AMIDE COMPOUNDS, COMPOSITIONS AND USES THEREOF

Inventors: Zhi-Liang Wei, Foster City, CA (US); Sumithra Gowdagar, Union City, CA (US); Carl Kaub, San Mateo, CA (US); Zhan Wang, Palo Alto, CA (US); Yeye Cao, Foster City, CA (US); John Kincaid, Union City, CA (US)

Appl. No.: 13/119,947
PCT Filed: Sep. 14, 2009
PCT No.: PCT/US09/05119
§ 371(c)(1), (2), (4) Date: Jun. 6, 2011

Related U.S. Application Data
Provisional application No. 61/192,581, filed on Sep. 18, 2008, provisional application No. 61/118,228, filed on Nov. 26, 2008, provisional application No. 61/180,915, filed on May 25, 2009.

Publication Classification
Int. Cl.
A61K 31/5377 (2006.01)
C07D 401/12 (2006.01)
C07D 403/12 (2006.01)
C07D 213/56 (2006.01)
C07D 401/14 (2006.01)
C07D 413/14 (2006.01)
A61K 31/506 (2006.01)

ABSTRACT
Compounds are provided according to formula (I), where A, B, W, X, L, R', R", R', R", and m' are as defined herein. Provided compounds and pharmaceutical compositions thereof are useful for the prevention and treatment of a variety of conditions in mammals including humans, including by way of non-limiting example, pain, inflammation, cognitive disorders, anxiety, depression, and others.
AMIDE COMPOUNDS, COMPOSITIONS AND USES THEREOF

FIELD

[0001] Provided herein are heterocyclic compounds and pharmaceutical compositions comprising such compounds. Also provided are methods for preventing and/or treating conditions in mammals, such as (but not limited to) arthritis, Parkinson’s disease, Alzheimer’s disease, asthma, myocardial infarction, pain syndromes (acute and chronic or neuropathic), neurodegenerative disorders, schizophrenia, cognitive disorders, anxiety, depression, inflammatory bowel disease and autoimmune disorders, and promoting neuroprotection, using the compounds and pharmaceutical compositions provided herein.

BACKGROUND

[0002] Therapeutic strategies for the effective management of pain and central nervous system disorders or diseases are sought.

[0003] International Patent Application, Publication Number WO 08/000,645 discloses tetratzo-substituted aryldiazides and related compounds which are said to be P2X3 and P2X2,3 receptor modulators.

[0004] International Patent Application, Publication Number WO 08/055,840 discloses thiazole and oxazole substituted aryldiazides and related compounds which are said to be P2X3 and P2X2,3 receptor modulators.


[0006] US 2007037974 describes heterocyclic inhibitors of P2X3 useful for treating pain, genitourinary, gastrointestinal, and respiratory disorders.

[0007] WO 06/119504 describes fused heterocyclic compounds as P2X3 and P2X2,3 modulators for use in the treatment of various diseases. WO04/56774 describes certain substituted biphenyl-4-carboxylic acid aryldiazide analogues having possible application as receptor modulators.


[0010] WO 05/065195 describes certain phenylamides and pyridylamides as β-secretase inhibitors.

[0011] WO 02/070469 describes certain substituted sulfonylalkylcarboxamides as selective pde5b inhibitors.

[0012] WO 04/039753 defines certain benzoxic acids and related compounds as EPI receptor antagonists for the treatment of prostaglandin mediated diseases.

[0013] Also, WO03/104230 describes certain bicyclic pyrimidine derivatives, and US Published Application Serial No. 20030092908 and WO02/087513 describe fused heterocyclic PDE7 inhibitors.

[0014] U.S. Pat. Nos. 3,424,760 and 3,424,761 both describe a series of 3-ureidopyrrolidines that are said to exhibit anagelseic, central nervous system, and psychopharmacologic activities. These patents specifically disclose the compounds 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea and 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea respectively. International Patent Applications, Publication Numbers WO 01/62737 and WO 00/69849 disclose a series of pyrazole derivatives which are stated to be useful in the treatment of disorders and diseases associated with the NPY receptor subtype Y5, such as obesity. WO 01/62737 specifically discloses the compound S-amino-N-isquinolin-5-yl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxamide. WO 00/69849 specifically discloses the compounds 5-methyl-N-quinoxin-8-yl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxamide, 5-methyl-N-quinoxin-7-yl-1-[3-trifluoromethyl]phenyl]-1H-pyrazole-3-carboxamide, 5-methyl-N-quoxin-3-yl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxamide, N-isquinolin-5-yl-5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxamide, 5-methyl-N-quoxin-5-yl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxamide, 5-methyl-N-quoxin-5-yl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxamide, and 5-methyl-N-quoxin-5-yl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxamide.

[0015] German Patent Application Number 2502588 describes a series of piperazine derivatives. This application specifically discloses the compound N-[3-[2-(diethylamino)ethyl]-1,2-dihydro-4-methyl-2-oxo-7-quinoxinyl]-4-phenyl-1-piperazincarbonamide.

SUMMARY

[0016] Fused heterocyclic compounds, and pharmaceutical compositions thereof, having potency and selectivity in the prevention and treatment of conditions that have been associated with neurological and inflammatory disorders and dysfunctions are provided herein.

[0017] In particular, compounds, pharmaceutical compositions and methods provided are useful to treat, prevent or ameliorate a range of conditions in mammals such as, but not limited to, pain of various genesis or etiology, for example acute, chronic, inflammatory and neuropathic pain, dental pain and headache (such as migraine, cluster headache and tension headache). In some embodiments, compounds, pharmaceutical compositions and methods provided are useful for the treatment of inflammatory pain and associated hyperalgasia and allodynia. In some embodiments, compounds, pharmaceutical compositions and methods provided are useful for the treatment of neuropathic pain and associated hyperalgasia and allodynia (e.g. trigeminal or herpetic neuralgia, diabetic neuropathy, causalgia, sympathetically maintained pain and deafferentation syndromes such as brachial plexus avulsion). In some embodiments, compounds, pharmaceutical compositions and methods provided are useful as anti-inflammatory agents for the treatment of arthritis, and as agents to treat Parkinson’s Disease, Alzheimer’s Disease, asthma, myocardial infarction, neurodegenerative disorders, inflammatory bowel disease and autoimmune disorders, renal disorders, obesity, eating disorders, cancer, schizophrenia, epilepsy, sleeping disorders, cognitive disorders, depression, anxiety, blood pressure, and lipid disorders.
Accordingly, in one aspect, compounds are provided that have formula 1:

\[
\begin{align*}
\text{X} & \quad \text{A} \quad \text{B} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{W} & \quad \text{L} \quad \text{R}_1
\end{align*}
\]

wherein

- each of A, B, and W are independently selected from CR and N; provided that not all A, B, and W are N at the same time;
- \(X\) is selected from CR\(^4\) and N;
- \(L\) is substituted or unsubstituted \(C_1-C_9\) alkenylene or \(C_1-C_9\) heteroalkylene;
- \(R_1\) is selected from substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;
- \(R_2\) is substituted or unsubstituted \(6-10\) membered aryl, or substituted or unsubstituted \(6-10\) membered heteroaryl; or
- \(R_1\) is substituted or unsubstituted N containing heterocycloalkyl; and the heterocycloalkyl is attached to the core group via the N;
- each \(R^*_a\) is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylaminio, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylamino, substituted or unsubstituted amino, substituted or unsubstituted arylalkyl, sulfon, substituted sulfon, substituted sulfinyl, substituted sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted aminosulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted arylsulfonyle, azido, substituted or unsubstituted carbamoyl, carboxyl, amino, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkylamino, halo, amino, and thiol;
- each \(R^{4e}\) and \(R^{4f}\) is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted alkyloxyl amino, substituted or unsubstituted alkyloxyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, sulfon, substituted sulfon, substituted sulfinyl, substituted sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted alkyloxyl, the substituent or unsubstituted arylsulfonyle, azido, substituted or unsubstituted carbamoyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkylamino, halo, amino, and thiol.

In one embodiment, with respect to formula 1, \(R^1\) is selected from substituted or unsubstituted aryl, or heteroaryl;

In one embodiment, with respect to formula 1, \(R^1\) is selected from substituted or unsubstituted 4-7 membered heterocycloalkyl.

In one embodiment, with respect to formula 1, \(R^1\) is selected from substituted or unsubstituted alkyl.

In one embodiment, with respect to formula 1, \(R^1\) is selected from substituted or unsubstituted cycloalkyl.

In one embodiment, with respect to formula 1, one of A, B, and W is N; and the rest are independently selected from CR\(^4\).

In another embodiment, with respect to formula 1, each A, B, and W is independently selected from CR\(^4\).

In one particular embodiment, with respect to formula 1, each A, B, and W is CH.

In one embodiment, with respect to formula 1, the compound is according to formula 2:

\[
\begin{align*}
\text{H} & \quad \text{L} \quad \text{R}_1 \\
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4 \\
\text{R}^{4e} & \quad \text{R}^{4f}
\end{align*}
\]

wherein

- \(X^*\), \(L\), \(R^1\), \(R^2\), \(R^{4e}\), \(R^{4f}\), and \(m^*\) are as described for formula 1;
- or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

In another aspect, pharmaceutical compositions are provided comprising a fused heterocyclic compound provided herein, and a pharmaceutical carrier, excipient or diluent. The pharmaceutical composition can comprise one or more of the compounds described herein.

It will be understood that compounds provided herein useful in the pharmaceutical compositions and treatment methods disclosed herein, can be pharmaceutically acceptable as prepared and used.

In another aspect, methods are provided for preventing, treating or ameliorating a condition from among those listed herein, and particularly, such condition as may be associated with, e.g., arthritis, asthma, myocardial infarction, lipid disorders, cognitive disorders, anxiety, schizophrenia, depression, memory dysfunctions such as Alzheimers disease, inflammatory bowel disease and autoimmune disorders, which method comprises administering to a mammal in nee thereof an amount of one or more of the compounds as pro-
vided herein, or pharmaceutical composition thereof, effective to prevent, treat or ameliorate the condition.

In yet another aspect, methods are provided for preventing, treating or ameliorating a neurodegenerative disease or disorder in a mammal. A neurodegenerative disease or disorder can, for example, be Parkinson’s disease, Alzheimer’s disease and multiple sclerosis; diseases and disorders which are mediated by or result in neuroinflammation such as, for example, encephalitis; centrally-mediated neuropsychiatric diseases and disorders such as, for example, depression, mania, bipolar disease, anxiety, schizophrenia, eating disorders, sleep disorders and cognition disorders; epilepsy and seizure disorders; prostate, bladder and bowel dysfunction such as, for example, urinary incontinence, urinary hesitancy, rectal hypersensitivity, fecal incontinence, benign prostatic hypertrophy and inflammatory bowel disease; respiratory and airway disease and disorders such as, for example, allergic rhinitis, asthma and reactive airway disease and chronic obstructive pulmonary disease; diseases and disorders which are mediated by or result in inflammation such as, for example, rheumatoid arthritis and osteoarthritis, myocardial infarction, various autoimmune diseases and disorders; itch/pruritus such as, for example, psoriasis; obesity; lipid disorders; and renal disorders. Typically, the methods comprise administering an effective condition-treating or condition-preventing amount of one or more of the compounds as provided herein, or pharmaceutical composition thereof, to the mammal in need thereof.

In addition to the methods of treatment set forth above, the present invention extends to the use of any of the compounds of the invention for the preparation of medicaments that may be administered for such treatments, as well as to such compounds for the treatments disclosed and specified.

In additional aspects, methods are provided for synthesizing the compounds described herein, with representative synthetic protocols and pathways described below. In certain embodiments, provided are methods of making enantiomerically pure compounds according to formula 1 by asymmetric synthesis. In certain embodiments, provided are methods of making enantiomerically pure compounds according to formula 1 by chiral resolution.

Accordingly, it is a principal object of this invention to provide a novel series of compounds, which can modify the activity of the P2X3 receptor and thus avert or treat any maladies that may be causally related thereto.

It is further an object of this invention to provide a series of compounds that can treat or alleviate maladies or symptoms of same, such as pain and inflammation, that may be causally related to the activation of the P2X3 receptor.

A still further object of this invention is to provide pharmaceutical compositions that are effective in the treatment or prevention of a variety of disease states, including the diseases associated with the central nervous system, cardiovascular conditions, chronic pulmonary obstructive disease COPD, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, and other diseases where an inflammatory component is present.

Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term “substituted” is to be defined as set out below. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein.

The articles “a” and “an” may be used herein to refer to one or to more than one (i.e. at least one) of the grammatical objects of the article. By way of example, “an analogue” means one analogue or more than one analogue.

