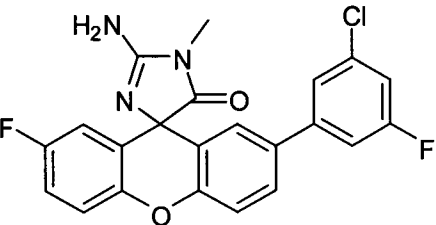
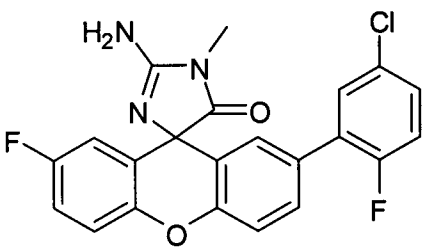
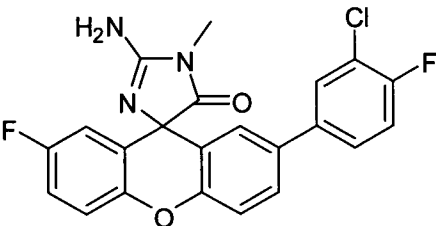
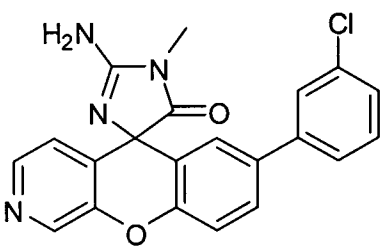
TABLE 1

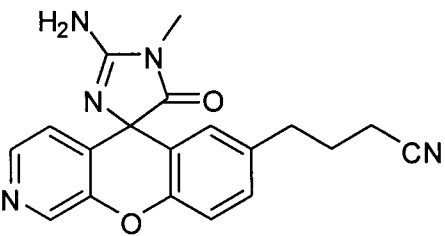
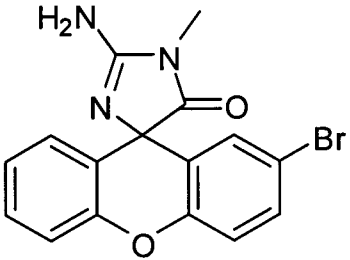
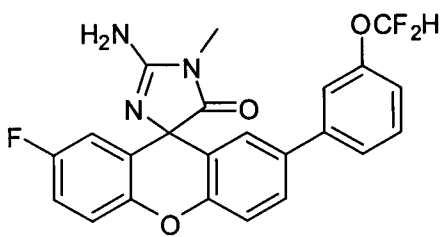
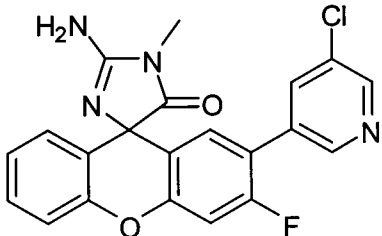
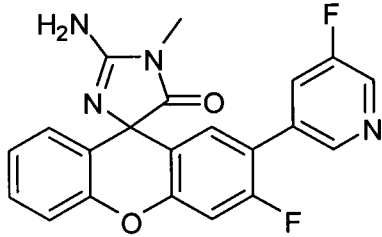
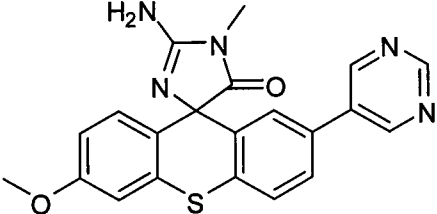
Ex. #	Structure	Name	NMR / MS
66		2-amino-2'-(3-(difluoromethoxy)phenyl)-1-methyl-7-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (APCI-pos) <i>M</i> +1 = 506.1

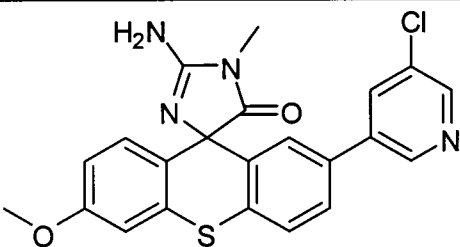
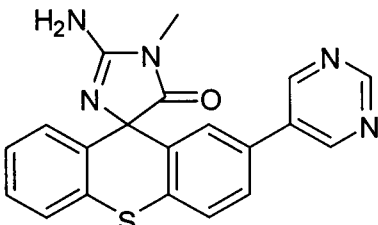
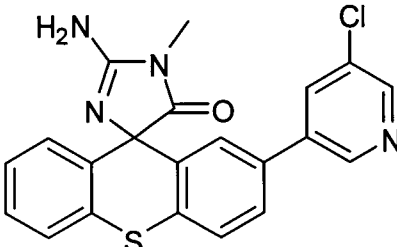
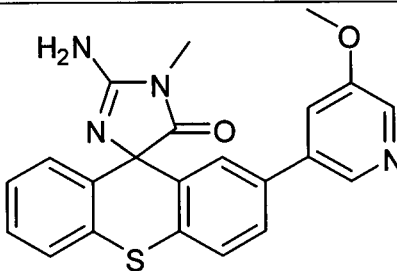
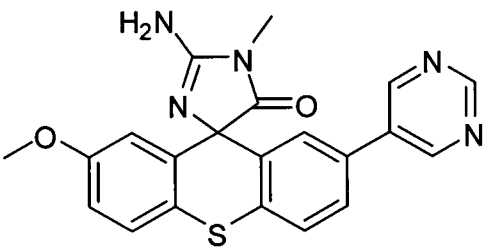
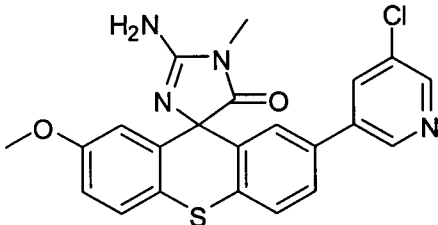
67		2-amino-2'-cyclohexyl-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (ES-API-pos) M+1 = 446.1
68		2-amino-2'-(3-fluorophenyl)-6'-methoxy-1,5'-dimethylspiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (APCI-pos) M+1 = 418.1
69		2-amino-2'-isopentyl-1-methyl-7'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (APCI-pos) M+1 = 434.2
70		2-amino-2'-fluoro-7'-(3-methoxyphenyl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (APCI-pos) M+1 = 404.1
71		2-amino-1-methyl-2'-(pyrimidin-5-yl)-6'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (APCI-pos) M+1 = 442.1
72		2-amino-2'-(5-chloropyridin-3-yl)-1-methyl-6'-(trifluoromethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (APCI-pos) M+1 = 475.0

73		2'-amino-7-(3-chloro-4-fluorophenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one	MS (APCI-pos) = 409.1 (M + 1)
74		2'-amino-7-(5-fluoropyridin-3-yl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one	MS (APCI-pos) = 376.1 (M + 1)
75		2-amino-2'-(3-chlorophenyl)-1'-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 390.1 (M + 1)
76		2'-amino-7-isopentyl-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one	MS (APCI-pos) = 351.2 (M + 1)
77		2'-amino-7-(3-chloro-2-fluorophenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one	MS (APCI-pos) = 409.1 (M + 1)

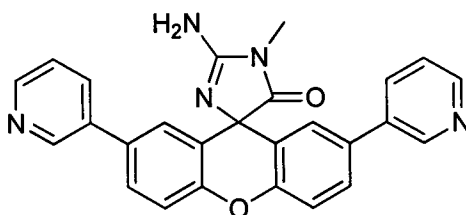
75		2-amino-2'-cyclohexyl-1'-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 362.2 (M + 1)
79		2'-amino-7-cyclohexyl-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one	MS (APCI-pos) = 363.2 (M + 1)
80		2'-amino-7-(3-fluorophenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one	MS (APCI-pos) = 375.1 (M + 1)
81		2-amino-2'-(3-chloro-2-fluorophenyl)-7'-fluoro-1'-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 426.1 (M + 1)
82		2-amino-2'-isopentyl-1'-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 350.2 (M + 1)

83		2-amino-2'-(3-chlorophenyl)-7'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 408.1 (M + 1)
84		2-amino-2'-(3-chloro-5-fluorophenyl)-7'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 426.1 (M + 1)
85		2-amino-2'-(5-chloro-2-fluorophenyl)-7'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 426.1 (M + 1)
86		2-amino-2'-(3-chloro-4-fluorophenyl)-7'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 426.1 (M + 1)
87		2'-amino-7-(3-chlorophenyl)-1'-methylspiro[chromeno[2,3-c]pyridine-5,4'-imidazol]-5'(1'H)-one	MS (APCI-pos) = 391.0 (M + 1)

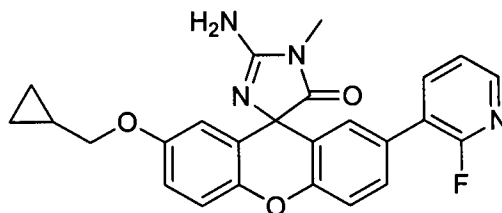
88		4-(2'-amino-1'-methyl-5'-oxo-1',5'-dihydrospiro[chromeno[2,3-c]pyridine-5,4'-imidazole]-7-yl)butanenitrile	MS (APCI-pos) = 348.1 (M + 1)
89		2-amino-2'-bromo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 358.0 (M + 1)
90		2-amino-2'-(3-(difluoromethoxy)phenyl)-7'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 440.1 (M + 1)
91		2-amino-2'-(5-chloropyridin-3-yl)-3'-fluoro-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> 409.1
92		2-amino-3'-fluoro-2'-(5-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> 393.1
93		2-amino-6'-methoxy-1-methyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 404.1

94		2-amino-2'-(5-chloropyridin-3-yl)-6'-methoxy-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 437.1
95		2-amino-1-methyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 374.1
96		2-amino-2'-(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 407.0
97		2-amino-2'-(5-methoxypyridin-3-yl)-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 403.1
98		2-amino-2'-methoxy-1-methyl-7'-(pyrimidin-5-yl)spiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 404.1
99		2-amino-2'-(5-chloropyridin-3-yl)-7'-methoxy-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 437.1

100		2-amino-2'-(2-fluoropyridin-3-yl)-7'-methoxy-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 421.1
101		2-amino-2'-methoxy-7'-(5-methoxypyridin-3-yl)-1-methylspiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 433.1
102		2-amino-2'-methoxy-1-methyl-7'-(pyridin-3-yl)spiro[imidazole-4,9'-thioxanthen]-5(1H)-one	<i>m/z</i> 403.1

Example 103**2-amino-1-methyl-2',7'-di(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one**

[00243] 2-Amino-1-methyl-2',7'-di(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedure of Example 26, substituting pyridin-3-ylboronic acid for (5-chloropyridin-3-yl)boronic acid to give 2-amino-1-methyl-2',7'-di(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one. ¹H NMR (400 MHz, CDCl₃) δ 8.76 (d, 2H), 8.51 (dd, 2H), 8.06 (m, 2H), 7.70 (dd, 2H), 7.51 (dd, 2H), 7.45 (d, 2H), 7.40 (d, 2H), 3.12 (s, 3H); *m/z* (APCI-pos) M+1 = 434.1.

Example 104

2-amino-2'-(cyclopropylmethoxy)-1-methyl-7'-(2-fluoropyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00244] Step A: A mixture of methyl 2-(2-fluoro-5-nitrophenyl)acetate (30.6 g, 144 mmol), 4-methoxyphenol (18.7 g, 151 mmol) and Cs_2CO_3 (70.2 g, 215 mmol) in DMF (144 mL, 144 mmol) under Argon was heated to 90°C for 4 hours. HPLC showed that the reaction was complete. The mixture was worked up with EtOAc and water. The organics were washed with water (5 X), and dried with brine and Na_2SO_4 . This was then concentrated down and purified on a column using EtOAc and hexanes to give methyl 2-(2-(4-methoxyphenoxy)-5-nitrophenyl)acetate (36.0 g, 113 mmol, 79.0% yield).

[00245] Step B: A mixture of methyl 2-(2-(4-methoxyphenoxy)-5-nitrophenyl)acetate (36.0 g, 113.5 mmol) and Pd/C (12.07 g, 113.5 mmol) in MeOH (4.596 mL, 113.5 mmol; d. 0.791) under hydrogen balloon was stirred at room temperature overnight. TLC showed that the reaction was complete. The mixture was filtered through GF/F paper, and the filtrate was concentrated down and purified on a column using EtOAc and hexanes to give methyl 2-(5-amino-2-(4-methoxyphenoxy)phenyl)acetate (30.14 g, 104.9 mmol, 92.46% yield).

[00246] Step C: A mixture of CuBr_2 (18.74 g, 83.92 mmol) and t-BuNO₂ (13.85 mL, 104.9 mmol) in acetonitrile (209.8 mL, 104.9 mmol) was stirred at 0°C for 30 minutes. Methyl 2-(5-amino-2-(4-methoxyphenoxy)phenyl)acetate (30.14 g, 104.9 mmol) in ACN was added, and this was stirred at room temperature for 30 minutes. TLC showed that the reaction was complete. The mixture was worked up with EtOAc and water. The organics were extracted twice, washed with brine and dried with Na_2SO_4 . This was then concentrated down and purified on a column using EtOAc and hexanes to give methyl 2-(5-bromo-2-(4-methoxyphenoxy)phenyl)acetate (18.87 g, 53.73 mmol, 51.22% yield).

[00247] Step D: A mixture of methyl 2-(5-bromo-2-(4-methoxyphenoxy)phenyl)acetate (18.87 g, 53.73 mmol) and NaOH (161.2 mL, 322.4 mmol) in ethanol (300 mL, 53.73 mmol) was heated to 60°C for 3 hours. TLC showed that the reaction was complete. The mixture was worked up with EtOAc and 2N HCl. The organics were extracted with EtOAc (2X), washed with brine and dried with Na_2SO_4 . This was concentrated down to give 2-(5-bromo-2-(4-methoxyphenoxy)phenyl)acetic acid (18.0 g, 53.39 mmol, 99.36% yield).

[00248] Step E: A mixture of 2-(5-bromo-2-(4-methoxyphenoxy)phenyl)acetic acid (18.0 g, 53.4 mmol) in PPA (5.23 g, 53.4 mmol) was stirred at 120°C for 4 hours. TLC showed that the reaction was complete. The mixture was poured onto ice and worked up with water and DCM. The organics were extracted twice with DCM, washed with brine and

dried with Na₂SO₄. This was concentrated down and purified on a column using EtOAc and hexanes to give 2-bromo-8-methoxydibenzo[b,f]oxepin-10(11H)-one (7.22 g, 22.6 mmol, 42.4% yield).

[00249] Step F: Trichloroborane (48.7 mL, 48.7 mmol) was added slowly to a mixture of 2-bromo-8-methoxydibenzo[b,f]oxepin-10(11H)-one (4.71 g, 14.8 mmol) and tetrabutylammonium iodide (6.00 g, 16.2 mmol) in DCM (29.5 mL, 14.8 mmol) at -78°C. This was then stirred at 0°C for 4 hours. TLC showed that the reaction was complete. The mixture was poured onto ice, and the organics were extracted with DCM twice, washed with brine and dried with Na₂SO₄. This was then concentrated down and purified on a column using EtOAc:hexanes to give 2-bromo-8-hydroxydibenzo[b,f]oxepin-10(11H)-one (2.6 g, 8.52 mmol, 57.7% yield).

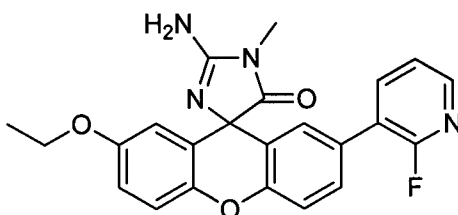
[00250] Step G: A mixture of selenium dioxide (2.08 g, 18.7 mmol) and 2-bromo-8-hydroxydibenzo[b,f]oxepin-10(11H)-one (2.6 g, 8.52 mmol) in dioxane (26 mL, 8.52 mmol) was heated to 90°C overnight. TLC showed that the reaction was complete. The mixture was filtered through GF/F paper, and then 1-methylguanidine hydrochloride (4.20 g, 38.3 mmol) was added followed by ethanol (26 mL, 8.52 mmol) and 2M Na₂CO₃ (19.2 mL, 38.3 mmol). This was stirred at 90°C overnight. HPLC showed that the reaction was complete. The mixture was worked up with water and DCM. The organics were extracted twice, washed with brine and dried with Na₂SO₄. This was then purified on a column to give 2-amino-2'-bromo-7'-hydroxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (1.44 g, 3.85 mmol, 45.2% yield).

[00251] Step H: A mixture of 2-amino-2'-bromo-7'-hydroxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.162 g, 0.433 mmol), 2-fluoropyridin-3-ylboronic acid (0.0915 g, 0.649 mmol), Na₂CO₃ (0.476 mL, 0.952 mmol) and Pd(PPh₃)₄ (0.0500 g, 0.0433 mmol) in dioxane (0.0381 g, 0.433 mmol) was heated to 90°C overnight. The mixture was filtered through GF/F paper and purified on a column to give 2-amino-2'-(2-fluoropyridin-3-yl)-7'-hydroxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.100 g, 0.256 mmol, 59.2% yield).

[00252] Step I: A mixture of 2-amino-2'-(2-fluoropyridin-3-yl)-7'-hydroxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.013 g, 0.03330 mmol), (bromomethyl)cyclopropane (0.004845 mL, 0.04995 mmol) and Cs₂CO₃ (0.02170 g, 0.06660 mmol) in DMF (0.1665 mL, 0.03330 mmol) was stirred at 90°C overnight. The mixture was worked up with DCM and water. The organics were washed with water (2X), then brine and dried with Na₂SO₄. This was then concentrated down and purified on a column to give 2-

amino-2'-(cyclopropylmethoxy)-1-methyl-7'-(2-fluoropyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one (0.0058 g, 0.01305 mmol, 39.19% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, 1H), 7.79 (m, 1H), 7.50 (d, 1H), 7.36 (s, 1H), 7.24 (m, 2H), 7.14 (d, 1H), 6.89 (dd, 1H), 6.74 (d, 1H), 3.74 (d, 2H), 3.10 (s, 3H), 0.84 (m, 1H), 0.64 (m, 2H), 0.34 (m, 2H); m/z (APCI-pos) $M+1 = 445.1$.

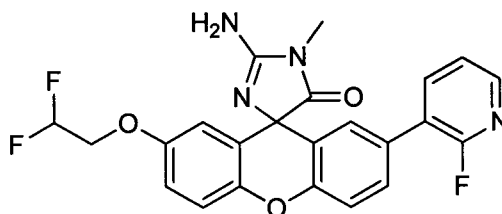
Example 105



2-amino-2'-ethoxy-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00253] 2-Amino-2'-ethoxy-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedure of Example 104, Step I, substituting bromoethane for (bromomethyl)cyclopropane. ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, 1H), 7.82 (m, 1H), 7.52 (d, 1H), 7.38 (s, 1H), 7.27 (m, 2H), 7.16 (d, 1H), 6.90 (dd, 1H), 6.72 (d, 1H), 3.98 (q, 2H), 3.11 (s, 3H), 1.39 (t, 3H); m/z (APCI-pos) $M+1 = 419.1$.

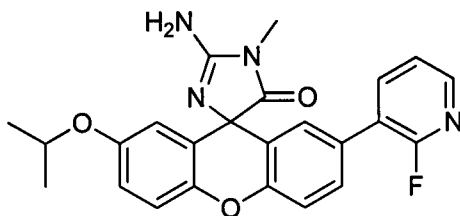
Example 106



2-amino-2'-(2,2-difluoroethoxy)-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00254] 2-Amino-2'-(2,2-difluoroethoxy)-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedure of Example 104, Step I, substituting 2-bromo-1,1-difluoroethane for (bromomethyl)cyclopropane. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, 1H), 7.82 (m, 1H), 7.51 (d, 1H), 7.36 (s, 1H), 7.26 (m, 2), 7.18, (d, 1H), 6.92 (dd, 1H), 6.75 (d, 1H), 6.06 (m, 1H), 4.14 (m, 2H), 3.10 (s, 3H); m/z (APCI-pos) $M+1 = 455.1$.