‘Acyl’ or ‘Alkanoyl’ refers to a radical —CO(OR)₂⁻, where R is hydrogen, C₁₋₆ alkyl, C₅₋₁₀ cycloalkyl, C₇₋₁₀ cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, aralkyl, 5-10 membered heteroaryl or heteroaryalkyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylo-carbonyl, cyclohexylmethyl-carbonyl, benzoyl and benzylo-carbonyl. Exemplary ‘acyl’ groups are —C(O)H, —C(O) —C₁₋₆ alkyi, —C(O)(—CH₂)(C₁₋₁₀ aryl), —C(O)(—CH₂)(5-10 membered heteroaryl), —C(O)(—CH₂)(C₅₋₁₀ cycloalkyl), and —C(O)(—CH₂)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

‘Substituted Acyl’ or ‘Substituted Alkanoyl’ refers to a radical —CO(R')⁻, wherein R’ is independently

C₁₋₆ alkyl, substituted with halo or hydroxy; or
C₅₋₁₀ cycloalkyl, 4-10 membered heterocycloalkyl, C₅₋₁₀ aryl, aralkyl, 5-10 membered heteroaryl or heteroaryalkyl, each of which is substituted with unsubstituted C₁₋₆ alkyl, halo, unsubstituted C₁₋₆ haloalkyl, unsubstituted C₁₋₆ hydroxalkyl, or unsubstituted C₁₋₆ haloalkoxy or hydroxy.
‘Acylamino’ refers to a radical —NR\(^2\)C(O)R\(^2\), where R\(^2\) is hydrogen, C\(_1\)-C\(_8\) alkyl, C\(_3\)-C\(_10\) cycloalkyl, 4-10 membered heterocycloalkyl, C\(_6\)-C\(_10\) aryl, aralkyl, 5-10 membered heteroaryl or heteroaryalkyl and R\(^3\) is hydrogen, C\(_1\)-C\(_8\) alkyl, C\(_3\)-C\(_10\) cycloalkyl, 4-10 membered heterocycloalkyl, C\(_6\)-C\(_10\) aryl, aralkyl, 5-10 membered heteroaryl or heteroaryalkyl, as defined herein. Exemplary ‘acylamo’ include, but are not limited to, formylamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino and benzylcarbonylamino. Particular exemplary ‘acylamino’ groups are —NR\(^2\)C(O)—C\(_8\) alky, —NR\(^2\)C(O)—(CH\(_3\))\(_2\), C\(_6\)-C\(_10\) aryl, —NR\(^2\)C(O)—(CH\(_3\))\(_2\)(5-10 membered heteroaryl), —NR\(^2\)C(O)—(CH\(_3\))\(_2\) (C\(_3\)-C\(_10\) cycloalkyl), and —NR\(^2\)C(O)—(CH\(_3\))\(_2\)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4, and each R\(^2\) is independently represents H or C\(_1\)-C\(_8\) alkyl.

‘Substituted Acyloxy’ refers to a radical —OC(O)R\(^2\), wherein:

R\(^2\) is hydrogen, C\(_1\)-C\(_8\) alkyl, substituted with halo or hydroxy; or

C\(_3\)-C\(_10\) cycloalkyl, 4-10 membered heterocycloalkyl, C\(_6\)-C\(_10\) aryl, aralkyl, 5-10 membered heteroaryl or heteroaryalkyl, each of which is substituted with unsubstituted C\(_1\)-C\(_4\) alkyl, halo, unsubstituted C\(_1\)-C\(_2\) alkoxy, unsubstituted C\(_1\)-C\(_2\) halooalkyl, unsubstituted C\(_1\)-C\(_4\) hydroxyalkyl, or unsubstituted C\(_1\)-C\(_4\) haloalkoxy or hydroxy; and

provided at least one of R\(^2\) is R\(^3\) and R\(^2\) is other than H.

‘Acyloxy’ refers to a radical —OC(O)R\(^2\), where R\(^2\) is hydrogen, C\(_1\)-C\(_8\) alkyl, C\(_3\)-C\(_10\) cycloalkyl, C\(_3\)-C\(_10\) cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, aralkyl, 5-10 membered heteroaryl or heteroaryalkyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexyloxy carbonyl, cyclohexylmethyloxycarbonyl, benzyl and benzylcarbonyl. Exemplary ‘acyl’ groups are —O(H), —O—(CH\(_3\))\(_2\), C\(_6\)-C\(_10\) aryl, —O—(CH\(_3\))\(_2\)(5-10 membered heteroaryl), —O—(CH\(_3\))\(_2\)(C\(_3\)-C\(_10\) cycloalkyl), and —O—(CH\(_3\))\(_2\)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

‘Substituted Acyloxy’ refers to a radical —OC(O)R\(^2\), wherein R\(^2\) is independently

C\(_1\)-C\(_8\) alkyl, substituted with halo or hydroxy; or

C\(_3\)-C\(_10\) cycloalkyl, 4-10 membered heterocycloalkyl, C\(_6\)-C\(_10\) aryl, aralkyl, 5-10 membered heteroaryl or heteroaryalkyl, each of which is substituted with unsubstituted C\(_1\)-C\(_4\) alkyl, halo, unsubstituted C\(_1\)-C\(_2\) alkoxy, unsubstituted C\(_1\)-C\(_2\) halooalkyl, unsubstituted C\(_1\)-C\(_4\) hydroxyalkyl, or unsubstituted C\(_1\)-C\(_4\) haloalkoxy or hydroxy.

‘Alkoxycarbonyl’ refers to a radical —C(O)—OR\(^2\), where R\(^2\) represents an C\(_1\)-C\(_2\) alkyl, C\(_3\)-C\(_10\) cycloalkyl, C\(_6\)-C\(_10\) cycloalkylalkyl, 4-10 membered heterocycloalkyl, arylalkyl, or 5-10 membered heteroaryalkyl as defined herein. Exemplary “alkoxycarbonyl” groups are CO\(_2\)C\(_1\)-C\(_8\) alkyl, —CO\(_2\)(CH\(_3\))\(_2\), C\(_6\)-C\(_10\) aryl, —CO\(_2\)(CH\(_3\))\(_2\)(5-10 membered heteroaryl), —CO\(_2\)(CH\(_3\))\(_2\)(C\(_3\)-C\(_10\) cycloalkyl), and —CO\(_2\)(CH\(_3\))\(_2\)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4.

‘Substituted Alkoxycarbonyl’ refers to a radical —C(O)—OR\(^2\), wherein R\(^2\) represents:

C\(_1\)-C\(_8\) alkyl, C\(_3\)-C\(_10\) cycloalkyl, C\(_6\)-C\(_10\) cycloalkylalkyl, or 4-10 membered heterocycloalkyl, each of which is substituted with halo, substituted or unsubstituted amino, or hydroxy; or

C\(_6\)-C\(_10\) aralkyl, or 5-10 membered heteroaryalkyl, each of which is substituted with unsubstituted C\(_1\)-C\(_4\) alkyl, halo, unsubstituted C\(_1\)-C\(_2\) alkoxy, unsubstituted C\(_1\)-C\(_2\) halooalkyl, unsubstituted C\(_1\)-C\(_4\) hydroxyalkyl, or unsubstituted C\(_1\)-C\(_4\) haloalkoxy or hydroxyl.

‘Arylalkoxycarbonyl’ refers to a radical —C(O)—OR\(^2\), where R\(^2\) represents an C\(_1\)-C\(_10\) aryl, as defined herein. Exemplary “arylalkoxycarbonyl” groups is —C(O)—(CH\(_3\))\(_2\) (C\(_6\)-C\(_10\) aryl).

‘Substituted Arylalkoxycarbonyl’ refers to a radical —C(O)—OR\(^2\), where R\(^2\) represents:

C\(_6\)-C\(_10\) aryl, substituted with unsubstituted C\(_1\)-C\(_4\) alkyl, halo, unsubstituted C\(_1\)-C\(_2\) alkoxy, unsubstituted C\(_1\)-C\(_2\) halooalkyl, unsubstituted C\(_1\)-C\(_4\) hydroxyalkyl, or unsubstituted C\(_1\)-C\(_4\) haloalkoxy or hydroxyl.

‘Heteroaryloxyalkyl’ refers to a radical —C(O)—OR\(^2\), where R\(^2\) represents a 5-10 membered heteroaryl, as defined herein. An exemplary “heteroaryloxyalkyl” group is —C(O)(O)-(5-10 membered heteroaryl).

‘Substituted Heteroaryloxyalkyl’ refers to a radical —C(O)—OR\(^2\), where R\(^2\) represents:

5-10 membered heteroaryl, substituted with unsubstituted C\(_1\)-C\(_4\) alkyl, halo, unsubstituted C\(_1\)-C\(_4\)
alkoxy, unsubstituted C₁-C₄ haloalkyl, unsubstituted C₁-C₄ hydroxyalkyl, or unsubstituted C₁-C₄ haloalkoxy or hydroxyl.

[0083] ‘Alkoxycarbonylaminol’ refers to the group —NR₃C(O)OR, where R₃ is hydrogen, C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, aralkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein, and R₃ is C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkylmethyl, 4-10 membered heterocycloalkyl, aryl, aralkyl, 5-10 membered heteroaryl or heteroarylalkyl as defined herein.

[0084] ‘Alkyl’ means straight or branched aliphatic hydrocarbons having 1 to 20 carbon atoms. Particular alkyl has 1 to 12 carbon atoms. More particular is lower alkyl which has 1 to 6 carbon atoms. A further particular group has 1 to 4 carbon atoms. Exemplary straight chained groups include methyl, ethyl, n-propyl, and n-butyl. Branched means that one or more lower alkyl groups such as methyl, ethyl, propyl or butyl is attached to a linear alkyl chain, exemplary branched chain groups include isopropyl, iso-butyl, t-butyl and isooynyl.

[0085] ‘Substituted alkyl’ refers to an alkyl group as defined above substituted with one or more of those groups recited in the definition of “substituted” herein, and particularly refers to an alkyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent, selected from the group consisting of acyl, acylamino, acyloxy (—O—acyl or —O(C(O))R), alkoxy, alkoxycarbonyl, alkoxycarbonylaminol (—NR₃C(O)OR), amino, substituted amino, aminocarbonylamino, aminocarbonyloxy, amino, substituted amino, amino, amino, substituted amino, aminocarbonylamino, amino, substituted amino, aminocarbonylamino, aminocarboxyamide, amino, substituted amino, aminocarbonylamino, aminocarbonyloxy, aryl, aryl, azido, carboxyl, cyano, cycloalkyl, halogen, hydroxy, heteroaryl, nitro, thiol, —SR, —S-aryl, —S-(O)-alkyl, —S-(O)-aryl, —S-O₅-alkyl, and —S-O₅-aryl. In a particular embodiment ‘substituted alkyl’ refers to a C₁-C₄ alkyl group substituted with halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, —NR₃SO₂R’, —SO₃ NR₃R’, —C(O)R’, —C(OR)₃, —OC(OR)₃, —NR₃C(O)R’, —C(O)NR₃R’, —NR₃R’ or —(CR₃R’), wherein each R’ is independently selected from H, C₁-C₄ alkyl, (CH₂)₇C₁-C₄ alkyl, —(CH₂)₇(5-10 membered heteroaryl), —(CH₂)₇C₁-C₄ alkyl, and —(CH₂)₇C₁-C₄ alkyl, wherein t is an integer from 0 to 4 and any aryl, heterocycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C₁-C₄ alkyl, halo, unsubstituted C₁-C₄ alkyl, unsubstituted C₁-C₄ haloalkyl, or unsubstituted C₁-C₄ haloalkoxy, or hydroxyl. Each of R” and R”’ independently represents H or C₁-C₄ alkyl.

[0086] ‘Alkylene’ refers to divalent saturated alkene radical groups having 1 to 11 carbon atoms and more particularly 1 to 6 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as methylene (—CH₂—), ethylene (—CH₂CH₂—), the propylene isomers (e.g., —CH₂CH₂CH₂— and —CH(CH₃)CH₂—) and the like.

[0087] ‘Substituted alkylene’ refers to those groups recited in the definition of “substituted” herein, and particularly refers to an alkylene group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxycarbonyl, alkoxycarbonylamino, aminocarbonyl, aminocarbonylaminol, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryl, azido, carboxyl, cyano, halogen, hydroxyl, keto, nitro, thioketoxyl, substituted thioketoxyl, thioaryloxy, thioketoxyl, thioketoxyl, alkyl-S(O)—, aryl-S(O)—, alkyl-S(O)₂— and aryl-S(O)₂—.

[0088] ‘Alkenyl’ refers to monovalent olefinically unsaturated hydrocarbyl groups preferably having 2 to 11 carbon atoms, particularly from 2 to 8 carbon atoms, and more particularly, from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. Particular alkenyl groups include ethenyl (—CH═CH₂), n-propenyl (—CH₂CH═CH₂), isopropenyl (—C(CH₃)═CH₂), vinyl and substituted vinyl, and the like.

[0089] ‘Substituted alkenyl’ refers to those groups recited in the definition of “substituted” herein, and particularly refers to an alkenyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryl, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioketoxyl, substituted thioketoxyl, thioaryloxy, thioketoxyl, thioketoxyl, alkyl-S(O)—, aryl-S(O)—, alkyl-S(O)₂— and aryl-S(O)₂—.

[0090] ‘Alkenylene’ refers to divalent olefinically unsaturated hydrocarbyl groups preferably having 2 to 11 carbon atoms, and more particularly 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. This term is exemplified by groups such as ethenylenol (—CH═CH—), the propenylenes isomers (e.g., —CH═CH═CH— and —CH(CH₃)═CH— and —CH=C(CH₃)—) and the like.

[0091] ‘Alkynyl’ refers to acetylenically or alkynically unsaturated hydrocarbyl groups preferably having 2 to 11 carbon atoms, and more particularly 2 to 6 carbon atoms which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of alkynyl unsaturation. Particular non-limiting examples of alkynyl groups include acetylenyl, ethynyl (—C≡CH), propargyl (—CH₂C≡CH), and the like.

[0092] ‘Substituted alkynyl’ refers to those groups recited in the definition of “substituted” herein, and particularly refers to an alkynyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, acyloxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryl, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioketoxyl, substituted thioketoxyl, thioaryloxy, thioketoxyl, thioketoxyl, alkyl-S(O)—, aryl-S(O)—, alkyl-S(O)₂— and aryl-S(O)₂—.

[0093] ‘Amino’ refers to the radical —NH₂.

[0094] ‘Substituted amino’ refers to an amino group substituted with one or more of those groups recited in the definition of ‘substituted’ herein, and particularly refers to the group —NR₃(R’), where each R₃ is independently selected from:
When both \( R^3 \) groups are hydrogen, \( -\text{NR}^3 \) is an amino group. Examples of substituted amino groups are \( \text{NR}^3 = \text{C}_1^\text{a}-\text{C}_6^\text{a} \) alkyl, \( \text{NH}^\text{C}_1^\text{a}-\text{C}_6^\text{a} \) aryl, \( \text{NH}^\text{C}_1^\text{a}-\text{C}_6^\text{a} \) haloalkyl, \( \text{NH}^\text{C}_1^\text{a}-\text{C}_6^\text{a} \) haloalkoxy, or unsubsti-
tuted \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) haloalkyl, or unsubsti-
tuted \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) haloalkoxy or hydroxy; or

both \( R^3 \) groups are joined to form an alkylene group.

Alkylamino’ refers to the group \(-\text{NH}^\text{R}^4\text{R}^4\), wherein \( R^4\) is \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) alkyl.

Substituted Alkylamino’ refers to the group

\(-\text{NR}^3\text{R}^3\), wherein \( R^3\) is \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) alkyl; and the alkyl group is

replaced with halo, substituted amino, amino, hydroxy, \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) cyclalkyl, 4-10 membered heterocy-

cloalkyl, \( \text{C}_7^\text{a}-\text{C}_{10}^\text{a} \) aryl, 5-10 membered heteroaryl, anil or heteroarylamino.

For the avoidance of doubt the term “substituted amino” includes the groups alkylamino, substituted alkylamino, alkyarylamin, sub-
nstituted alkylarylamin, arylamin, and dialkylamino, as defined below.

Alkylamino’ refers to the group \(-\text{NR}^4\text{R}^4\), wherein \( R^4\) is \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) alkyl.

Substituted Alkylamino’ refers to the group

\(-\text{NR}^3\text{R}^3\), wherein \( R^3\) is \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) alkyl and the alkyl group is

replaced with halo, substituted amino, amino, hydroxy, \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) cyclalkyl, 4-10 membered heterocy-

cloalkyl, \( \text{C}_7^\text{a}-\text{C}_{10}^\text{a} \) aryl, 5-10 membered heteroaryl, anil or heteroarylamino.

For the avoidance of doubt the term “substituted amino” includes the groups alkylamino, substituted alkylamino, alkyarylamin, sub-
nstituted alkylarylamin, arylamin, and dialkylamino, as defined below.

Alkylamino’ refers to the group \(-\text{NR}^4\text{R}^4\), wherein \( R^4\) is \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) alkyl.

Substituted Alkylamino’ refers to the group

\(-\text{NR}^3\text{R}^3\), wherein \( R^3\) is \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) alkyl and the alkyl group is

substituted with halo, substituted amino, amino, hydroxy, \( \text{C}_1^\text{a}-\text{C}_6^\text{a} \) cyclalkyl, 4-10 membered heterocy-

cloalkyl, \( \text{C}_7^\text{a}-\text{C}_{10}^\text{a} \) aryl, 5-10 membered heteroaryl, anil or heteroarylamino.

For the avoidance of doubt the term “substituted amino” includes the groups alkylamino, substituted alkylamino, alkyarylamin, sub-
nstituted alkylarylamin, arylamin, and dialkylamino, as defined below.
or poly-cyclic that includes from 5 to 12 ring members, more usually 6 to 10. Where the aryl group is a monocyclic ring system it preferentially contains 6 carbon atoms. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acenaphthene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexylene, hexylene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthene, rubene, triphenylene and triphenathylene. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydrophenyl.

[0117] ‘Substituted Aryl’ refers to an aryl group substituted with one or more of those groups recited in the definition of ‘substituted’ herein, and particularly refers to an aryl group that may optionally be substituted with 1 or more substituents, for instance from 1 to 5 substituents, particularly 1 to 3 substituents, in particular 1 substituent. Particularly, ‘Substituted Aryl’ refers to an aryl group substituted with one or more of groups selected from halo, C1-C8 alkyl, C1-C4 haloalkyl, cyano, hydroxy, C1-C4 haloxy, and amino.

[0118] Examples of representative substituted aryls include the following

![Diagram of substituted aryls]

In these formulae one of R56 and R57 may be hydrogen and at least one of R56 and R57 is each independently selected from C1-C4 alkyl, C1-C4 haloalkyl, 4-10 membered heterocycloalkyl, alkanoyl, C1-C4 alkoxo, heteroarylalkoxy, arylamino, N-acylamino, NR2COR, NR2SOR, NR2NR2SO, COOaryl, CONR2, CONR2OR, CONR2SR, CONR2SO, NR2SO, SO2aryl, S-aryl, SOaryl, saryl, SO2aryl; or R56 and R57 may be formed to join a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O or S. R60 and R61 are independently hydrogen, C1-C8 alkyl, C1-C4 haloalkyl, C1-C4 haloalkoxy, 4-10 membered heterocycloalkyl, C6-C10 aryl, substituted aryl, 5-10 membered heteroaryl.

[0119] ‘Fused Aryl’ refers to an aryl having two of its ring carbon in common with a second aryl ring or with an aliphatic ring.

[0120] ‘Arylalkylxylo’ refers to an –O-alkylaryl radical where alkylaryl is as defined herein.

[0121] ‘Substituted Arylalkylxylo’ refers to an –O-alkylaryl radical where alkylaryl is as defined herein; and any aryl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, cyano, unsubstituted C1-C4 alkoxo, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 haloalkoxy, or unsubstituted C1-C4 haloxy or hydroxy.

[0122] ‘Azido’ refers to the radical —N3.

[0123] ‘Carbamoyl or amido’ refers to the radical —C(O)NH2.

[0124] ‘Substituted Carbamoyl or substituted amido’ refers to the radical —C(O)NR2(R56)2 wherein each R56 is independently

[0125] H, C1-C4 alkyl, C5-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C1-C4 haloalkyl, 5-10 membered heteroaryl, and heteroarylalkyl; or

[0126] C1-C4 alkyl substituted with halo or hydroxy; or

[0127] C5-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C5-C10 aryl, 5-10 membered heteroaryl, or heteroarylalkyl, each of which is substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 haloalkoxy, unsubstituted C1-C4 haloxy, unsubstituted C1-C4 haloalkoxy or hydroxy;

provided that at least one R56 is other than H.

Exemplary ‘Substituted Carbamoyl’ groups are —C(O)NR2-R56-C1-C4 alkyl, —C(O)NR2-R56—(CH2)2-C6-C10 aryl, —C(O)NR2-R56—(CH2)3(5-10 membered heteroaryl), —C(O)NR2-R56—(CH2)3-C6-C10 cycloalkyl, and —C(O)NR2-R56—(CH2)3-C6-C10 cycloalkyl, wherein t is an integer from 0 to 4, each R56 independently represents H or C1-C4 alkyl and any aryl, heteroaryl, cycloalkyl or heteroarylalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 haloalkoxy, unsubstituted C1-C4 haloxy, unsubstituted C1-C4 haloalkoxy or hydroxy.

[0128] ‘Carboxy’ refers to the radical —C(O)OH.

[0129] ‘Cycloalkyl’ refers to cyclic non-aromatic hydrocarbyl groups having from 3 to 10 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopentyl, cyclobutyl, cyclopropyl, and cyclooctyl.

[0130] ‘Substituted cycloalkyl’ refers to a cycloalkyl group as defined above substituted with one or more of those groups recited in the definition of ‘substituted’ herein, and particularly refers to a cycloalkyl group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, in particular 1 substituent.

[0131] ‘Cyano’ refers to the radical —CN.

[0132] ‘Halo’ or ‘halogen’ refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Partial halo groups are either fluoro or chloro.

[0133] ‘Hetero’ when used to describe a compound or a group present on a compound that means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, e.g. heteroaryl, cycloalkyl, e.g. heterocycloalkyl, ary1, e.g. heteroaryl, cycloalkyl, e.g. cyclohexylalkyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0134] ‘Heteroaryl’ means an aromatic ring structure, mono-cyclic or poly-cyclic, that includes one or more heteroatoms and 5 to 12 ring members, more usually 5 to 10 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom.
In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups. Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazoimidazole. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzothiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzothiazole, benzisothiazole, isobenzofuran, indole, isoindole, isoindolone, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine, triazolopyrimidine, benzodioxole and pyrazolopyridine groups. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiocromane, chromene, isochromene, chroman, isochroman, benzodioxan, quinolinizine, benzoazaine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinoline, phthalazine, naphthyridine and pteridine groups. Particular heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

Examples of representative heteroaryls include the following:

![Heteroaryl Examples](image1)

[0135] Examples of representative heteroaryls include the following:

![Heteroaryl Examples](image2)

wherein each Y is selected from carbonyl, N, NR, O and S; and R is independently hydrogen, C1-C8 alkyl, C2-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, and 5-10 membered heteroaryl.

[0136] Examples of representative aryl having hetero atoms containing substitution include the following:

![Aryl Examples](image3)

wherein each W is selected from C(R), NR, O and S; and each Y is selected from carbonyl, NR, O and S; and R is independently hydrogen, C1-C8 alkyl, C2-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, and 5-10 membered heteroaryl.

[0137] As used herein, the term 'heterocycloalkyl' refers to a 4-10 membered, stable heterocyclic non-aromatic ring and/or including rings containing one or more heteroatoms independently selected from N, O and S, fused thereto. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyridoline (e.g. 1-pyrididinyl, 2-pyrididinyl and 3-pyrididinyl), pyrrolidine, pyrrole (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydropyran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxa- nane, tetrahydrofuran (e.g. 4-tetrahydro pyran), imidazoline, imidazolidone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperezine, and N-alkyl piperezines such as N-methyl piperezine. Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include azetidine, piperidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Particular examples of heterocycloalkyl groups are shown in the following illustrative examples:

![Heterocycloalkyl Examples](image4)

wherein each W is selected from CR, C(R), NR, O and S; and each Y is selected from NR, O and S; and R is independently hydrogen, C1-C8 alkyl, C2-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C10 aryl, 5-10 membered heteroaryl. These heterocycloalkyl rings may be optionally substituted with one or more groups selected from the group consisting of acyl, acylamino, acyloxy, alkox,
alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, amino carbonyl (carbamoylamino), aminosulfonyl, sulfonamido, aryl, aryloxy, azido, carbonyl, cyano, cycloalkyl, halogen, hydroxy, keto, nitro, thiol, —S—alkyl, —S—aryl, —S(O)alkyl, —S(O)aryl, —S(O)2alkyl, and —S(O)2aryl. Substituting groups include carbonyl or thio carbonyl which provide, for example, lactam and urea derivatives.

[0138] ‘Hydroxyl’ refers to the radical —OH.

[0139] ‘Nitro’ refers to the radical —NO2.

[0140] ‘Substituted’ refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents may be selected from the group consisting of:

halogen, —R85 —O—, —O— —OR86, —SR87, —S—, —S—NR88R89, —NR88R89, —CCl83, —CF83, —CN, —OCN, —SCN, —NO2, —NO2, —N2, —N3, —SO(O)O—, —SO(O)R88, —OS(O)2O—, —OS(O)2R88, —P(O)OR88, —P(O)OR88 —O—, —O—(OR88)OR89, —OR88, —CR87—R88, —CR87—OR88, —CR87—NR88R89, —CN—CN, —CNR88R89, —NR87—CNR88R89, —NR87—CNR88R89, —NR87—CNR88R89, —NR87—CNR88R89, —NR87—CNR88R89, —NR87—CNR88R89, —NR87—CNR88R89, wherein each R85, R86, R87 and R88 are independently:

[0141] hydrogen, C1—C6 alkyl, C1—C6 aryl, aralkyl, C5—C10 cycloalkyl, 4—10 membered heterocycloalkyl, 5—10 membered heterocycloalkyl, or

[0142] C1—C6 alkyl substituted with halo or hydroxyl; or

[0143] C1—C6 aryl, 5—10 membered heteroaryl, C1—C6 cycloalkyl or 4—10 membered heterocycloalkyl each of which is substituted by unsubstituted C1—C6 alkyl, halo, unsubstituted C1—C6 alkyl, unsubstituted C1—C6 halalkyl, unsubstituted C1—C6 hydroxyalkyl, or unsubstituted C1—C6 haloalkoxy or hydroxyl.

In a particular embodiment, substituted groups are substituted with one or more substituents, particularly with 1 to 3 substituents, in particular with one substituent group.

[0144] In a further particular embodiment the substituent group or groups are selected from halo, cyano, nitro, trifluoro methyl, trifluoromethoxy, azido, —NR25SO2R27, —SO2NR25R26, —C(O)R27, —C(O)R27, —OC(O)R27, —OC(O)R27, —NR25C(O)R27, —OC2NR25R26, —NR25—C(O)R27, —(CR25R26)2, wherein each R25 is independently selected from H, C1—C6 alkyl, (CH2)2C1—C6 aryl), (CH2)2C1—C6 cycloalkyl), and (CH2)2C1—C6 cycloalkyl), and wherein R25 is an integer from 0 to 4; and

[0145] any alkyl groups present, may themselves be substituted by halo or hydroxyl; and

[0146] any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1—C6 alkyl, halo, unsubstituted C1—C6 alkoxy, unsubstituted C1—C6 haloalkyl, unsubstituted C1—C6 haloalkoxy or hydroxy. Each R1 independently represents H or C1—C6 alkyl.