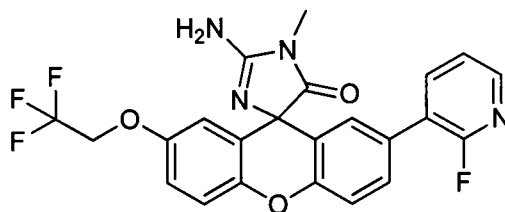
Example 107



2-amino-2'-(2-fluoropyridin-3-yl)-7'-isopropoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00255] 2-Amino-2'-(2-fluoropyridin-3-yl)-7'-isopropoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according the procedure of Example 104, Step I, substituting 2-bromopropane for (bromomethyl)cyclopropane. ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, 1H), 7.82 (m, 1H), 7.52 (d, 1H), 7.38 (s, 1H), 7.26 (m, 2H), 7.16 (d, 1H), 6.90 (dd, 1H), 6.74 (d, 1H), 4.47 (m, 1H), 3.11 (s, 3H), 1.30 (dd, 6H); m/z (APCI-pos) $M+1 = 433.1$.

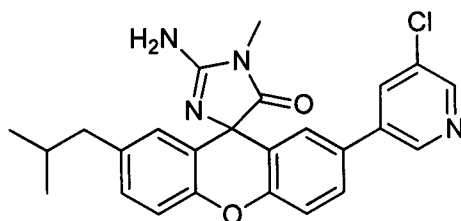
Example 108



2-amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-(2,2,2-trifluoroethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00256] 2-Amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-(2,2,2-trifluoroethoxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedure of Example 104, Step I, substituting 2-bromo-1,1,1-trifluoroethane for (bromomethyl)cyclopropane. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, 1H), 7.85 (m, 1H), 7.58 (m, 1H), 7.36 (s, 1H), 7.30 (m, 2H), 7.22 (d, 1H), 6.96 (dd, 1H), 6.79 (d, 1H), 4.38 (q, 2H), 3.11 (s, 3H); m/z (APCI-pos) $M+1 = 473.0$.

Example 109

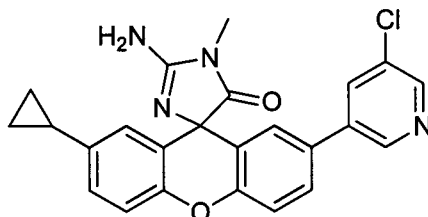


2-amino-2'-(5-chloropyridin-3-yl)-7'-isobutyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00257] 2-Amino-2'-(5-chloropyridin-3-yl)-7'-isobutyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according the procedure of Example 30, substituting

isobutylzinc(II) bromide for propylzinc(II) bromide. ^1H NMR (400 MHz, CDCl_3) δ 8.63 (d, 1H), 8.52 (d, 1H), 7.77 (t, 1H), 7.50 (dd, 1H), 7.35 (d, 1H), 7.29 (d, 1H), 7.12 (s, 2), 6.93 (s, 1H), 3.15 (s, 3H), 2.42 (d, 2H), 1.80 (m, 1H), 0.87 (dd, 6H); m/z (APCI-pos) $M+1 = 447.1$.

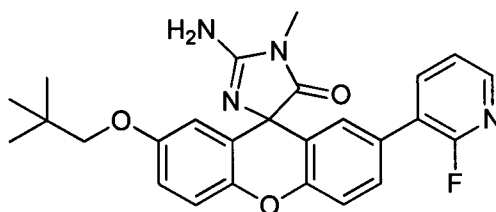
Example 110



2-amino-2'-(5-chloropyridin-3-yl)-7'-cyclopropyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00258] 2-Amino-2'-(5-chloropyridin-3-yl)-7'-cyclopropyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedure of Example 30, substituting cyclopropylzinc(II) bromide for propylzinc(II) bromide. ^1H NMR (400 MHz, CDCl_3) δ 8.64 (s, 1H), 8.52 (d, 1H), 7.77 (s, 1H), 7.50 (d, 1H), 7.34 (s, 1H), 7.28 (d, 1H), 7.10 (m, 1H), 6.97 (m, 2H), 3.15 (s, 3H), 1.86 (m, 1H), 1.37 (s, 2H), 1.34 (s, 2H); m/z (APCI-pos) $M+1 = 431.1$.

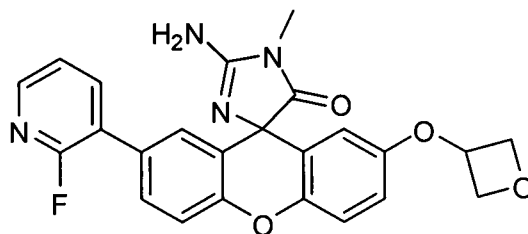
Example 111



2-amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-(neopentyloxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00259] 2-Amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-(neopentyloxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedure of Example 104, Step I, substituting 1-bromo-2,2-dimethylpropane for (bromomethyl)cyclopropane. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, 1H), 7.82 (m, 1H), 7.53 (d, 1H), 7.40 (s, 1H), 7.28 (m, 2H), 7.17 (d, 1H), 6.92 (dd, 1H), 6.72 (d, 1H), 3.55 (s, 2H), 3.15 (s, 3H), 1.03 (s, 9H); m/z (APCI-pos) $M+1 = 461.2$.

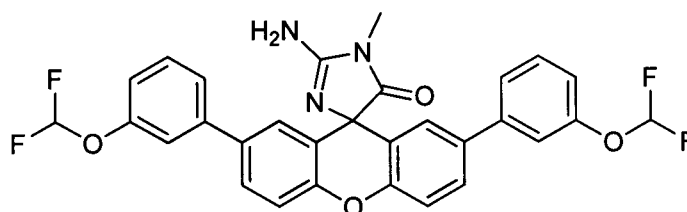
Example 112



2-amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-(oxetan-3-yloxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00260] 2-Amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-(oxetan-3-yloxy)spiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedure of Example 104, Step I, substituting 3-bromooxetane for (bromomethyl)cyclopropane. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, 1H), 7.82 (m, 1H), 7.53 (m, 1H), 7.38 (s, 1H), 7.29 (m, 2H), 7.17 (d, 1H), 6.66 (dd, 1H), 6.61 (d, 1H), 5.16 (m, 1H), 4.93 (m, 2H), 4.73 (m, 2H), 3.13 (s, 3H); *m/z* (APCI-pos) *M*+1 = 447.1.

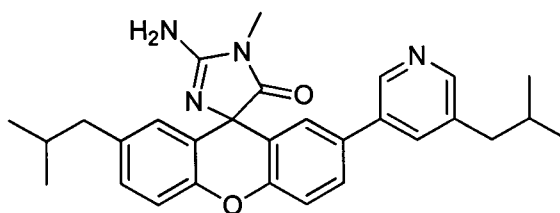
Example 113



2-amino-2',7'-bis(3-(difluoromethoxy)phenyl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00261] 2-Amino-2',7'-bis(3-(difluoromethoxy)phenyl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was made according to the procedure of Example 26, substituting (3-(difluoromethoxy)phenyl)boronic acid for (5-chloropyridin-3-yl)boronic acid. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (m, 2H), 7.51 (dd, 2H), 7.46 (m, 2H), 7.37 (d, 2H), 7.34 (m, 2H), 7.22 (m, 2H), 7.07 (d, 2H), 6.53 (t, 2H), 3.13 (s, 3H); *m/z* (APCI-pos) *M*+1 = 564.1.

Example 114

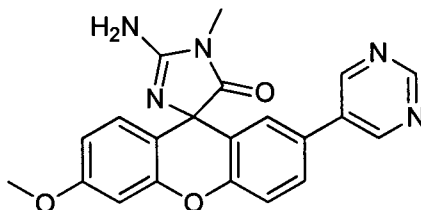


2-amino-2'-isobutyl-7'-(5-isobutylpyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00262] A mixture of 2-amino-2'-bromo-7'-(5-chloropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.020 g, 0.043 mmol), isobutylzinc(II)

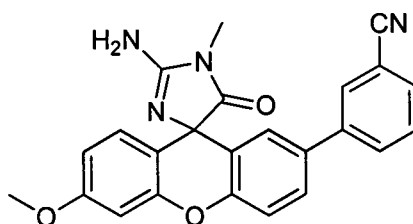
bromide (0.27 mL, 0.14 mmol) and bis(tri-*t*-butylphosphine)palladium (0) (0.0022 g, 0.0043 mmol) in THF (1 mL, 0.043 mmol) was heated to 90°C in a sealed vial overnight. Mass spec showed product in the mixture. The mixture was loaded onto a column using DCM:MeOH:NH₄OH (90:10:1) to give 2-amino-2'-isobutyl-7'-(5-isobutylpyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (0.0071 g, 0.015 mmol, 36% yield). *m/z* (APCI-pos) *M*+1 = 469.2.

Example 115



2-amino-6'-methoxy-1-methyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one
[00263] 2-Amino-6'-methoxy-1-methyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 64, substituting pyrimidin-5-yl boronic acid for (5-chloropyridin-3-yl) boronic acid. ¹H NMR (400 MHz, CDCl₃) δ 9.18 (s, 1H), 8.88 (s, 2H), 7.5 (d, 1H), 7.30 (m, 2H), 7.08 (m, 1H), 6.7 (d, 1H), 6.65 (m, 1H), 3.80 (s, 3H), 3.15 (s, 3H); *m/z* (APCI-pos) *M*+1 = 388.1.

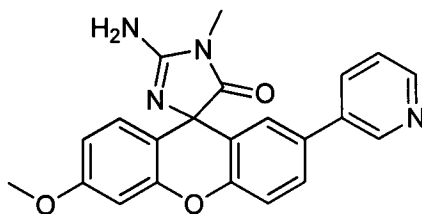
Example 116



3-(2-amino-3'-methoxy-1-methyl-5-oxo-1,5-dihydrospiro[imidazole-4,9'-xanthen]-7'-yl)benzonitrile

[00264] 3-(2-Amino-3'-methoxy-1-methyl-5-oxo-1,5-dihydrospiro[imidazole-4,9'-xanthen]-7'-yl)benzonitrile was prepared according to Example 64, substituting (3-cyanophenyl) boronic acid for (5-chloropyridin-3-yl) boronic acid. ¹H NMR (400 MHz, CDCl₃) δ 7.75 (s, 1H), 7.70 (d, 1H), 7.60 (d, 1H), 7.55 (m, 2H), 7.32 (m, 1H), 7.28 (d, 1H), 7.10 (br d, 1H), 6.72 (d, 1H), 6.68 (br d, 1H), 3.82 (s, 3H), 3.18 (s, 3H); *m/z* (APCI-pos) *M*+1 = 411.1.