[0147] ‘Substituted sulfanyl’ refers to the group —SR74, wherein R74 is selected from:

[0148] C1—C6 alkyl, C1—C6 cycloalkyl, 4—10 membered heterocycloalkyl, C1—C6 ary1, aralkyl, 5—10 membered heteroaryl, and heteroaryalkyl; or

[0149] C1—C6 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxyl; or

[0150] C1—C6 cycloalkyl, 4—10 membered heterocycloalkyl, C1—C6 aryl, aralkyl, 5—10 membered heteroaryl, or heteroaryalkyl, each of which is substituted by unsubstituted C1—C6 alkyl, halo, unsubstituted C1—C6 alkoxy, unsubstituted C1—C6 haloalkyl, unsubstituted C1—C6 haloalkoxy or hydroxy.

[0151] Exemplary ‘substituted sulfanyl’ groups are —S—(C1—C6 alkyl) and —S—(C1—C6 cycloalkyl), —S—(CH2)2C1—C6 aryl), —S—(CH2)2(5—10 membered heteroaryl), —S—(CH2)2C1—C6 cycloalkyl), and —S—(CH2)2(4—10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1—C6 alkyl, halo, unsubstituted C1—C6 alkoxy, unsubstituted C1—C6 haloalkyl, unsubstituted C1—C6 haloalkoxy or hydroxy.

[0152] ‘Alkylthio’ or ‘Alkylsulfanyl’ refers to a radical —SR74, where R74 is a C1—C6 alkyl group as defined herein. Representative examples include, but are not limited to, methylthio, ethylthio, propylthio and butylthio.

[0153] ‘Substituted Alkylthio’ or ‘Substituted alkylsulfanyl’ refers to the group —SR76 where R76 is a C1—C6 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxyl.

[0154] ‘Cycloalkylthio’ or ‘Cycloalkylsulfanyl’ refers to a radical —SR76 where R76 is a C1—C6 cycloalkyl group as defined herein. Representative examples include, but are not limited to, cyclopentylthio, cyclohexylthio, and cyclopentylthio.

[0155] ‘Substituted cycloalkylthio’ or ‘Substituted cycloalkylsulfanyl’ refers to the group —SR78 where R78 is a C1—C6 cycloalkyl substituted with halo, substituted or unsubstituted amino, or hydroxyl.

[0156] ‘Arythio’ or ‘Arylsulfanyl’ refers to a radical —SR79 where R79 is a C6—C10 aryl group as defined herein.

[0157] ‘Heteroarythio’ or ‘Heteroarylsulfanyl’ refers to a radical —SR80 where R80 is a 5—10 membered heteroaryl group as defined herein.

[0158] ‘Substituted sulfanyl’ refers to the group —SR81, wherein R81 is selected from:

[0159] C1—C6 alkyl, C1—C6 cycloalkyl, 4—10 membered heterocycloalkyl, C1—C6 aryl, aralkyl, 5—10 membered heteroaryl, and heteroaryalkyl; or

[0160] C1—C6 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxyl; or

[0161] C1—C6 cycloalkyl, 4—10 membered heterocycloalkyl, C1—C6 ary1, aralkyl, 5—10 membered heteroaryl, or heteroaryalkyl, each of which is substituted by unsubstituted C1—C6 alkyl, halo, unsubstituted C1—C6 alkoxy, unsubstituted C1—C6 haloalkyl, unsubstituted C1—C6 haloalkoxy or hydroxy.

[0162] Exemplary ‘substituted sulfanyl’ groups are —S—(C1—C6 alkyl) and —S—(C1—C6 cycloalkyl), —S—(CH2)2C1—C6 aryl), —S—(CH2)2(5—10 membered heteroaryl), —S—(CH2)2C1—C6 cycloalkyl), and —S—(CH2)2(4—10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl groups present, may themselves be sub-
stituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy. The term substituted sulfinyl includes the groups ‘alkylsulfinyl’, ‘substituted alkylsulfinyl’, ‘cycloalkylsulfinyl’, ‘substituted cycloalkylsulfinyl’, ‘arylsulfinyl’ and ‘hetereoaryl sulfinyl’ as defined herein.

0163. ‘Alkylsulfinyl’ refers to a radical —S(O)R82 where R82 is a C1-C4 alkyl group as defined herein. Representative examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl.

0164. ‘Substituted Alkylsulfinyl’ refers to a radical —S(O)R83 where R83 is a C1-C4 alkyl group as defined herein, substituted with halo, substituted or unsubstituted amino, or hydroxy.

0165. ‘Cycloalkylsulfinyl’ refers to a radical —S(O)R84 where R84 is a C5-C10 cycloalkyl or group as defined herein. Representative examples include, but are not limited to, cyclopropylsulfinyl, cyclobutylsulfinyl, and cyclopentylsulfinyl. Exemplary ‘cycloalkylsulfinyl’ groups are S(O)—C5=C4 cycloalkyl.

0166. ‘Substituted cycloalkylsulfinyl’ refers to the group —S(O)R85 where R85 is a C5-C10 cycloalkyl substituted with halo, substituted or unsubstituted amino, or hydroxy.

0167. ‘Arylsulfinyl’ refers to a radical —S(O)R86 where R86 is a C6-C15 aryl group as defined herein.

0168. ‘Hetereoaryl sulfinyl’ refers to a radical —S(O)R87 where R87 is a 5-10 membered heteroaryl group as defined herein.

0169. ‘Substituted sulfinyl’ refers to the group —S(O)R88, wherein R88 is selected from:

0170. C1-C4 alkyl, C5-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C15 aryl, aralkyl, 5-10 membered heteroaryl, and heteroaryl, or

0171. C1-C4 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or

0172. C5-C10 cycloalkyl, C6-C15 aryl, aralkyl, 5-10 membered heteroaryl, or heteroarylalkyl, each of which is substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

0173. Exemplary ‘substituted sulfinyl’ groups are —S(O)—(C1-C4 alkyl) and —S(O)2—(C1-C4 cycloalkyl), —S(O)—(CH2)(C6-C15 aryl), —S(O)2—(CH2)(5-10 membered heteroaryl), —S(O)—(CH2)(C5-C10 cycloalkyl), and —S(O)2—(CH2)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any ary, heteroary, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy. The term substituted sulfinyl includes the groups alkylsulfinyl, substituted alkylsulfinyl, cycloalkylsulfinyl, substituted cycloalkylsulfinyl, arylsulfinyl and hetereoaryl sulfinyl.

0174. ‘Alkylsulfinyl’ refers to a radical —S(O)R89, where R89 is an C1-C4 alkyl group as defined herein. Representative examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl.

0175. ‘Substituted Alkylsulfinyl’ refers to a radical —S(O)2R90, wherein R90 is an C1-C4 alkyl group as defined herein, substituted with halo, substituted or unsubstituted amino, or hydroxy.

0176. ‘Cycloalkylsulfinyl’ refers to a radical —S(O)2R91, wherein R91 is a C5-C10 cycloalkyl or group as defined herein. Representative examples include, but are not limited to, cyclopropylsulfinyl, cyclobutylsulfinyl, and cyclopentylsulfinyl.

0177. ‘Substituted cycloalkylsulfinyl’ refers to the group —S(O)2R92, wherein R92 is a C5-C10 cycloalkyl, substituted with halo, substituted or unsubstituted amino, or hydroxy.

0178. ‘Arylsulfinyl’ refers to a radical —S(O)2R93, wherein R93 is an C6-C15 aryl group as defined herein.

0179. ‘Hetereoaryl sulfinyl’ refers to a radical —S(O)2R94, wherein R94 is a 5-10 membered hetereoaryl group as defined herein.

0180. ‘Sulfo’ or ‘sulfonic acid’ refers to a radical such as —SO2H.

0181. ‘Substituted sulfo’ or ‘sulfonic acid ester’ refers to the group —SO2OR95, wherein R95 is selected from:

0182. C1-C4 alkyl, C5-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C15 aryl, aralkyl, 5-10 membered heteroaryl, and heteroarylalkyl, or

0183. C1-C4 alkyl substituted with halo, substituted or unsubstituted amino, or hydroxy; or

0184. C5-C10 cycloalkyl, 4-10 membered heterocycloalkyl, C6-C15 aryl, aralkyl, 5-10 membered hetereoaryl, or heteroarylalkyl, each of which is substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

0185. Exemplary ‘Substituted sulfo’ or ‘sulfonic acid ester’ groups are —SO2—O—(C1-C4 alkyl) and —SO2—O—(C5-C10 cycloalkyl), —SO2—O—(CH2)(C6-C15 aryl), —SO2—O—(CH2)(5-10 membered heteroaryl), —SO2—O—(CH2)(C5-C10 cycloalkyl), and —SO2—O—(CH2)(4-10 membered heterocycloalkyl), wherein t is an integer from 0 to 4 and any ary, heteroary, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

0186. ‘Thiol’ refers to the group —SH.

0187. ‘Aminocarbonylamino’ refers to the group —NR=CO(NH)R96, wherein R96 is independently hydrogen or any ary, heteroary, cycloalkyl or heterocycloalkyl groups present, may themselves be substituted by unsubstituted C1-C4 alkyl, halo, unsubstituted C1-C4 alkoxy, unsubstituted C1-C4 haloalkyl, unsubstituted C1-C4 hydroxyalkyl, or unsubstituted C1-C4 haloalkoxy or hydroxy.

0188. ‘Bicycloalkyl’ refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent bicycloaromatic ring system. Typical bicycloalyl groups include, but are not limited to, groups derived from indane, indene, naphthalene, tetrahydroanthracene, and the like. Particularly, an ary group comprises from 8 to 11 carbon atoms.

0189. ‘Bicyclohetereal’ refers to a monovalent bicycloaromatic group derived by the removal of one hydrogen atom from a single carbon atom of a parent bicycloaromatic ring system. Typical bicyclohetereal groups include, but are not limited to, groups derived from benzofuran, benzimi-
dazole, benzindazole, benzodioxane, chromene, chromane, cinnoline, pthalazine, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, benzoindazole, benzoxazole, naphthyridine, benzoazidinone, pteridine, purine, benzopyran, benzpyrazine, pyridopyrimidine, quinoxaline, quinoline, quinolizine, quinoxaline, benzomorph, tetrahydroquinoline, and the like. Preferably, the bicycloheptaryl group is between 9-11 membered bicycloheptyl, with 5-10 membered heteroaryl being particularly preferred. Particular bicycloheptaryl groups are those derived from benzoindophene, benzofuran, benzoindazole, indole, quinoline, isoquinoline, benzimidazole, benzoxazole, and benzodioxane.

[0190] ‘Compounds of the present invention’, and equivalent expressions, are meant to embrace the compounds as hereinafter described, in particular compounds according to any of the formulae herein recited and/or described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[0191] ‘Cycloalkylalkyl’ refers to a radical in which a cycloalkyl group is substituted for a hydrogen atom of an alkyl group. Typical cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclooctylmethyl, cyclopentylethyl, cyclobutylethyl, cyclopentylyl, cyclohexylethyl, cycloheptyl, and cyclocptylyl, and the like.

[0192] ‘Heterocycloalkylalkyl’ refers to a radical in which a heterocyclocalkyl group is substituted for a hydrogen atom of an alkyl group. Typical heterocycloalkylalkyl groups include, but are not limited to, pyrrolidinylmethyl, piperidinylmethyl, piperazineylmethyl, morpholinylmethyl, pyrrolidinylethyl, piperidinylethyl, piperazineylethyl, morpholinylethyl, and the like.

[0193] ‘Cycloalkeny1’ refers to cyclic hydrocarbyl groups having from 3 to 10 carbon atoms and having a single cyclic ring or multiple condensed rings, including fused and bridged ring systems and having at least one and particularly from 1 to 2 sites of olefinic unsaturation. Such cycloalkeny1 groups include, by way of example, single ring structures such as cyclohexenyl, cyclopentenyl, cyclopropenyl, and the like.

[0194] ‘Substituted cycloalkeny1’ refers to those radicals recited in the definition of ‘substituted’ herein, and particularly refers to a cycloalkeny1 group having 1 or more substituents, for instance from 1 to 5 substituents, and particularly from 1 to 3 substituents, selected from the group consisting of acyl, acylamino, aroyl, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarboxyamino, aminocarbamoyl, ary1, ary1oxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, ketc, nitro, thioalkoxy, substituted thioalkoxy, thioary1oxy, thioketo, thiol, alkyl-S(O)2, aryl-S(O)2, alkyl-S(O)2, and aryl-S(O)2.

[0195] ‘Fused Cycloalkeny1’ refers to a cycloalkeny1 having two or more ring carbon atoms in common with a second aliphatic or aromatic ring and having its olefinic unsaturation located to impart aromaticity to the cycloalkeny1 ring.

[0196] ‘Ethynyl’ refers to substituted or unsubstituted —(C≡C)—.

[0197] ‘Ethylene’ refers to substituted or unsubstituted —(C=C)—.

[0198] ‘Ethynyl’ refers to —(C≡C)—.

[0199] ‘Hydrogen bond donor’ group refers to a group containing O—H, or N—H functionality. Examples of ‘hydrogen bond donor’ groups include —OH, —NH2, and —NH—R7 and wherein R7 is alkyl, acylethyl, aryl, or heteroaryl.

[0200] ‘Dihydroxyphosphoryl’ refers to the radical —PO(OH)2.

[0201] ‘Substituted dihydroxyphosphoryl’ refers to those groups recited in the definition of ‘substituted’ herein, and particularly refers to a dihydroxyphosphoryl radical wherein one or both of the hydroxy groups are substituted. Suitable substituents are described in detail below.

[0202] ‘Aminohydroxyphosphoryl’ refers to the radical —PO(OH)NH2.

[0203] ‘Substituted aminohydroxyphosphoryl’ refers to those groups recited in the definition of ‘substituted’ herein, and particularly refers to an aminohydroxyphosphoryl wherein the amino group is substituted with one or two substituents. Suitable substituents are described in detail below. In certain embodiments, the hydroxyl group can also be substituted.

[0204] ‘Nitrogen-Containing Heterocycloalkyl’ group means a 4 to 7 membered non-aromatic cyclic group containing at least one nitrogen atom, for example, but without limitation, morpholine, piperidine (e.g. 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 2-pyrrolidinyl and 3-pyrrolidinyl), azetidine, pyrrolidone, imidazolidinone, 2-pyrrolidone, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Particular examples include azetidine, piperidine and piperrzone.

[0205] ‘Thioketo’ refers to the group —S.

[0206] One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non-aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

[0207] ‘Pharmaceutically acceptable’ means approved or approved by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals; and more particularly, in humans.

[0208] ‘Pharmaceutically acceptable salt’ refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanol sulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluene sulfonic acid.
acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxyproline acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term “pharmaceutically acceptable cation” refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

[0209] ‘Pharmaceutically acceptable vehicle’ refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[0210] ‘Prodrugs’ refers to compounds, including derivatives of the compounds of the invention, which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0211] ‘Solvate’ refers to forms of the compound that are associated with a solvent, usually by a solvolytic reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the invention may be prepared e.g. in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalloid. ‘Solvate’ encompasses both solution- and isolex solvates. Representative solvates include hydrates, ethanolates and methanoulates.

[0212] ‘Subject’ includes humans. The terms ‘human’, ‘patient’ and ‘subject’ are used interchangeably herein.

[0213] ‘Therapeutically effective amount’ means the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[0214] ‘Preventing’ or ‘prevention’ refers to a reduction in risk of acquiring or developing a disease or disorder (i.e., causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset.

[0215] The term ‘prophylaxis’ is related to ‘prevention’, and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0216] ‘Treating’ or ‘treatment’ of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment “treating” or “treatment” refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, ‘treating’ or ‘treatment’ refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In a further embodiment, “treating” or “treatment” relates to slowing the progression of the disease.

[0217] ‘Compounds of the present invention’, and equivalent expressions, are meant to embrace compounds of the Formula(e) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[0218] When ranges are referred to herein, for example but without limitation, C1-C4 alkyl, the citation of a range should be considered a representation of each member of said range.

[0219] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acylxy)alkyl esters or ((alkoxy)carbonyl)oxy)alkylesters. Particularly the C1 to C8 alkyl, C2 to C4 alkenyl, aryl, C3 to C12 substituted aryl, and C7 to C12 aryalkyl esters of the compounds of the invention.

[0220] As used herein, the term ‘isotopic variant’ refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an ‘isotopic variant’ of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (H or D), carbon-13 (13C), nitrogen-15 (15N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be H/D, any carbon may be 13C, or any nitrogen may be 15N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. 3H, and carbon-14, i.e. 14C, are particularly useful for this pur-
pose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as $^{11}$C, $^{18}$F, $^{15}$O, and $^{15}$N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0221] All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

[0222] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 'isomers'. Isomers that differ in the arrangement of their atoms in space are termed 'stereoisomers'.

[0223] Stereoisomers that are not mirror images of one another are termed 'diastereomers' and those that are non-supernumerable mirror images of each other are termed 'enantiomers'. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (−)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a 'racemic mixture'.

[0224] 'Tautomers' refer to compounds that are interconvertible forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro-forms of phenyl nitromethane, that are likewise formed by treatment with acid or base.

[0225] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0226] As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (i.e., in enantiomeric excess). In other words, an “S” form of the compound is substantially free from the “R” form of the compound and is, thus, in enantiomeric excess of the “R” form. The term “enantiomerically pure” or “pure enantiomer” denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

[0227] As used herein and unless otherwise indicated, the term “enantiomerically pure R-compound” refers to at least about 80% by weight R-compound and at most about 20% by weight S-compound, at least about 90% by weight R-compound and at most about 10% by weight S-compound, at least about 95% by weight R-compound and at most about 5% by weight S-compound, at least about 99% by weight R-compound and at most about 1% by weight S-compound, at least about 99.9% by weight R-compound or at most about 0.1% by weight S-compound. In certain embodiments, the weights are based upon total weight of compound.

[0228] As used herein and unless otherwise indicated, the term “enantiomerically pure S-compound” or “S-compound” refers to at least about 80% by weight S-compound and at most about 20% by weight R-compound, at least about 90% by weight S-compound and at most about 10% by weight R-compound, at least about 95% by weight S-compound and at most about 5% by weight R-compound, at least about 99% by weight S-compound and at most about 1% by weight R-compound or at least about 99.9% by weight S-compound and at most about 0.1% by weight R-compound. In certain embodiments, the weights are based upon total weight of compound.

[0229] In the compositions provided herein, an enantiomerically pure compound or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure R-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R-compound. In certain embodiments, the enantiomerically pure R-compound in such compositions can, for example, comprise, at least about 95% by weight R-compound and at most about 5% by weight S-compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure S-compound can comprise, for example, about 90% excipient and 10% enantiomerically pure S-compound. In certain embodiments, the enantiomerically pure S-compound in such compositions can, for example, comprise, at least about 95% by weight S-compound and at most about 5% by weight R-compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

[0230] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

The Compounds

[0231] In certain aspects, provided herein are compounds useful for preventing and/or treating a broad range of conditions, among them, arthritis, Parkinson's disease, Alzheimer's disease, stroke, uveitis, asthma, myocardial infarction, the treatment and prophylaxis of pain syndromes (acute and chronic or neuropathic), traumatic brain injury, acute spinal cord injury, neurodegenerative disorders, alopecia (hair loss), inflammatory bowel disease and autoimmune disorders or conditions in mammals.
In one aspect, provided herein are compounds according to formula 1:

![Chemical Structure Image]

wherein

- Each of A, B, and W are independently selected from CR^k and N; provided that not all A, B, and W are N at the same time;
- X is selected from CR^k and N;
- L is substituted or unsubstituted C_1-C_9 alkyne or C_1-C_9 heteroalkylene;
- R^3 is selected from substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;
- R^3 is substituted or unsubstituted 6-10 membered aryl, or substituted or unsubstituted 6-10 membered heteroaryl; or
- R^3 is substituted or unsubstituted N containing heterocycloalkyl; and the heterocycloalkyl is attached to the core group via the N;
- Each R^2 is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyoxycarbonyl, substituted or unsubstituted alkylamino, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted sulfonyl, substituted or unsubstituted sulfinyl, substituted or unsubstituted sulfanyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted aminosulfinyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted carboxamoyl, carboxy, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkylamino, halo, nitro, and thiol;
- Each R^4 is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxythio, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxythio, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylamino, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted carboxamoyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkylamino, halo, nitro, and thiol.

In one embodiment, with respect to formula 1, R^3 is substituted or unsubstituted halo, hydroxy, nitro, and thiol; or substituent m' is selected from 0-4;

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

In one embodiment, with respect to formula 1, R^3 is unsubstituted or substituted 4-7 membered heterocycloalkyl.

In one embodiment, with respect to formula 1, R^3 is unsubstituted alkyl.

In one embodiment, with respect to formula 1, R^3 is unsubstituted alkylamino or substituted 4-7 membered heterocycloalkyl.

In one embodiment, with respect to formula 1, R^3 is unsubstituted halo, hydroxy, alkoxyl, arylxoy, or heteroarylxy. For the sake of clarity, the invention does not include compounds wherein R^3 is hydroxy, alkoxyl, arylxoy, or heteroarylxy.

In one embodiment, with respect to formula 1, one of A, B, and W is N; and the rest are independently selected from CR^k.

In another embodiment, with respect to formula 1, each A, B, and W is CH.

In one particular embodiment, with respect to formula 1, R^3 is unsubstituted halo, hydroxy, alkoxyl, arylxoy, or heteroarylxy.

In one particular embodiment, with respect to formula 1, one of A, B, and W is CH.

In one particular embodiment, with respect to formula 1, R^3 is unsubstituted halo, hydroxy, alkoxyl, arylxoy, or heteroarylxy.

In one particular embodiment, with respect to formula 1, the compound is according to formula 2:

![Chemical Structure Image]

wherein

- X, L, R^1, R^3, R^4, R^6, and m' are as described for formula 1;
- or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

In one embodiment, with respect to formulae 1 and 2, L is selected from —CH_2—, —CHMe—, —CMe_2—, —(CH_2)_2—, —CH(CH_3)CH—, —CH(CH_3)OCH_2—, —CH(Me)F—, —CH(CH_3)H—, —CH(CH_2)H—, —CH(CH_3)OH—, and —CH(CH_2)OH—;

In another embodiment, with respect to formulae 1 and 2, L is selected from —CH_2—, —CHMe—, —CMe_2—, —(CH_2)_2—, —CH(CH_3)CH—, —CH(CH_3)OCH_2—, —CH(Me)F—, —CH(CH_3)H—, —CH(CH_2)H—, —CH(CH_3)OH—, and —CH(CH_2)OH—.

In one particular embodiment, with respect to formulae 1 and 2, L is selected from —CH_2—, —(CH_2)_2—, —CMe_2—, and —O(CH_2)H—.
In another aspect, provided herein are compounds according to formula 2a:

\[
\begin{align*}
\text{X} & \quad \text{R}' \quad \text{R}''_1 \quad \text{R}''_2 \quad \text{R}''_3 \\
\text{H} & \quad \text{N} \quad \text{L} \quad \text{R}''_1 \quad \text{O} \\
\end{align*}
\]

wherein

- \( X \) is selected from \( \text{C}^{\text{ar}} \) and \( N \);
- \( R''_1 \) is selected from substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;
- each of \( R''_1 \) and \( R''_2 \) is independently selected from hydrogen, \( \text{C}_1 \text{-C}_4 \) alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, dialkylaminoalkyl, haloalkyl, and halo; or \( R''_1 \) and \( R''_2 \) join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms;
- \( R''_1 \) is substituted or unsubstituted 6-10 membered aryl, or substituted or unsubstituted 6-10 membered heteroaryl; and when \( R''_1 \) is 6, 5 fused bicyclic heteroaryl then \( R''_1 \) is joined to the core group via the 6 membered ring;
- \( R''_1 \) is \( N \) containing heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alkylsulfonylalkyl, and oxo; and the heterocycloalkyl is attached to the core group via the \( N \);
- each \( R''_1 \) and \( R''_2 \) is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxyamino, substituted or unsubstituted alkoxyaminocarbonyl, substituted or unsubstituted alkylaminocarbonyl, substituted or unsubstituted arylalkylamino, substituted or unsubstituted aryalkyloxoy, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, sulfol, substituted sulfon-, substituted sulfonyl, substituted sulfamyl, substituted sulfanyl, substituted or unsubstituted aminosulfon-, substituted or unsubstituted alkenesulfon-, alkylsulfon-, and oxo, and the substituent is selected from o-4; and the subscript \( n' \) is 0 or 1;
- or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;
- provided that
- when \( n' = 0 \), \( R''_1 \) is other than \( \text{Me} \); or
- provided that
- \( R''_1 \) is 3,5-di(4-fluorophenyl)benzoic acid N-[1-methyl-2-[4-(pyrimidin-2-yl)piperazin-1-yl]ethyl]amide;
- 3,5-di(4-fluorophenyl)benzoic acid N-[1-methyl-2-[4-(pyrimidin-2-yl)piperazin-1-yl]ethyl]amide;
- 3,5-di(4-fluorophenyl)benzoic acid N-[1-methyl-2-(4-acetylpiperazin-1-yl)ethyl]amide;
In another embodiment, with respect to formula 2aa, R is azetidine, pyrrolidine, piperidinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, or azepinyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminooalkyl, dialkylaminoalkyl, alkylsulfonylalkyl, and oxo.

In another embodiment, with respect to formula 2aa, R is azetidine, pyrrolidine, piperidinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, or azepinyl, substituted with oxo.

In another embodiment, with respect to formula 2aa, R is

and wherein R' is independently selected from hydrogen, or substituted or unsubstituted alkyl.

In another embodiment, with respect to formula 2aa, the compound is according to formula 3aa, 4aa, 5aa, 6aa, 7aa, or 8aa:

wherein X', R', R', and m' are as described for formula 1; and R' is as described above;

each of R' and R' is independently selected from hydrogen, C1-C4 alkyl, or halo; or R' and R' join together to form a cycloalkyl or cyclohexylalkyl ring of 3-7 atoms;

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

In one embodiment, with respect to formulae 2aa-8aa, the subscript m' is 1, 2 or 3.

In another embodiment, with respect to formulae 2aa-8aa, the subscript m' is 1.
In another embodiment, with respect to formula 2aa, the compound is according to formula 9aa, 10aa, 11aa, 12aa, 13aa, or 14aa:

[0297] wherein

X', R', R'', R', and m' are as described for formula 1; and R^46 is as described above;

[0298] each of R^2a and R^2b is independently selected from hydrogen, C_1-C_4 alkyl, or halo; or R^2a and R^2b join together to form a cycloalkyl or cyclohexanoalkyl ring of 3-7 atoms;

[0299] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0300] In one embodiment, with respect to formulae 3aa-14aa, each of R* and R' is hydrogen.
In one embodiment, with respect to formulae 3aa-14aa, one of R* and R' is methyl, hydroxymethyl or hydroxyethyl.