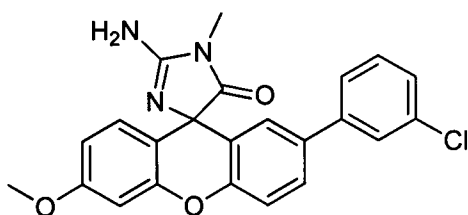
Example 117



2-amino-6'-methoxy-1-methyl-2'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00265] 2-Amino-6'-methoxy-1-methyl-2'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 64, substituting pyridin-3-ylboronic acid for (5-chloropyridin-3-yl) boronic acid. ^1H NMR (400 MHz, CDCl_3) δ 8.75 (d, 1H), 8.56 (dd, 1H), 7.78 (m, 1H), 7.55 (dd, 1H), 7.32 (m, 2H), 7.28 (d, 1H), 7.10 (d, 1H), 6.72 (d, 1H), 6.64 (dd, 1H), 3.82 (s, 3H), 3.14 (s, 3H); m/z (APCI-pos) $M+1 = 387.1$.

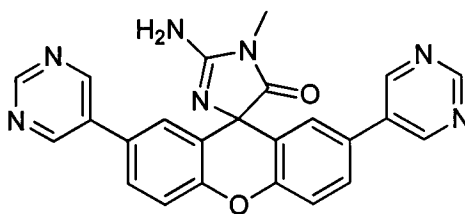
Example 118



2-amino-2'-(3-chlorophenyl)-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00266] 2-Amino-2'-(3-chlorophenyl)-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 64, substituting (3-chlorophenyl) boronic acid for (5-chloropyridin-3-yl) boronic acid. ^1H NMR (400 MHz, CDCl_3) δ 7.66 (m, 1H), 7.50 (m, 2H), 7.35 (m, 3H), 7.24 (d, 1H), 7.10 (d, 1H), 6.72 (d, 1H), 6.64 (dd, 1H), 3.82 (s, 3H), 3.14 (s, 3H); m/z (APCI-pos) $M+1 = 420.1$.

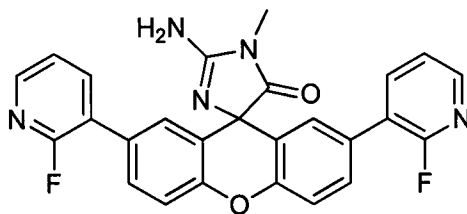
Example 119



2-amino-1-methyl-2',7'-di(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00267] 2-Amino-1-methyl-2',7'-di(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 26, substituting pyrimidin-5-ylboronic acid for (5-chloropyridin-3-yl) boronic acid. ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.23 (s, 2H), 9.19 (s, 4H), 8.05 (dd, 2H), 7.92 (d, 2H), 7.58 (d, 2H), 3.25 (s, 3H); m/z (APCI-pos) $M+1 = 436.1$.

Example 120



2-amino-2',7'-bis(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one
[00268] 2-Amino-2',7'-bis(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 26, substituting (2-fluoropyridin-3-yl)boronic acid for (5-chloropyridin-3-yl) boronic acid. ¹H NMR (400 MHz, (CD₃)₂SO) δ 8.22 (m, 2H), 8.10 (m, 2H), 7.62 (m, 2H), 7.48 (m, 2H), 7.42 (d, 2H), 7.35 (m, 2H), 32.95 (s, 3H); *m/z* (APCI-pos) *M*+1 = 470.1.

Example 121



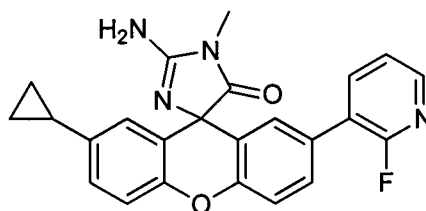
2-amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00269] Step A: 2-Amino-2',7'-dibromo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (337 mg, 0.771 mmol; Example 26, Step D) and 2-fluoropyridin-3-ylboronic acid (109 mg, 0.771 mmol) were diluted with dioxane (2 mL), followed by the addition of Pd(PPh₃)₄ (8.91 mg, 0.00771 mmol) and Na₂CO₃ (771 μL, 1.54 mmol). The reaction was sealed, heated to 85°C and stirred for 12 hours. The reaction was allowed to cool, diluted with ethyl acetate and water. The organics were dried over MgSO₄, filtered and concentrated. The residue was triturated with ether to afford 2-amino-2'-bromo-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (100 mg, 0.221 mmol, 28.6% yield) as a solid.

[00270] Step B: 2-Amino-2'-bromo-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (25 mg, 0.055 mmol) and pyridin-3-ylboronic acid (8.8 mg, 0.072 mmol) were diluted with dioxane (1 mL), followed by the addition of Pd(PPh₃)₄ (0.64 mg, 0.00055 mmol) and Na₂CO₃ (83 μL, 0.17 mmol). The reaction was sealed, heated to 85°C and stirred for 12 hours. The reaction was allowed to cool, diluted with ethyl acetate and water. The organics were dried over MgSO₄, filtered and concentrated. The residue was purified on silica gel eluting with 1-10% methanol/DCM (1%

NH_4OH) to afford 2-amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one (10 mg, 0.022 mmol, 40% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.79 (m, 1H), 8.59 (d, 1H), 8.19 (m, 1H), 7.82 (m, 2H), 7.55 (m, 2H), 7.35 (m, 5H), 7.18 (m, 1H), 3.14 (s, 3H); m/z (APCI-pos) $M+1 = 452.1$.

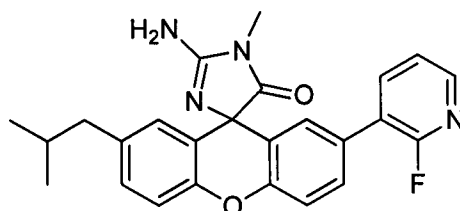
Example 122



2-amino-2'-cyclopropyl-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

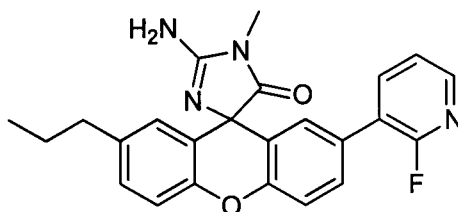
[00271] Cyclopropylzinc bromide (882 μL , 0.44 mmol) was added to 2-amino-2'-bromo-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (20 mg, 0.044 mmol; Example 121, Step A) and bis(tri-*t*-butylphosphine)palladium (0) (1.1 mg, 0.0022 mmol). The reaction was sealed, heated to 80°C and stirred for 12 hours. The reaction was allowed to cool, loaded onto silica gel and eluted with 1-10% methanol/DCM (with 1% NH_4OH) to yield 2-amino-2'-cyclopropyl-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (8 mg, 0.019 mmol, 44% yield). ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, 1H), 7.80 (t, 1H), 7.52 (d, 1H), 7.40 (s, 1H), 7.26 (m, 2H), 7.12 (d, 1H), 7.00 (m, 2H), 3.15 (s, 3H), 1.85 (m, 1H), 0.92 (m, 2H), 0.62 (m, 2H); m/z (APCI-pos) $M+1 = 415.1$.

Example 123



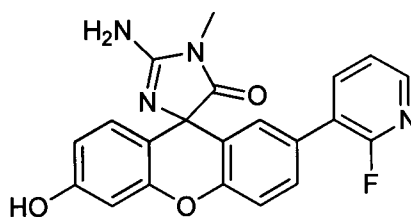
2-amino-2'-(2-fluoropyridin-3-yl)-7'-isobutyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00272] 2-Amino-2'-(2-fluoropyridin-3-yl)-7'-isobutyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 122, substituting isobutyl zinc bromide for cyclopropyl zinc bromide. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, 1H), 7.80 (t, 1H), 7.52 (d, 1H), 7.42 (s, 1H), 7.30 (d, 1H), 7.15 (m, 3H), 6.95 (s, 1H), 3.16 (s, 3H), 2.42 (d, 2H), 1.80 (m, 1H), 0.88 (m, 6H); m/z (APCI-pos) $M+1 = 431.2$.

Example 124

2-amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-propylspiro[imidazole-4,9'-xanthen]-5(1H)-one

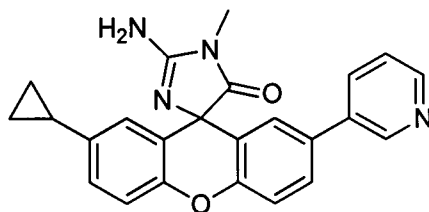
[00273] 2-Amino-2'-(2-fluoropyridin-3-yl)-1-methyl-7'-propylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 122, substituting propyl zinc bromide for cyclopropyl zinc bromide. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, 1H), 7.80 (t, 1H), 7.52 (d, 1H), 7.42 (s, 1H), 7.30 (d, 1H), 7.15 (m, 3H), 7.01 (s, 1H), 3.16 (s, 3H), 2.55 (t, 2H), 1.60 (m, 2H), 0.92 (t, 3H); *m/z* (APCI-pos) *M*+1 = 417.1.

Example 125

2-amino-2'-(2-fluoropyridin-3-yl)-6'-hydroxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00274] 2-Amino-2'-(2-fluoropyridin-3-yl)-6'-methoxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (30 mg, 0.074 mmol; Example 65) and tetrabutylammonium iodide (33 mg, 0.089 mmol) were diluted with DCM, placed under nitrogen and cooled to -78°C. BCl₃ (297 μL, 0.30 mmol) was added, and the reaction was allowed to warm to ambient temperature. After stirring for 1 hour, the reaction was quenched with saturated bicarbonate and extracted with DCM. The organics were dried over MgSO₄, filtered and concentrated. The material was purified on silica gel, eluting with 1-10% methanol/DCM (1% NH₄OH) to yield 2-amino-2'-(2-fluoropyridin-3-yl)-6'-hydroxy-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (10 mg, 0.026 mmol, 35% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, 1H), 7.85 (t, 1H), 7.53 (d, 1H), 7.35 (s, 1H), 7.28 (m, 2H), 7.00 (d, 1H), 6.70 (d, 1H), 6.63 (dd, 1H), 3.12 (s, 3H); *m/z* (APCI-pos) *M*+1 = 391.1.