In one embodiment, with respect to formulae 3aa-14aa, each of R* and R' is methyl.

In one embodiment, with respect to formulae 3aa-14aa, R* and R' join together to form a cycloalkyl ring.

In one embodiment, with respect to formulae 3aa-14aa, R* and R' join together to form a cyclopropyl ring.

In one embodiment, with respect to formulae 3aa-14aa, R* is selected from Me, Et, n-Pr, i-Bu, CF₃, CH₂OH, CH₂CH₂OH, CH₂CH₂OAc, CH₂(CH₂)₂OH, CH₂(CH₂)₂NHMe, CH₂NHMe₂, CH₂CH₂NHMe, CH₂CONH₂, CH₂COOH, CH₂CH₂COOH, CH₂(CH₂)₃COOH, CH₂OMe, and CH₂CH₂OMe; and R* is H.

In one embodiment, with respect to formulae 3aa-14aa, R* is selected from CH₂NR²R²⁺, CH₂CH₂NR²R²⁺, CH₂CH₂CH₂NR²R²⁺ and wherein R* and R²⁺ can join together to form a heterocyclic ring; and R* is H.

In one embodiment, with respect to formulae 3aa-14aa, R* is selected from cyclopropyl, cyclobutyl or cyclohexyl; and R* is H.

In one embodiment, with respect to formulae 3aa-14aa, R* is CH₂OH or CH₂CH₂OH; and R* is H.

In one embodiment, with respect to formulae 2aa-14aa, R² is substituted or unsubstituted alkyl.

In one embodiment, with respect to formulae 2aa-14aa, R² is Me, Et, i-Pr, or t-Bu.

In one embodiment, with respect to formulae 2aa-14aa, R² is substituted or unsubstituted aryl or heteroaryl.

In one embodiment, with respect to formulae 2aa-14aa, R² is substituted or unsubstituted bicycloalkyl, bicycloalkyl, or bicyclic heteroaryl.

In one embodiment, with respect to formulae 2aa-14aa, R² is substituted or unsubstituted phenyl.

In one embodiment, with respect to formulae 2aa-14aa, R² is substituted or unsubstituted pyridyl, pyrimidinyl or pyrazinyl.

In one embodiment, with respect to formulae 2aa-14aa, R² is selected from substituted or unsubstituted quinolyl, isoquinolyl, methylenedioxyphenyl, imidazopyridyl, benzooxazolyl, and indolyl.

In one embodiment, with respect to formulae 2aa-14aa, R² is selected from substituted or unsubstituted sulfinyl, substituted or unsubstituted sulfanyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted arylsulfonyl, sulfonic acid, sulfonic acid ester, substituted or unsubstituted dihydroxophosphoryl, substituted or unsubstituted amidohydroxophosphoryl, azido, substituted or unsubstituted carbamoyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted dialkylamino, halo, heteroaryloxy, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroalkyl, hydroxy, nitro and thiol.

In one embodiment, with respect to formulae 2aa-14aa, R¹ is as described above and the subscript n2 is 1, 2 or 3.

In one embodiment, with respect to formulae 2aa-14aa, R¹ is as described above and the subscript n2 is 1 or 2.

In one embodiment, with respect to formulae 2aa-14aa, R¹ is as described above and the subscript n2 is 1 or 2.

In one embodiment, with respect to formulae 2aa-14aa, each R² is independently selected from H, alkyl, halo, cyano, alkoxy, and alkoxyalkyl.

In one embodiment, with respect to formulae 2aa-14aa, each R² is as described above and each R² is independently selected from H, Me, Et, Pr, iso-Pr, Ph, Cl, F, Br, CN, OH, OMe, OEt, OPt, COPh, CO₂Me, CH₃—N-morpholino, CH₂—N-(4-Me-piperidino), NH₂, CONH₂, CF₃, CHF₂, OCF₂, OFHF₂, t-Bu, SMe, CH—CH—CO₂H, SMe, SO₂Me, SO₂CF₃, SO₂NH₂, SO₃H, SO₃Me, cyclopropyl, triazolyl, morpholinyl, and pyridyl.

In one embodiment, with respect to formulae 2aa-14aa, each R² is independently selected from H, Cl, F, Me, or CF₃.

With regard to formula 2aa, in certain embodiments, the compound is selected from the group consisting of:
In one embodiment, with respect to formulae 1, 2 and 2a, \( R^2 \) is substituted or unsubstituted 6-10 membered aryl.

In another embodiment, with respect to formulae 1, 2 and 2a, \( R^2 \) is substituted or unsubstituted 6-10 membered heteroaryl. For the sake of clarity the invention does not include 5 membered heteroarials, for example pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl and the like.

In another embodiment, with respect to formulae 1, 2 and 2a, \( R^2 \) is substituted or unsubstituted bicycloaryl, bicycloalkyl, or bicyclocarboxyl.

In another embodiment, with respect to formulae 1, 2 and 2a, \( R^2 \) is substituted or unsubstituted phenyl.

In another embodiment, with respect to formulae 1, 2 and 2a, \( R^2 \) is substituted or unsubstituted pyridyl, pyrazinyl or unsubstituted pyrimidinyl.

In another embodiment, with respect to formulae 1, 2 and 2a, \( R^2 \) is selected from substituted or unsubstituted quinolinyl, isoquinolinyl, methylenedioxyphenyl, imidazopyridyl, benoxazolyl, and indolyl.

In another embodiment, with respect to formulae 1, 2 and 2a, \( R^2 \) is

and wherein subscript n1 is selected from 1-5 and each \( R^{5-11} \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, aryloxy, alkoxyacarbonyl, substituted alkoxyacarbonyl, substituted or unsubstituted alkylaminocarbonyl, arylalkyl, substituted arylalkoxy, amino, aryl, substituted aryl, arylalkyl, sulfo, substituted sulfo, substituted sulfanyl, substituted sulfonil, substituted sulfonil, substituted sulfinyl, substituted sulfinyl, amino, aryl, substituted aryl, alkenyl, substituted alkenyl, substituted alkynyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted alkyl, substitu...
one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminooalkyl, dialkylaminooalkyl, alkylsulfonylalkyl, and oxo.

[0346] In one embodiment, with respect to formulae 1, 2 or 2a, R¹ is heterocycloalkyl, substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminooalkyl, dialkylaminooalkyl, alkylsulfonylalkyl, and oxo.

[0347] In another aspect, provided herein are compounds according to formulae 3, 4, or 5:

[0348] wherein

[0349] X is selected from CR and N;

[0350] R¹ is selected from substituted or unsubstituted aryl, and heteroary or

[0351] R¹ is substituted or unsubstituted cycloalkyl; or

[0352] R¹ is selected from alkyl, and hydroxyalkyl; or

[0353] R¹ is heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminooalkyl, dialkylaminooalkyl, alkylsulfonylalkyl, and oxo;

[0354] each of R²a and R²b is independently selected from hydrogen, C₁-C₄ alkyl, hydroxyalkyl, alkoxyalkyl, aminooalkyl, alklyaminooalkyl, dialklyaminooalkyl, halooalkyl, and halo; or R²a and R²b join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms;

[0355] each R⁴a, and R⁴b is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkalamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy alkylaminooalkyl, substituted or unsubstituted alklysulfonylalkyl, and oxo.

[0356] each R⁵ is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkalamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy alkylaminooalkyl, substituted or unsubstituted alklysulfonylalkyl, and oxo.

[0357] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;

[0358] provided that

[0359] a) when n₂ is 0, R³ is other than Me; or

[0360] b) the compound is other than

[0361] i) 3-(3-fluoro-2-pyridinyl)-N-[2-hydroxy-1-(3-methyl-1,2,4-oxadiazol-5-yl)propyl]-5-(5-methyl-2-pyridinyl)-benzamide.

[0362] In one embodiment, with respect to formulae 3, 4, and 5, the subscript m₁ is 1, 2 or 3.

[0363] In one embodiment, with respect to formulae 3, 4, and 5, the subscript m₂ is 1.

[0364] In one embodiment, with respect to formulae 3, 4, and 5, R² is selected from substituted or unsubstituted aryl, and heteroary or

[0365] R² is substituted or unsubstituted cycloalkyl; or

[0366] R² is selected from alkyl, and hydroxyalkyl; or

[0367] R² is heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminooalkyl, alkylsulfonylalkyl, and oxo.
In another embodiment, with respect to formula 2a, the compound is according to formulae 6, 7, 8, 9, 10, or 11:

[0369] wherein

[0370] R', R', R', R', R', R', n1 and n2 are as described for formula 3-5;

[0371] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0372] In one embodiment, with respect to formulae 3-11, the subscript n2 is 0.

[0373] In another embodiment, with respect to formulae 3-11, the subscript n2 is 1.

[0374] In another embodiment, with respect to formulae 3-6, 8, and 10, each \( R^{4b} \) is independently H, C\(_1\)-C\(_4\) alkyl, halo C\(_1\)-C\(_4\) alkyl, CN, NO\(_2\), or halo.

[0375] In one embodiment, with respect to formulae 3-6, 8, and 10, each \( R^{4b} \) is H, Me, CF\(_3\), Cl, F, CN or NO\(_2\).

[0376] In one embodiment, with respect to formulae 3-6, 8, and 10, \( R^{4b} \) is Cl or CN.

[0377] In one embodiment, with respect to formulae 1-11, \( R^{4b} \) is H, C\(_1\)-C\(_4\) alkyl or halo C\(_1\)-C\(_4\) alkyl or halo.

[0378] In one embodiment, with respect to formulae 1-11, \( R^{4b} \) is H, Me, CF\(_3\), Cl or F.

[0379] In one embodiment, with respect to formulae 3-11, subscript n1 is 1, 2 or 3.

[0380] In one embodiment, with respect to formulae 3-11, subscript n1 is 1 or 2.

[0381] In one embodiment, with respect to formulae 3-11, subscript n1 is 1.

[0382] In one embodiment, with respect to formulae 3-11, each \( R^{4b} \) is independently selected from H, alkyl, halo, cyano, alkoxyl, and haloalkyl.

[0383] In one embodiment, with respect to formulae 3-11, each \( R^{4b} \) is independently selected from H, Me, Et, Pr, iso-Pr, Ph, Cl, F, Br, CN, OH, OMe, OEt, OPn, COPn, CO\(_2\)Me, Cl\(_2\)—N-morpholino, Cl\(_2\)—N-(4-Me-piperidino), NH\(_2\),
CONH₂, CF₃, CHF₂, OCF₂, OCHF₂, t-Bu, SM, CH=C=CH—CO₂H, SO₂Me, SO₂C²F₆, SO₂NH₂, SO₂H, SO₂Me, cyclopropyl, triazolyl, morpholinyl, and pyridyl.

[0384] In one embodiment, with respect to formulae 3-11, each R₁ is independently selected from H, Cl, F, Me, or CF₃.

[0385] In one embodiment, with respect to formulae 3-11, each R₂ is H.

[0386] In one embodiment, with respect to formulae 3-11, R¹ is selected from substituted or unsubstituted aryl, and heteroaryl.

[0387] In one embodiment, with respect to formulae 3-11, substituted or unsubstituted cycloalkyl.

[0388] In one embodiment, with respect to formulae 3-11, R₁ is selected from alkyl, and hydroxyalkyl; or R₂ is heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alky sulfonfylalkyl, and oxo.

[0389] In one embodiment, with respect to formulae 3-11, R₁ is heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alky sulfonfylalkyl, and oxo.

[0390] In one embodiment, with respect to formulae 3-11, R₁ is selected from aryl, or heteroaryl.

[0391] In one embodiment, with respect to formulae 3-11, R₁ is unsubstituted aryl or heteroaryl.

[0392] In one embodiment, with respect to formulae 3-11, R₁ is selected from substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl.

[0393] In one embodiment, with respect to formulae 3-11, R₁ is substituted or unsubstituted alkyl.

[0394] In one embodiment, with respect to formulae 3-11, R₁ is alkyl.

[0395] In one embodiment, with respect to formulae 3-11, R₁ is hydroxyalkyl.

[0396] In one embodiment, with respect to formulae 3-11, R₁ is unsubstituted heterocycloalkyl.

[0397] In one embodiment, with respect to formulae 3-11, R₁ is heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, and oxo.

[0398] In one embodiment, with respect to formulae 3-11, R₁ is heterocycloalkyl, substituted with one or more groups selected from alkoxyalkyl, aminoalkyl, and dialkylaminoalkyl, alky sulfonfylalkyl, and oxo.

[0399] In one embodiment, with respect to formulae 3-11, R₁ is heterocycloalkyl, substituted with alkyl sulfonfylalkyl.

[0400] In one embodiment, with respect to formulae 3-11, each of R₂ and R₃ is independently selected from hydrogen, C₂-C₅ alkyl, hydroxyalkyl, and halo. In another embodiment, each of R₂ and R₃ is independently selected from hydrogen, C₂-C₅ alkyl, and hydroxyalkyl.

[0401] In one embodiment, with respect to formulae 3-11, R₁ and R₂ join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms.

[0402] In one embodiment, with respect to formulae 3-11, R₁ and R₂ join together to form a cycloalkyl ring of 3-7 atoms.

[0403] In one embodiment, with respect to formulae 3-11, R₁ and R₂ join together to form a cyclopropyl ring.

[0404] In one embodiment, with respect to formulae 3-11, the subscript n₂ is 1; and R¹ is unsubstituted heterocycloalkyl.

[0405] In one embodiment, with respect to formulae 3-11, the subscript n₂ is 1; and R¹ substituted heterocycloalkyl.

[0406] In one embodiment, with respect to formulae 3-11, the subscript n₂ is 1; and R¹ is heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alkyl sulfonfylalkyl, and oxo.

[0407] In one embodiment, with respect to formulae 3-11 R¹ is heterocycloalkyl, substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alkyl sulfonfylalkyl, and oxo.

[0408] In one embodiment, with respect to formulae 3-11, R¹ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alkyl sulfonfylalkyl, and oxo.

[0409] In one embodiment, with respect to formulae 3-11, R¹ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, substituted with oxo.

[0410] In one embodiment, with respect to formulae 3-11, R¹ is selected from morpholinyl, and 1,1-dioxo-thiomorpholinyl.

[0411] In one embodiment, with respect to formulae 3-11, the subscript n₂ is 1; and R¹ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alkyl sulfonfylalkyl, and oxo.

[0412] In one embodiment, with respect to formulae 3-11, the subscript n₂ is 1; and R¹ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, unsubstituted or substituted with alkyl.

[0413] In one embodiment, with respect to formulae 3-11, the subscript n₂ is 1; and R¹ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, substituted with oxo.

[0414] In one embodiment, with respect to formulae 3-11, the subscript n₂ is 1; and R¹ is selected from morpholinyl, and 1,1-dioxo-thiomorpholinyl.

[0415] In yet another aspect, provided herein are compounds according to formula 2a:

[0416] wherein

[0417] X' is selected from CR₆⁺ and N;

[0418] R¹ is selected from substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

[0419] each of R₂ and R₃ is independently selected from hydrogen, C₂-C₅ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, dialkylaminoalkyl, haloalkyl, and halo; or R₂ and R₃ join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms;
R² is N containing heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminooalkyl, dialkylaminoalkyl, alkysulfonylalkyl, and oxo; and the heterocycloalkyl is attached to the core group via the N.

Each R⁴⁺⁻, and R⁴⁺⁻ is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkyamine, substituted or unsubstituted alkylthio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted alkoxy acrylamide, substituted or unsubstituted aryalkyl, substituted or unsubstituted aryalkoxy, substituted or unsubstituted aryalkylthio, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, sulfonic acid, substituted sulfonic acid, substituted sulfanyl, substituted sulfonamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted dialkylaminoalkyl, substituted or unsubstituted dialkylaminoalkyl, substituted or unsubstituted dialkylsulfonylalkyl, and oxo.

In one embodiment, with respect to formula 2a, R² is N containing heterocycloalkyl, substituted with hydroxyalkyl.

In one embodiment, with respect to formula 2a, R³ is N containing heterocycloalkyl, substituted with oxo.

In one embodiment, with respect to formula 2a, R³ is unsubstituted azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, or azepinyl.

In another embodiment, with respect to formula 2a, R² is azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, or azepinyl, substituted with one or more groups selected from hydroxyalkyl, alkoxalkyl, aminooalkyl, dialkylaminoalkyl, alkoxyalkyl, and oxo.

In another embodiment, with respect to formula 2a, R² is azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, or azepinyl, substituted with one or more groups selected from hydroxyalkyl, alkoxalkyl, aminooalkyl, dialkylaminoalkyl, alkoxyalkyl, and oxo.

In another embodiment, with respect to formula 2a, R² is azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, or azepinyl, substituted with one or more groups selected from hydroxyalkyl, alkoxalkyl, aminooalkyl, dialkylaminoalkyl, alkoxyalkyl, and oxo.

In another embodiment, with respect to formula 2a, R² is azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, or azepinyl, substituted with one or more groups selected from hydroxyalkyl, alkoxalkyl, aminooalkyl, dialkylaminoalkyl, alkoxyalkyl, and oxo.
[0441] and wherein \( R^2 \) is independently selected from hydrogen, or substituted or unsubstituted alkyl.

[0442] In another embodiment, with respect to formula 2a, the compound is according to formula 12, 13, 14, 15, 16, or 17:

[0443] wherein

[0444] \( X', R^1, R^2, R_1, R_2, m' \) and \( n_2 \) are as described for formula 2a;

[0445] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0446] In one embodiment, with respect to formulae 1-8, the subscript \( m' \) is 1, 2 or 3.

[0447] In another embodiment, with respect to formulae 1-8, the subscript \( m' \) is 1.

[0448] In another embodiment, with respect to formula 2a, the compound is according to formulae 18, 19, 20, 21, 22, or 23:
wherein

[X], [R], [R₂a, R₂b], and [n₂] are as described for formula 2a;

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

In one embodiment, with respect to formulae 12-23, each of [R₂a] and [R₂b] is independently selected from hydrogen, C₁₋C₄ alkyl, and halo. In another embodiment, each of [R₂a] and [R₂b] is independently selected from hydrogen, and C₁₋C₄ alkyl.

In one embodiment, with respect to formulae 12-23, [R₂a] and [R₂b] join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms.

In one embodiment, with respect to formulae 12-23, [R₂a] and [R₂b] join together to form a cycloalkyl ring of 3-7 atoms.

In one embodiment, with respect to formulae 3-23, each of [R₂a] and [R₂b] is hydrogen.

In one embodiment, with respect to formulae 3-23, one of [R₂a] and [R₂b] is hydrogen.

In one embodiment, with respect to formulae 3-23, one of [R₂a] and [R₂b] is methyl, hydroxymethyl or hydroxyethyl.

In one embodiment, with respect to formulae 3-23, each of [R₂a] and [R₂b] is methyl.

In one embodiment, with respect to formulae 3-23, [R₂a] and [R₂b] join together to form a cycloalkyl ring.

In one embodiment, with respect to formulae 3-23, [R₂a] and [R₂b] join together to form a cyclopropyl ring.

In one embodiment, with respect to formulae 3-23, [R₂a] is selected from Me, Et, n-Pr, t-Bu, CF₃, CH₂OH, CH₂CH₂OH, CH₃(CH₂)₂OH, CH₂CH₃NHMe, CH₃NO₂, CH₂CH₂NMe₂, CH₂OMe, and CH₂OMe; and [R₂b] is H.

In one embodiment, with respect to formulae 3-23, [R₂a] is selected from Me, Et, n-Pr, t-Bu; and [R₂b] is H.

In one embodiment, with respect to formulae 3-23, [R₂a] is selected from CH₃OH, CH₂CH₂OH, CH₂(CH₂)₂OH, CH₂OMe, and CH₂CH₂OMe; and [R₂b] is H.

In one embodiment, with respect to formulae 3-23, [R₂a] is selected from CF₃ and CH₂Cl; and [R₂b] is H.

In one embodiment, with respect to formulae 3-23, [R₂a] is selected from CH₃NR⁻R₂, CH₂CH₂NR⁻R₂, CH₂CH₂CH₂NR⁻R₂, and wherein [R₂a] and [R₂b] can join together to form a heterocyclic ring; and [R₂b] is H.
In one embodiment, with respect to formulae 3-23, R' is selected from cyclopropyl, cyclobutyl or cyclohexyl; and R^2^ is H.

In one embodiment, with respect to formulae 3-23, R^3^ is CH_2_2OH or CH_2_2CH_2OH; and R^2^ is H.

In one embodiment, with respect to formulae 12-23, the subscript n2 is 0.

In another embodiment, with respect to formulae 12-23, the subscript n2 is 1.

In one embodiment, with respect to formulae 15 or 21, R^6_ is H or alkyl.

In another embodiment, with respect to formulae 15 or 21, R^6_ is H, Me, Et, or i-Pr.

In one embodiment, with respect to formulae 1-23, X' is CR^4_6_.

In another embodiment, with respect to formulae 1-23, X' is N.

In one embodiment, with respect to formulae 1-23, X' is CR^4_6_ and R^4_ is independently H, C^1^-C^6_ alkyl, halo C^1^-C^6_ alkyl, CN, NO_2_, or halo.

In one embodiment, with respect to formulae 1-23, X' is CR^4_6_ and R^4_ is H, Me, CF_3_, Cl, F, CN or NO_2_.

In one embodiment, with respect to formulae 1-23, X' is CR^4_6_ and R^4_ is Cl or CN.

In another embodiment, with respect to formulae 1-23, R^5_ is H, C^1^-C^6_ alkyl or halo C^1^-C^6_ alkyl or halo.

In another embodiment, with respect to formulae 1-23, R^5_ is H, Me, CF_3_, Cl or F.

In one embodiment, with respect to formulae 12-23, R^1_ is other than aryl or heteroaryl.

In one embodiment, with respect to formulae 12-23, R^1_ is aryl or heteroaryl.

In one embodiment, with respect to formulae 12-23, R^1_ is selected from substituted or unsubstituted alkyl, cycloalkyl, heterocycalkyl, aryl, and heteroaryl.

In one embodiment, with respect to formulae 12-23, R^1_ is substituted or unsubstituted alkyl.

In one embodiment, with respect to formulae 12-23, R^1_ is hydroxyalkyl.

In one embodiment, with respect to formulae 12-23, R^1_ is alkyl.

In one embodiment, with respect to formulae 12-23, R^1_ is Et, i-Pr, or t-Bu.

In one embodiment, with respect to formulae 12-23, R^1_ is substituted or unsubstituted cycloalkyl.

In one embodiment, with respect to formulae 12-23, R^1_ is substituted or unsubstituted heterocycalkyl.

In one embodiment, with respect to formulae 12-23, R^1_ is selected from substituted or unsubstituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, and azepinyl.

In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from substituted or unsubstituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, and azepinyl.

In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminooalkyl, dialkyaminooalkyl, alkysulfonylealkyl, and oxo.

In one embodiment, with respect to formulae 12-23, R^1_ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, substituted with oxo.

In one embodiment, with respect to formulae 12-23, R^1_ is selected from morpholinyl, and 1,1-dioxo-thiomorpholinyl.

In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from substituted or unsubstituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, and azepinyl.

In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminooalkyl, dialkyaminooalkyl, alkysulfonylealkyl, and oxo.

In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, substituted with oxo.

In one embodiment, with respect to formulae 1-23, R^1_ is

\[
\text{[0492]} \quad \text{In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from substituted or unsubstituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, and azepinyl.}
\]

\[
\text{[0493]} \quad \text{In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminooalkyl, dialkyaminooalkyl, alkysulfonylealkyl, and oxo.}
\]

\[
\text{[0494]} \quad \text{In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, substituted with oxo.}
\]

\[
\text{[0495]} \quad \text{In one embodiment, with respect to formulae 12-23, the subscript n2 is 1; and R^1_ is selected from morpholinyl, and 1,1-dioxo-thiomorpholinyl.}
\]

\[
\text{[0496]} \quad \text{In one embodiment, with respect to formulae 1-23, R^1_ is selected from substituted or unsubstituted bicycloarly, bicycloalkyl, or bicyclohetearly.}
\]

\[
\text{[0497]} \quad \text{In one embodiment, with respect to formulae 1-23, R^1_ is selected from substituted or unsubstituted pyridyl, pyrazinyl or unsubstituted pyrimidinyl.}
\]

\[
\text{[0498]} \quad \text{In one embodiment, with respect to formulae 1-23, R^1_ is selected from substituted or unsubstituted quinolinyl, isoquinolinyl, methylenedioxyphenyl, imidazopyridyl, benzoxazoly, and indolyl.}
\]

\[
\text{[0499]} \quad \text{In one embodiment, with respect to formulae 1-23, R^1_ is}
\]

\[
\text{[0500]} \quad \text{and wherein subscript n2 is selected from 1-5 and each R^5_b is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylaminio, substituted or unsubstituted alkylaminio, substituted or unsubstituted alklythio, substituted or unsubstituted alkoxy, aryloxy, alkoxyarboxyl, substituted alkoxyarboxyl, substituted or unsubstituted alklylamino, aryalkoxy, substituted aryalkoxy, amino, aryl, substituted aryl, aryalkyl, sulfo, substituted sulfio, substituted sulfinyl, substituted sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted alkylsulfonyle, substituted or unsubstituted arylsulfonyle, azido, substituted or unsubstituted carbamoyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocykloalkyl, substituted or unsubstituted dialkyaminio, halo, heteroaryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaryl, hydroxy, nitro, and thiol}
\]

\[
\text{[0501]} \quad \text{In one embodiment, with respect to formulae 1-23, subscript n3 is 1, 2 or 3.}
\]
[0502] In one embodiment, with respect to formulae 1-23, subscript \( n_3 \) is 1 or 2.

[0503] In one embodiment, with respect to formulae 1-23, \( R^1 \) is

\[
\text{[Diagram]}
\]

[0504] and wherein \( R^{5b} \) is as described above.

[0505] In one embodiment, with respect to formulae 1-23, each \( R^{5b} \) is independently selected from H, alkyl, halo, cyano, alkoxy, and haloalkyl.

[0506] In one embodiment, with respect to formulae 1-23, each \( R^{5a} \) is independently selected from H, Me, Et, Pr, iso-Pr, Ph, Cl, F, Br, CN, OH, OMe, OEt, OP, COPh, CO₂Me, CH₂-N-morpholino, CH₂-N(4-Me-piperidino), NH₂, CONH₂, CF₃, CHF₂, OCF₃, OCHF₂-t-Bu, SmMe, CH=CH—CO₂H, SOMe, SO₂Me, SO₂CF₃, SO₂NH₂, SO₂H, SO₃Me, cyclopropyl, triazolyl, morpholinyl, and pyridyl.

[0507] In one embodiment, with respect to formulae 1-23, each \( R^{5b} \) is independently selected from H, Cl, F, Me, or CF₃.