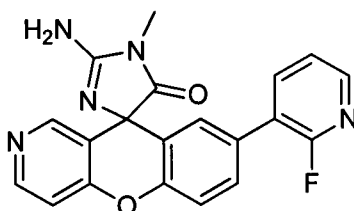
Example 126



2-amino-2'-cyclopropyl-1-methyl-7'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00275] 2-Amino-2'-cyclopropyl-1-methyl-7'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 8, substituting pyridin-3-ylboronic acid for (2-fluoropyridin-3-yl) boronic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H), 8.55 (d, 1H), 7.85 (d, 1H), 7.55 (d, 1H), 7.30-7.40 (m, 3H), 7.15 (d, 1H), 7.00 (d, 1H), 6.95 (s, 1H), 3.14 (s, 3H), 1.90 (m, 1H), 0.92 (m, 2H), 0.62 (m, 2H); *m/z* (APCI-pos) *M*+1 = 397.1.

Example 127



2'-amino-8-(2-fluoropyridin-3-yl)-1'-methylspiro[chromeno[3,2-c]pyridine-10,4'-imidazol]-5'(1'H)-one

[00276] Step A: Ethyl 2-(5-bromo-2-hydroxyphenyl)acetate (4.29 g, 16.6 mmol) and 4-chloronicotinaldehyde (2.34 g, 16.6 mmol) were diluted with DMF (40 mL), followed by the addition of TEA (2.31 mL, 16.6 mmol; d. 0.726). The reaction was heated to 80°C and stirred for 12 hours. The reaction was allowed to cool and diluted with ethyl acetate and water. The layers were separated, and the organics were dried over MgSO₄, filtered and concentrated. The material was purified on silica gel, eluting with 10-70% ethyl acetate/hexanes to yield ethyl 8-bromobenzo[6,7]oxepino[3,2-c]pyridine-10-carboxylate (1.4 g, 4.04 mmol, 24.4% yield).

[00277] Step B: Ethyl 8-bromobenzo[6,7]oxepino[3,2-c]pyridine-10-carboxylate (400 mg, 1.16 mmol) and 2-fluoropyridin-3-ylboronic acid (179 mg, 1.27 mmol) were diluted with dioxane (3 mL), followed by the addition of Pd(PPh₃)₄ (13.4 mg, 0.0116 mmol) and Na₂CO₃ (1155 μL, 2.31 mmol). The reaction was sealed, heated to 85°C and stirred for 12 hours. The reaction was loaded directly onto silica gel and eluted with 1-10% methanol/DCM (1% NH₄OH) to afford ethyl 8-(2-fluoropyridin-3-yl)benzo[6,7]oxepino[3,2-c]pyridine-10-carboxylate (250 mg, 0.690 mmol, 59.7% yield).

[00278] Step C: Ethyl 8-(2-fluoropyridin-3-yl)benzo[6,7]oxepino[3,2-c]pyridine-10-

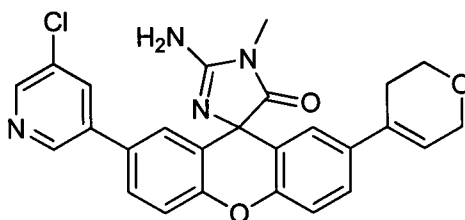
carboxylate (329 mg, 0.908 mmol) was diluted with THF (2 mL) and ethanol (1 mL), followed by the addition of NaOH (1362 μ L, 2.72 mmol). After stirring for 4 hours, the pH was adjusted to 6 (with 2N HCl), and the product was extracted with ethyl acetate. The organics were dried over MgSO₄, filtered and concentrated to yield 8-(2-fluoropyridin-3-yl)benzo[6,7]oxepino[3,2-c]pyridine-10-carboxylic acid (300 mg, 0.897 mmol, 98.8% yield).

[00279] Step D: 8-(2-Fluoropyridin-3-yl)benzo[6,7]oxepino[3,2-c]pyridine-10-carboxylic acid (300 mg, 0.897 mmol) was diluted with quinoline (5 mL), followed by the addition of CuSO₄ (286 mg, 1.79 mmol). The reaction was sealed and heated in the microwave (180°C) for 30 minutes. The reaction was concentrated and diluted with ethyl acetate and water. The organics were dried over MgSO₄, filtered and concentrated. The residue was purified on silica gel eluting with 5-50% ethyl acetate/hexanes to yield 8-(2-fluoropyridin-3-yl)benzo[6,7]oxepino[3,2-c]pyridine (30 mg, 0.103 mmol, 11.5% yield).

[00280] Step E: 8-(2-Fluoropyridin-3-yl)benzo[6,7]oxepino[3,2-c]pyridine (25 mg, 0.086 mmol) was diluted with acetone (300 μ L), followed by the addition of NaHCO₃ (69 μ L, 0.069 mmol) and MgSO₄ (21 mg, 0.17 mmol) in water (60 μ L). KMnO₄ (34 mg, 0.22 mmol) was added, and the reaction mixture was stirred for 1 hour at ambient temperature. The reaction was diluted with ethyl acetate and hexanes (1:1) and diluted with water. The layers were separated, and the organics were dried over MgSO₄, filtered and concentrated to yield 8-(2-fluoropyridin-3-yl)benzo[6,7]oxepino[3,2-c]pyridine-10,11-dione (28 mg, 0.087 mmol, 102% yield). The material was pushed forward without purification.

[00281] Step F: 8-(2-Fluoropyridin-3-yl)benzo[6,7]oxepino[3,2-c]pyridine-10,11-dione (20 mg, 0.0624 mmol) was diluted with dioxane (1 mL), followed by the addition of methylguanidine hydrochloride (27.4 mg, 0.250 mmol) and Na₂CO₃ (125 μ L, 0.250 mmol). The reaction was heated to 90°C and stirred for 12 hours. The reaction was purified on silica gel eluting with 10% methanol/DCM (with 1% NH₄OH) to yield 2'-amino-8-(2-fluoropyridin-3-yl)-1'-methylspiro[chromeno[3,2-c]pyridine-10,4'-imidazol]-5'(1'H)-one (800 μ g, 0.00213 mmol, 3.41% yield). *m/z* (APCI-pos) M+1 = 376.1.

Example 128



2'-amino-2'-(5-chloropyridin-3-yl)-7'-(3,6-dihydro-2H-pyran-4-yl)-1-methylspiro[imidazole-

4,9'-xanthen]-5(1H)-one

[00282] Step A: Ethyl 2-(5-bromo-2-hydroxyphenyl)acetate (15.25 g, 58.86 mmol), 1,4-diiodobenzene (46.60 g, 141.3 mmol), N,N-dimethylglycine hydrochloride (4.929 g, 35.32 mmol), Cu(I)Cl (3.496 g, 35.32 mmol) and Cs₂CO₃ (46.03 g, 141.3 mmol) were diluted with dioxane (200 mL), purged with argon and heated to 70°C. The reaction was stirred for 12 hours, allowed to cool and diluted with ethyl acetate and water. The layers were separated, and the organics were dried over MgSO₄, filtered and concentrated. The material was purified on silica gel eluting with 5% ethyl acetate/hexanes to yield ethyl 2-(5-bromo-2-(4-iodophenoxy)phenyl)acetate (13 g, 28.19 mmol, 47.90% yield).

[00283] Step B: Ethyl 2-(5-bromo-2-(4-iodophenoxy)phenyl)acetate (13.33 g, 28.91 mmol) was diluted with ethanol (100 mL), followed by the addition of NaOH (57.82 mL, 115.6 mmol). After stirring for 3 hours, the reaction was diluted with ethyl acetate and 2N HCl. The layers were separated, and the organics were dried over MgSO₄, filtered and concentrated to yield 2-(5-bromo-2-(4-iodophenoxy)phenyl)acetic acid (12.37 g, 28.57 mmol, 98.81% yield).

[00284] Step C: 2-(5-Bromo-2-(4-iodophenoxy)phenyl)acetic acid (12.37 g, 28.57 mmol) was diluted with PPA (100 mL), placed under nitrogen and heated to 110°C. After stirring for 12 hours, the reaction was poured into ice water and extracted with DCM. The organics were dried over MgSO₄, filtered and concentrated. The residue was triturated with ether to afford 2-bromo-8-iododibenzo[b,f]oxepin-10(11H)-one (6.6 g, 15.90 mmol, 55.67% yield).

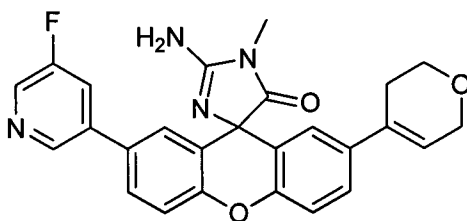
[00285] Step D: 2-Bromo-8-iododibenzo[b,f]oxepin-10(11H)-one (6.6 g, 16 mmol) was diluted with dioxane (70 mL) and water (700 µL), followed by the addition of selenium dioxide (3.5 g, 32 mmol). The reaction was heated to reflux and stirred for 12 hours. The reaction was cooled and then filtered. 1-Methylguanidine hydrochloride (5.2 g, 48 mmol) and ethanol (50 mL) were added, followed by the addition of Na₂CO₃ (24 mL, 48 mmol). The reaction was heated to 80°C and stirred for 12 hours. The reaction was allowed to cool and diluted with ethyl acetate and water. The layers were separated, and the organics were dried over MgSO₄, filtered and concentrated. The material was triturated with diethyl ether to afford 2-amino-2'-bromo-7'-iodo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (6.0 g, 12 mmol, 78% yield).

[00286] Step E: 2-Amino-2'-bromo-7'-iodo-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (500 mg, 1.03 mmol) and 3,6-dihydro-2H-pyran-4-boronic acid (132 mg, 1.03 mmol) were diluted with dioxane (3 mL), followed by the addition of Pd(PPh₃)₄ (35.8 mg,

0.0310 mmol) and Na_2CO_3 (1291 μL , 2.58 mmol). The reaction was sealed, heated to 85°C and stirred for 12 hours. The reaction was diluted with ethyl acetate and water. The layers were separated, and the organic was dried over MgSO_4 , filtered and concentrated. The material was purified on silica gel eluting with 1-10% methanol/DCM (1% NH_4OH) to yield 2-amino-2'-bromo-7'-(3,6-dihydro-2H-pyran-4-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (100 mg, 0.227 mmol, 22.0% yield).

[00287] Step F: 2-Amino-2'-bromo-7'-(3,6-dihydro-2H-pyran-4-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (20 mg, 0.045 mmol) and 5-chloropyridin-3-ylboronic acid (14 mg, 0.091 mmol) were diluted with dioxane (300 μL), followed by the addition of $\text{Pd}(\text{PPh}_3)_4$ (2.6 mg, 0.0023 mmol) and Na_2CO_3 (68 μL , 0.14 mmol). The reaction was sealed, heated to 85°C and stirred for 12 hours. The reaction was diluted with ethyl acetate and water. The layers were separated, and the organic were dried over MgSO_4 , filtered and concentrated. The material was purified on RP silica gel eluting with 5-95% ACN/water (0.1% TFA) to afford 2-amino-2'-(5-chloropyridin-3-yl)-7'-(3,6-dihydro-2H-pyran-4-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one (1.5 mg, 0.0032 mmol, 7.0% yield). ^1H NMR (400 MHz, CD_3OD) δ 8.80 (s, 1H), 8.60 (s, 1H), 8.20 (s, 1H), 7.85 (dd, 1H), 7.75 (d, 1H), 7.62 (dd, 1H), 7.48 (d, 1H), 7.38 (d, 1H), 7.35 (d, 1H), 6.20 (m, 1H), 4.30 (m, 2H), 3.92 (t, 2H), 3.33 (s, 3H), 2.55 (m, 2H); m/z (APCI-pos) $M+1 = 473.1$.

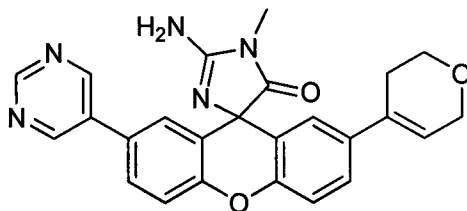
Example 129



2-amino-2'-(3,6-dihydro-2H-pyran-4-yl)-7'-(5-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

[00288] 2-Amino-2'-(3,6-dihydro-2H-pyran-4-yl)-7'-(5-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 128, substituting (5-fluoropyridin-3-yl)boronic acid for (5-chloropyridin-3-yl)boronic acid. ^1H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1H), 8.55 (s, 1H), 7.99 (d, 1H), 7.85 (d, 1H), 7.75 (s, 1H), 7.62 (d, 1H), 7.48 (d, 1H), 7.38 (s, 1H), 7.35 (d, 1H), 6.20 (m, 1H), 4.30 (s, 2H), 3.92 (t, 2H), 3.33 (s, 3H), 2.55 (m, 2H); m/z (APCI-pos) $M+1 = 457.1$.

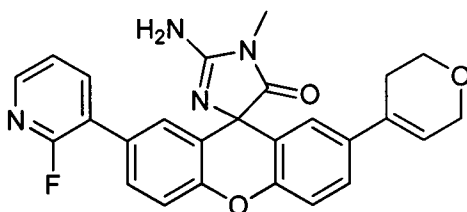
Example 130



2-amino-2'-(3,6-dihydro-2H-pyran-4-yl)-1-methyl-7'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one

[00289] 2-Amino-2'-(3,6-dihydro-2H-pyran-4-yl)-1-methyl-7'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 128, substituting pyrimidin-5-ylboronic acid for (5-chloropyridin-3-yl)boronic acid. ¹H NMR (400 MHz, CD₃OD) δ 9.15 (s, 1H), 9.08 (s, 2H), 7.90 (dd, 1H), 7.80 (d, 1H), 7.62 (dd, 1H), 7.50 (d, 1H), 7.38 (d, 1H), 7.35 (d, 1H), 6.20 (m, 1H), 4.30 (m, 2H), 3.92 (t, 2H), 3.33 (s, 3H), 2.55 (m, 2H); *m/z* (APCI-pos) *M*+1 = 440.1.

Example 131



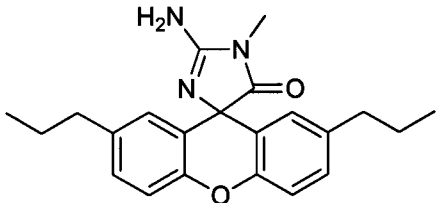
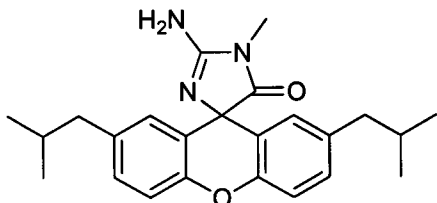
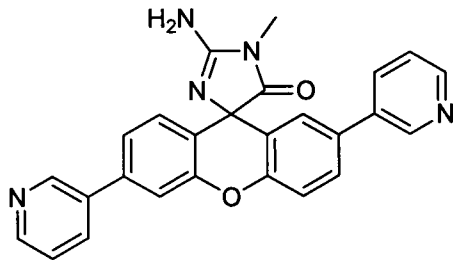
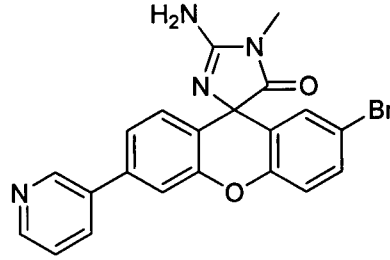
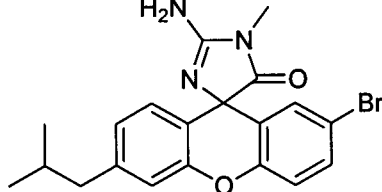
2-amino-2'-(3,6-dihydro-2H-pyran-4-yl)-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one

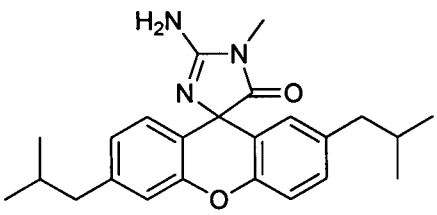
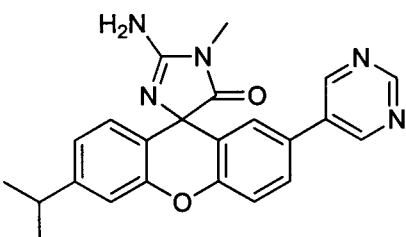
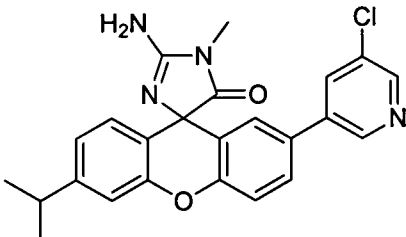
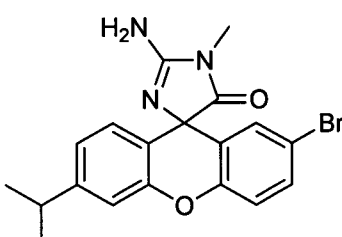
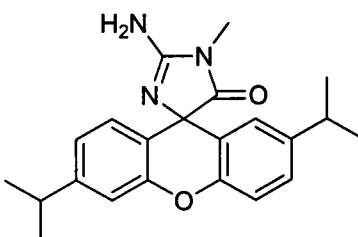
[00290] 2-Amino-2'-(3,6-dihydro-2H-pyran-4-yl)-7'-(2-fluoropyridin-3-yl)-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one was prepared according to Example 128, substituting (2-fluoropyridin-3-yl)boronic acid for (5-chloropyridin-3-yl)boronic acid. ¹H NMR (400 MHz, CD₃OD) δ 8.18 (d, 1H), 8.05 (m, 1H), 7.70 (d, 1H), 7.63 (s, 1H), 7.60 (dd, 1H), 7.45 (d, 1H), 7.40 (m, 1H), 7.36 (d, 1H), 7.32 (d, 1H), 6.20 (m, 1H), 4.30 (m, 2H), 3.92 (t, 2H), 3.33 (s, 3H), 2.55 (m, 2H); *m/z* (APCI-pos) *M*+1 = 457.1.

[00291] The following compounds in Table 2 were prepared according to the above procedures using appropriate intermediates.

TABLE 2

Ex. #	Structure	Name	NMR / MS
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132		2-amino-2',7'-dicyclopropyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (APCI-pos) M+1 = 360.1
133		2-amino-1-methyl-2',7'-dipropylspiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (ES-API-pos) M+1 = 364.2
134		2-amino-2',7'-diisobutyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	<i>m/z</i> (APCI-pos) M+1 = 392.2
135		2-amino-1-methyl-2',6'-di(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 434.1 (M + 1)
136		2-amino-2'-bromo-1-methyl-6'-(pyridin-3-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 376.1 (M + 1)
137		2-amino-2'-bromo-6'-isobutyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 416.0 (M + 1)

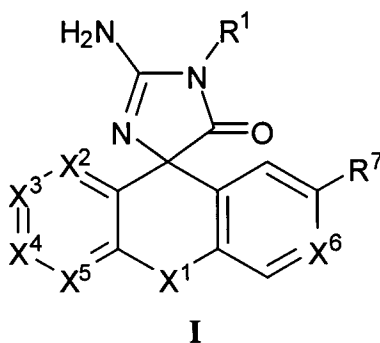
			1)
138		2-amino-2',6'-diisobutyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 392.2 (M + 1)
139		2-amino-6'-isopropyl-1-methyl-2'-(pyrimidin-5-yl)spiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 400.1 (M + 1)
140		2-amino-2'-(5-chloropyridin-3-yl)-6'-isopropyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 433.1 (M + 1)
141		2-amino-2'-bromo-6'-isopropyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 400.0 (M + 1)
142		2-amino-2',6'-diisopropyl-1-methylspiro[imidazole-4,9'-xanthen]-5(1H)-one	MS (APCI-pos) = 364.2 (M + 1)

[00292] It will be understood that the enumerated embodiments are not intended to

limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications and equivalents, which may be included within the scope of the present invention as defined by the claims. Thus, the foregoing description is considered as illustrative only of the principles of the invention.

What is claimed is:

1. A compound selected from Formula I:



and stereoisomers, diastereomers, enantiomers, tautomers and pharmaceutically acceptable salts thereof, wherein:

X^1 is selected from O, S, S(O), SO₂, NR¹¹ or CHR¹¹;

X^2 is selected from CR² or N;

X^3 is selected from CR³ or N;

X^4 is selected from CR⁴ or N;

X^5 is selected from CR⁵ or N;

X^6 is selected from CR⁶ or N, wherein only one of X^2 , X^3 , X^4 , X^5 or X^6 may be N;

R^1 is selected from hydrogen, alkyl, aralkyl, heteroaryl or heteroaralkyl;

R^2 is selected from hydrogen, halogen and alkyl;

R^3 is selected from hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle;

R^4 is selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle or a heterocycle wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or heterocycle optionally substituted with hydroxy, halogen, amino, cyano, nitro,

alkyl, alkoxy, acyl and haloalkyl;

R^5 is selected from hydrogen, halogen, alkyl, alkoxy and a carbocycle;

R^6 is selected from hydrogen, halogen and alkyl;

R^7 is selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, a carbocycle, a heterocycle or $-O(\text{heterocycle})$ wherein said alkyl, alkoxy, acyl, acyloxy, alkoxycarbonyl, sulfonyl, sulfinyl, sulfanyl, aryloxy, carbocycle and heterocycle are optionally substituted with hydroxy, halogen, amino, cyano, nitro, oxo, optionally substituted alkyl, optionally substituted alkoxy, sulfanyl, acyl, alkoxycarbonyl, haloalkyl and optionally substituted carbocycle; and

R^{11} is selected from hydrogen and alkyl.

2. The compound of Claim 1, wherein:

X^1 is selected from O, S, $S(O)$, SO_2 , NR^{11} or CHR^{11} ;

X^2 is CR^2 ;

X^3 is CR^3 or N;

X^4 is selected from CR^4 or N;

X^5 is CR^5 ;

X^6 is CR^6 ;

R^1 is selected from hydrogen, benzyl or C_1 - C_3 alkyl optionally substituted with R^a ;

R^2 is hydrogen;

R^3 is selected from hydrogen, halogen, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, a 3 to 6 membered carbocycle, a 3 to 6 membered heterocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, heterocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C_1 - C_6 alkoxy optionally substituted with halogen;

R^4 is selected from hydrogen, halogen, OH, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, phenyl, a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, phenyl and heteroaryl are optionally substituted with halogen, or

R^3 and R^4 together with the atoms to which they are attached form a 3 to 6 membered carbocycle or 3 to 6 membered heterocycle;

R^5 is selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy or a 3 to 6 membered carbocycle;

R^6 is selected from hydrogen, halogen or C_1 - C_6 alkyl;

R^7 is selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, a 3

to 6 membered saturated or partially unsaturated carbocycle, a 3 to 6 membered saturated or partially unsaturated heterocycle, phenyl, 5 to 6 membered heteroaryl and -O(3 to 6 membered heterocycle), wherein the alkyl, alkenyl, alkynyl, carbocycle, heterocycles, phenyl and heteroaryl are optionally substituted with halogen, CN, C₁-C₆ alkyl or C₁-C₆ alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen;

R¹¹ is selected from hydrogen and C₁-C₆ alkyl; and

each R^a is independently selected from OH, OCH₃, halogen, a 5 to 6 membered heteroaryl, and a 3-6 membered heterocyclyl optionally substituted with C₁-C₃ alkyl optionally substituted with oxo.

3. The compound of Claim 1 or 2, wherein:

X¹ is selected from O or S;

X² is CR²;

X³ is selected from CR³ or N;

X⁴ is selected from CR⁴ or N;

X⁵ is CR⁵;

X⁶ is CR⁶;

R¹ is C₁-C₃ alkyl;

R² is hydrogen;

R³ is selected from hydrogen, halogen, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, a 3 to 6 membered carbocycle, phenyl, and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy, carbocycle, phenyl and heteroaryl are optionally substituted with halogen, a 3 to 6 membered carbocycle or C₁-C₆ alkoxy optionally substituted with halogen;

R⁴ is selected from hydrogen, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy and a 5 to 6 membered heteroaryl, wherein the alkyl, alkoxy and heteroaryl are optionally substituted with halogen, or

R³ and R⁴ together with the atoms to which they are attached form a 3 to 6 membered heterocycle;

R⁵ is selected from hydrogen or C₁-C₆ alkyl;

R⁶ is selected from hydrogen or halogen; and

R⁷ is selected from halogen, C₁-C₆ alkyl, a 3 to 6 membered carbocycle, a 3 to 6 membered saturated or partially unsaturated heterocycle, phenyl, 5 to 6 membered heteroaryl and -O(3 to 6 membered heterocycle), wherein the alkyl, phenyl, heteroaryl and heterocycle are optionally substituted with halogen, CN, C₁-C₆ alkyl or C₁-C₆ alkoxy, wherein the alkyl and alkoxy are optionally substituted with halogen.

4. The compound as claimed in any one of Claims 1 to 3, wherein R⁷ is Br, isopentyl, propyl, isobutyl, isopropyl, 4-butanenitrile, cyclopropyl, cyclohexyl, 3,6-dihydro-2H-pyran-4-yl, phenyl, 3-(difluoromethoxy)phenyl, 3-methoxyphenyl, 3-chloro-5-methoxyphenyl, 3-ethoxyphenyl, 3-cyanophenyl, 5-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-chloro-5-fluorophenyl, 3-chlorophenyl, 3-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-2-fluorophenyl, 5-chloro-2-fluorophenyl, pyridin-3-yl, 5-methoxypyridin-3-yl, 2-fluoropyridin-3-yl, 5-cyanopyridin-3-yl, 5-chloropyridin-3-yl, 5-fluoropyridin-3-yl, 5-(trifluoromethyl)pyridin-3-yl, 5-chloro-2-fluoropyridin-3-yl, 5-isobutylpyridin-3-yl, pyrimidin-5-yl or oxetan-3-yloxy.

5. The compound as claimed in any one of Claims 1 to 4, wherein R⁶ is hydrogen or F.

6. The compound as claimed in any one of Claims 1 to 5, wherein R⁵ is hydrogen or methyl.

7. The compound as claimed in any one of Claims 1 to 6, wherein R⁴ is hydrogen, -OH, isobutyl, isopropyl, -OCH₃, -OCF₃ and pyridin-3-yl.

8. The compound as claimed in any one of Claims 1 to 7, wherein R³ is hydrogen, Br, F, CN, propyl, isobutyl, -OCH₃, -OCF₃, cyclopropylmethoxy, -OCH₂CH₃, -OCH₂CHF₂, -OCH(CH₃)₂, -OCH₂CF₃, -OCH₂C(CH₃)₃, cyclopropyl, 3-(difluoromethoxy)phenyl, 5-chloropyridin-3-yl, pyridin-3-yl, 2-fluoropyridin-3-yl, 5-fluoropyridin-3-yl and pyrimidin-5-yl.

9. The compound as claimed in any one of Claims 1 to 6, wherein R³ and R⁴ together with the atoms to which they are attached form a 3 to 6 membered heterocycle, wherein the heterocycle formed is a tetrahydrofuran.

10. The compound as claimed in any one of Claims 1 to 9, wherein R² is hydrogen.

11. The compound as claimed in any one of Claims 1 to 10, wherein R¹ is selected from benzyl, methyl, ethyl, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂CH₂OCH₃, -CH₂CH₂CH₂OCH₃, -CH₂CF₃, pyridin-2-ylmethyl, pyridin-4-ylmethyl and (1-acetylpiperidin-4-yl)methyl.

12. The compound as claimed in any one of Claims 1 to 11, wherein R¹ is methyl.

13. The compound as claimed in any one of Claims 1 to 12, wherein X¹ is O.

14. The compound as claimed in any one of Claims 1 to 12, wherein X¹ is S.

15. A compound of Formula I as defined in any one of Claims 1, 2 or 3 and named in any one of Example 1 to 142 herein, or a stereoisomer, diastereomer, enantiomer,

tautomer or pharmaceutically acceptable salt thereof.

16. A compound of Formula I as defined in any one of Claims 1, 2 or 3 and named in any one of Example 1 to 102 herein, or a stereoisomer, diastereomer, enantiomer, tautomer or pharmaceutically acceptable salt thereof.

17. A method of inhibiting cleavage of APP by β -secretase in a mammal comprising administering to said mammal an effective amount of a compound of any one of Claims 1 to 16.

18. A method for treating a disease or condition mediated by the cleavage of APP by β -secretase in a mammal, comprising administering to said mammal an effective amount of a compound of any one of Claims 1 to 16.

19. The method of Claim 18, wherein the disease is Alzheimer's disease.

20. A pharmaceutical compositions comprising a compound of any one of Claims 1 to 16 and a pharmaceutically acceptable carrier, diluent or excipient.

21. Use of a compound of any one of Claims 1 to 16 in the manufacture of a medicament for the treatment of a neurodegenerative disease.

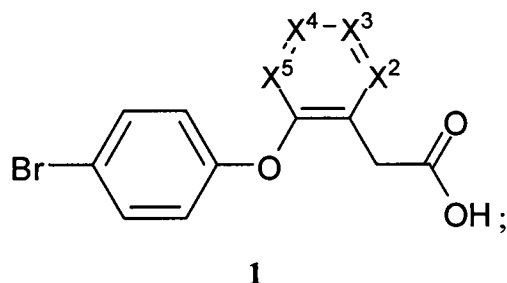
22. The use of Claim 21, wherein the disease is Alzheimer's disease.

23. A compound of any one of Claims 1 to 16 for the treatment of a neurodegenerative disease.

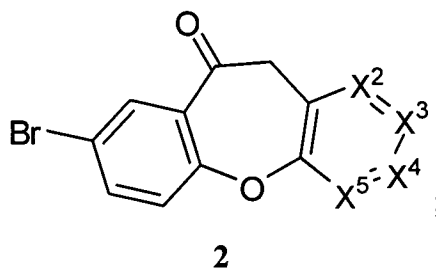
24. The compound of Claim 23, wherein the disease is Alzheimer's disease.

25. A process for preparing compounds of Formula 4 is provided, comprising:

(a) reacting a compound of Formula 1:

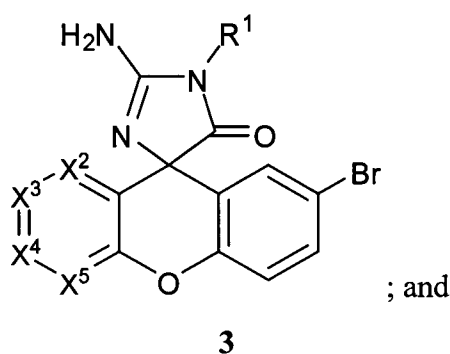


with a ring closing agent to provide a compound of Formula 2:

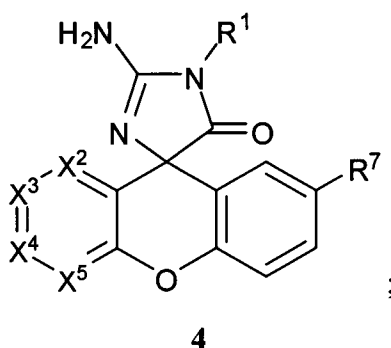


(b) reacting a compound of Formula 2 with an oxidizing agent, followed by 1-

methylguanidine to provide a compound of Formula 3:



(c) optionally (when R⁷ is not bromine) performing a Suzuki, Negishi or Stille coupling to install the R⁷ group provides compound 4:



wherein, X², X³, X⁴, X⁵, R¹ and R⁷ are as defined in Claim 1.

26. The process of Claim 25, wherein X², X³, X⁴, X⁵, R¹ and R⁷ are as defined in Claim 2.

27. The process of Claims 25 or 26, wherein X², X³, X⁴, X⁵, R¹ and R⁷ are as defined in Claim 3.

28. The process of any one of Claims 25 to 27, wherein the ring closing agent is selected from polyphosphoric acid, SOCl₂ followed by AlCl₃, or COCl₂ followed by AlCl₃.

29. The process of any one of Claims 25 to 28, wherein the ring closing agent is polyphosphoric acid.

30. The process of any one of Claims 25 to 29, wherein the oxidizing agent is selected from selenium dioxide, CuBr followed by DMSO, or N(=O)OR wherein the R is alkyl.

31. The process of any one of Claims 25 to 30, wherein the oxidizing agent is selenium dioxide.

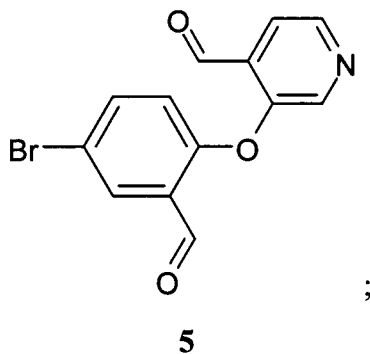
32. The process of any one of Claims 25 to 30, wherein the optional Step C is a Suzuki coupling.

33. The process of any one of Claims 25 to 30, wherein the ring closing agent is

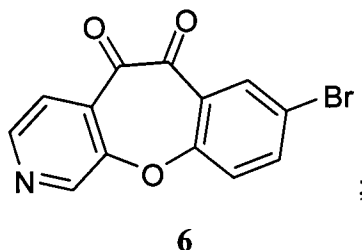
polyphosphoric acid, the oxidizing agent is selenium dioxide, and the optional Step C is a Suzuki coupling.

34. A process for preparing compounds of Formula 8 is provided, comprising:

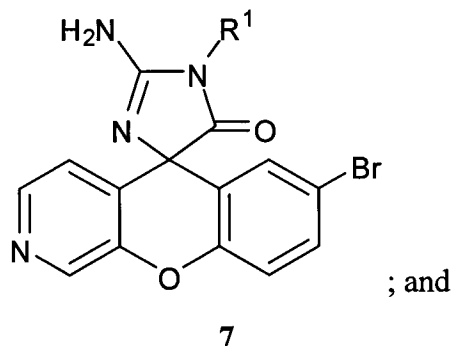
(a) reacting a compound of Formula 5:



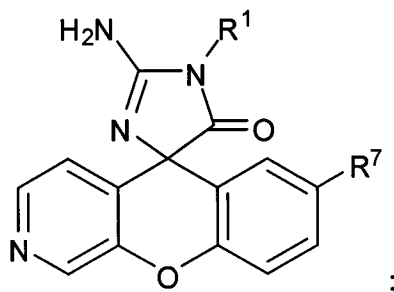
with a ring closing agent to provide a compound of Formula 6:



(b) reacting a compound of Formula 6 with an oxidizing agent, followed by 1-methylguanidine to provide a compound of Formula 7:



(c) optionally (when R^7 is not bromine) performing a Suzuki, Negishi or Stille coupling to install the R^7 group provides compound 8:



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wherein R¹ and R⁷ are as defined in Claim 1.

35. The process of Claim 34, wherein R¹ and R⁷ are as defined in Claim 2.

36. The process of Claims 34 or 35, wherein R¹ and R⁷ are as defined in Claim 3.

37. The process of any one of Claims 34 to 36, wherein, the ring closing agent is KCN under an open air atmosphere.

38. The process of any one of Claims 34 to 37, wherein the oxidizing agent is selected from selenium dioxide, CuBr followed by DMSO, or N(=O)OR wherein the R is alkyl.

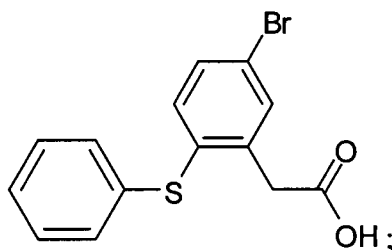
39. The process of any one of Claims 34 to 38, wherein the oxidizing agent is selenium dioxide.

40. The process of any one of Claims 34 to 39, wherein the optional Step C is a Suzuki coupling.

41. The process of any one of Claims 34 to 36, wherein the ring closing agent is KCN under an open air atmosphere, the oxidizing agent is selenium dioxide, and the optional Step C is a Suzuki coupling.

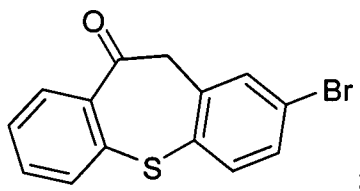
42. A process for preparing compounds of Formula 14 is provided, comprising:

(a) reacting a compound of Formula 10:



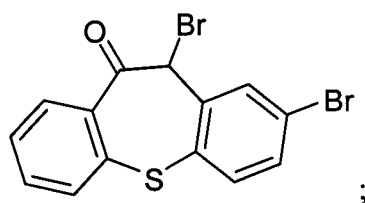
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with a ring closing agent to provide a compound of Formula 11:



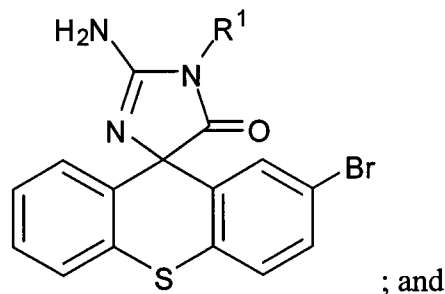
11

(b) brominating Formula 11 to provide a compound of Formula 12:



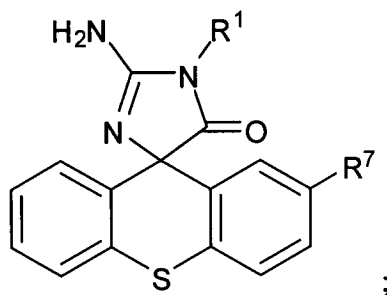
12

(c) reacting a compound of Formula 12 with KI, followed by 1-methylguanidine to provide a compound of Formula 13:



13

(d) optionally (when R⁷ is not bromine) performing a Suzuki, Negishi or Stille coupling to install the R⁷ group provides compound 14:



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wherein R¹ and R⁷ are as defined in Claim 1.

43. The process of Claim 42, wherein R¹ and R⁷ are as defined in Claim 2.
44. The process of Claims 42 or 43, wherein R¹ and R⁷ are as defined in Claim 3.
45. The process of any one of Claims 42 to 44, wherein the ring closing agent is polyphosphoric acid.
46. The process of any one of Claims 42 to 45, wherein the bromination in Step B is performed with a brominating agent.
47. The process of any one of Claims 42 to 46, wherein the bromination in Step B is performed with a brominating agent, wherein the brominating agent is CuBr₂.
48. The process of any one of Claims 42 to 47, wherein the optional Step C is a Suzuki coupling.

49. The process of any one of Claims 42 to 44, wherein the ring closing agent is polyphosphoric acid, the brominating agent is CuBr_2 , and the optional Step C is a Suzuki coupling.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/032894

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/20 C07D491/107 A61K31/4188 A61P25/28
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/030954 A1 (AMGEN INC [US]; WHITE RYAN [US]; AMEGADZIE ALBERT [US]; BRYAN MARIAN C) 18 March 2010 (2010-03-18) page 1; claims 13-15 page 1 example 3	1-49
Y	WO 2010/021680 A2 (VITAE PHARMACEUTICALS INC [US]; DILLARD LAWRENCE W [US]; YUAN JING [US]) 25 February 2010 (2010-02-25) page 1 claims 58-62 page 627; example 319 ----- -/-	1-49



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

20 May 2011

Date of mailing of the international search report

27/05/2011

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/032894

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/100536 A1 (WYETH CORP [US]; QUAGLIATO DOMINICK ANTHONY [US]; ANDRAE PATRICK MICHA) 7 September 2007 (2007-09-07) page 1; claim 14 claim 1 example 12 -----	1-49

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/032894

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010030954 A1	18-03-2010	AU 2009291602 A1	18-03-2010
		CA 2736130 A1	18-03-2010
		US 2010087429 A1	08-04-2010
WO 2010021680 A2	25-02-2010	AR 073046 A1	06-10-2010
		UY 32062 A	26-03-2010
WO 2007100536 A1	07-09-2007	NONE	