[0508] In another embodiment, with respect to formula 1, the compound is according to formulae 3a, 4a, or 5a:

\[
\text{[Diagram]}
\]

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0511] In another embodiment, with respect to formula 1, the compound is according to formulae 6a, 7a, 8a, 9a, 10a, or 11a:
[0512] wherein

[0513] X', R', R", and m' are as described for formula 1; each of R' and R" is independently selected from hydrogen, C₁⁻C₄ alkyl, and halo; or R' and R" join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms; each R' is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylaminoo, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, aryloxy, alkoxyalkyl, substituted alkoxyalkyl, substituted or unsubstituted alkylarylamino, substituted or unsubstituted aryalkyl, substituted aryalkyl, amino, aryl, substituted aryl, arylalkyl, sulfo, substituted sulfo, substituted sulfanyl, substituted sulfonil, substituted sulfanyl, substituted or unsubstituted aminosulfonil, substituted or unsubstituted arylsulfonil, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted carboxyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkylamino, halo, heteroaryloxy, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroalkyl, hydroxy, nitro, and thiol; the subscript n1 is selected from 1-5;

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0514] In another embodiment, with respect to formula 1, the compound is according to formula 12a, 13a, 14a, 15a, 16a, or 17a:
[0515] \( X, \ R^1, \ R^{46}; \) and \( m' \) are as described for formula 1; each of \( R^{2a} \) and \( R^{2b} \) is independently selected from hydrogen, \( C_1-C_4 \) alkyl, and halo; or \( R^{2a} \) and \( R^{2b} \) join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms; \( R^{3a} \) is as described above; the subscript \( n1 \) is selected from 1-5;

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0516] In another embodiment, with respect to formula 1, the compound is according to formulae 18a, 19a, 20a, 21a, 22a, or 23a:
[0517] wherein

[0518] $X', R^1, R^{16}';$ and $m'$ are as described for formula 1; each of $R^{2a}$ and $R^{2b}$ is independently selected from hydrogen, $C_1-C_4$ alkyl, and halo; or $R^{2a}$ and $R^{2b}$ join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms; $R^{3a}$ is as described above; or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0519] In one embodiment, with respect to formulae 3a-23a, $R^1$ is selected from pyrrolidinyl, piperidinyl, morpholyl, thiomorpholyl, 1,1-dioxothiomorpholyl, piperezinyl, and azepinyl.

[0520] In one embodiment, with respect to formulae 3a-23a, $R^1$ is selected from pyrrolidinyl, piperidinyl, morpholyl, thiomorpholyl, piperezinyl, and azepinyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alkylsulfonylalkyl, and oxo.
[0545] wherein

[0546] X', R', R'; and m' are as described for formula 1; and R'm is as described above;

[0547] each of R' and R' is independently selected from hydrogen, C1-C4 alkyl, or halo; or R' and R' join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms;

[0548] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0549] In one embodiment, with respect to formulae 1b-8b, the subscript m' is 1, 2 or 3.

[0550] In another embodiment, with respect to formulae 1b-8b, the subscript m' is 1.

[0551] In another embodiment, with respect to formula 1, the compound is according to formula 9b, 10b, 11b, 12b, 13b, or 14b:
[0553] wherein 

[0554] each of R<sub>2a</sub> and R<sub>2b</sub> is independently selected from hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or halo; or R<sub>2a</sub> and R<sub>2b</sub> join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms; 

[0555] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0556] In one embodiment, with respect to formula 6b or 12b, R<sup>m'</sup> is H or alkyl.

[0557] In another embodiment, with respect to formulae 6b or 12b, R<sup>m''</sup> is H, Me, Et, or i-Pr.

[0558] In another embodiment, with respect to formula 1, the compound is according to formula 3c, 4c, or 5c:

[0559] wherein 

[0560] each of R<sup>2a</sup> and R<sup>2b</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or halo; or R<sub>2a</sub> and R<sub>2b</sub> join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms; 

[0561] X', R<sup>1</sup>, R<sup>4a</sup>, R<sup>4b, </sup>and m<sup>'</sup> are as described for formula 1; and R<sup>3a</sup> is as described above; 

[0562] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0563] In another embodiment, with respect to formulae 3c, 4c, and 5c, the subscript m<sup>'</sup> is 1, 2 or 3.
In another embodiment, with respect to formulae 3c, 4c, and 5c, the subscript \( m' \) is 1.

In another embodiment, with respect to formula 1, the compound is according to formula 6c, 7c, 8c, 9c, 10c or 11c:

[0566] wherein each of \( R^* \) and \( R' \) is independently selected from hydrogen, \( C_1-C_4 \) alkyl, or halo; or \( R^{2a} \) and \( R^{2b} \) join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms; 

[0567] each of \( R^{3a} \) and \( R^{3b} \) is independently selected from hydrogen, \( C_1-C_4 \) alkyl, or halo; or \( R^{2a} \) and \( R^{2b} \) join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms; 

[0568] \( X, R^1, R^{4a}, R^{4b}, \) and \( m' \) are as described for formula 1; and \( R^{2a} \) and \( n' \) are as described above; 

[0569] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0570] In one embodiment, with respect to formulae 3b-14b, \( X' \) is CR

[0571] In another embodiment, with respect to formulae 3b-14b, \( X' \) is N.

[0572] In one embodiment, with respect to formulae 3b-14b, \( X' \) is CR; and \( R^{3a} \) is independently \( H, C_1-C_4 \) alkyl, halo \( C_1-C_4 \) alkyl, CN, NO₂, or halo.

[0573] In one embodiment, with respect to formulae 3b-14b, \( X' \) is CR; and \( R^{3a} \) is \( H, Me, CF_3, Cl, F, CN \) or NO₂.

[0574] In another embodiment, with respect to formulae 3b-14b, \( X' \) is CR; and \( R^{3a} \) is Cl or CN.

[0575] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, \( R^{4a} \) is \( H, C_1-C_4 \) alkyl or halo \( C_1-C_4 \) alkyl or halo.

[0576] In another embodiment, with respect to formulae 3b-14b, and 3c-11c, \( R^{3a} \) is \( H, Me, CF_3, Cl \) or F.

[0577] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, each of \( R^{2a} \) and \( R^{2b} \) is hydrogen.

[0578] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, one of \( R^{2a} \) and \( R^{2b} \) is methyl, hydroxymethyl or hydroxyethyl.

[0579] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, each of \( R^{2a} \) and \( R^{2b} \) is methyl.
[0580] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, R²⁶ and R²ᵇ join together to form a cycloalkyl ring.

[0581] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, R² and R²ᵇ join together to form a cyclopropyl ring.

[0582] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, R² is selected from Me, Et, n-Pr, t-Bu, CF₃, CH₂OH, CH₂CH₂OH, CH₂CH₂OAc, CH₂(CH₂)OH, CH₂CH₂NMMe₂, CH₂NMMe₂, CH₂CH₂NMMe₂, CH₂CONH₂, CH₂CONMe₂, CH₂COOH, CH₂CH₂COOH, CF₃(CH₂)₂COOH, CH₂OMe, and CH₂CH₂OMe; and R²ᵇ is H.

[0583] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, R² is selected from CH₂NR²⁺R²⁻, CH₂CH₂NR²⁺R²⁻, CH₂CH₂CH₂NR²⁺R²⁻ and wherein R² and R²ᵇ can join together to form a heterocyclic ring; and R²ᵇ is H.

[0584] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, R² is selected from cyclopropyl, cyclobutyl or cyclohexyl; and R²ᵇ is H.

[0585] In one embodiment, with respect to formulae 3b-14b, and 3c-11c, R² is CH₂OH or CH₂CH₂OH; and R²ᵇ is H.

[0586] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is substituted or unsubstituted bicycloalkyl, bicycloalkenyl, or bicycloheteroaryl.

[0587] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is substituted or unsubstituted phenyl.

[0588] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is substituted or unsubstituted pyridyl, pyrimidinyl or pyrazinyl.

[0589] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is selected from substituted or unsubstituted quinolinyl, isoquinolinyl, methylenedioxyphenyl, imidazopyridyl, benzoxazolyl, and indolyl.

[0590] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is substituted or unsubstituted carbamoyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkylamino, halo, heterocycloxy, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroalkyl, hydroxy, nitro and thiol.

[0592] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is as described above and the subscript n³ is 1, 2 or 3.

[0593] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is as described above and the subscript n³ is 1 or 2.

[0594] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is as described above and the subscript n³ is 1 or 2.

[0595] and wherein R²ᵇ is as described above.

[0596] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, each R²ᵇ is independently selected from H, alkyl, halo, cyano, alkoxyl, and haloalkyl.

[0597] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, R¹ is as described above and each R²ᵇ is independently selected from H, Me, Et, Pr, iso-Pr, Ph, Cl, F, Br, CN, OH, OMe, OEt, OPh, COPh, CO₂Me, CH₂—N-morpholino, CH₂—N-(4-Me-piperidino), NH₂, CONH₂, CF₃, CHF₂, OCT₂, OCHF₂, t-Bu, SMe, CH═CH—CO₂H, SOMe, SO₂Me, SO₂CF₂, SO₂NH₂, SO₃H, SO₃Me, cyclopropyl, triazolyl, morpholinyl, and pyridyl.

[0598] In one embodiment, with respect to formulae 1-23, 3b-14b, and 3c-11c, each R²ᵇ is independently selected from H, Cl, F, Me, or CF₃.

[0599] and wherein the subscript n³ is selected from 1-5 and each R²ᵇ is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, arylxoy, alkoxy carbonyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylaminooxy, aralkylxoy, substituted aralkylxoy, amino, aryl, substituted aryl, aralkyl, substituted or unsubstituted sulfinyl, substituted or unsubstituted sulfonyl, substituted or unsubstituted sulfoxyl, substituted or unsubstituted sulfanyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted arylsulfonl, sulfonic acid, sulfonic acid ester, substituted or unsubstituted dihydroxyphosphoryl, substituted or unsubstituted aminodihydroxyphosphoryl, azido, substituted or unsubstituted carbamoyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkylamino, halo, heteroarylxy, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroalkyl, hydroxy, nitro and thiol.

[0600] In one embodiment, with respect to formulae 3-23, the subscript n² is 2; and R¹ is substituted or unsubstituted aryl or heteroaryl.

[0601] In one embodiment, with respect to formulae 3-23, the subscript n² is 2; and R¹ is substituted or unsubstituted bicycloalkyl, bicycloalkenyl, or bicycloheteroaryl.

[0602] In one embodiment, with respect to formulae 3-23, the subscript n² is 2; and R¹ is substituted or unsubstituted phenyl.

[0603] In one embodiment, with respect to formulae 3-23, the subscript n² is 2; and R¹ is substituted or unsubstituted pyridyl, pyrimidinyl or pyrazinyl.
In one embodiment, with respect to formulae 3-23, the subscript \( n_2 \) is 0; and \( R' \) is

![Chemical structure](Image)

and wherein subscript \( n_3 \) is selected from 1-5 and each \( R_3 \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkanethio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklyl, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklylcarbonyl, amino, aryl, substituted aryalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfonfyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aminosulfonfyl, substituted or unsubstituted arylsulfonic acid, substituted or unsubstituted dihydroxyaryl, or substituted or unsubstituted aminodiarylsulfonic acid, substituted or unsubstituted carbamoyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylthio, substituted or unsubstituted carboxylic acid, or substituted or unsubstituted halogen.

In one embodiment, with respect to formulae 3-23, each \( R_3 \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkanethio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklylcarbonyl, amino, aryl, substituted aryalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfonfyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aminosulfonfyl, substituted or unsubstituted arylsulfonic acid, substituted or unsubstituted dihydroxyaryl, or substituted or unsubstituted aminodiarylsulfonic acid, substituted or unsubstituted carbamoyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylthio, substituted or unsubstituted carboxylic acid, or substituted or unsubstituted halogen.

In one embodiment, with respect to formulae 3-23, the subscript \( n_2 \) is 0; and \( R' \) is

![Chemical structure](Image)

and wherein \( R_3 \) is as described above.

In one embodiment, with respect to formulae 3-23, the subscript \( n_2 \) is 0; and each \( R_3 \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkanethio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklylcarbonyl, amino, aryl, substituted aryalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfonfyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aminosulfonfyl, substituted or unsubstituted arylsulfonic acid, substituted or unsubstituted dihydroxyaryl, or substituted or unsubstituted aminodiarylsulfonic acid, substituted or unsubstituted carbamoyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylthio, substituted or unsubstituted carboxylic acid, or substituted or unsubstituted halogen.

In one embodiment, with respect to formulae 3-23, the subscript \( n_2 \) is 0; and each \( R_3 \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkanethio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklylcarbonyl, amino, aryl, substituted aryalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfonfyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aminosulfonfyl, substituted or unsubstituted arylsulfonic acid, substituted or unsubstituted dihydroxyaryl, or substituted or unsubstituted aminodiarylsulfonic acid, substituted or unsubstituted carbamoyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylthio, substituted or unsubstituted carboxylic acid, or substituted or unsubstituted halogen.

In one embodiment, with respect to formulae 3-23, the subscript \( n_2 \) is 0; and each \( R_3 \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkanethio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklylcarbonyl, amino, aryl, substituted aryalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfonfyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aminosulfonfyl, substituted or unsubstituted arylsulfonic acid, substituted or unsubstituted dihydroxyaryl, or substituted or unsubstituted aminodiarylsulfonic acid, substituted or unsubstituted carbamoyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylthio, substituted or unsubstituted carboxylic acid, or substituted or unsubstituted halogen.

In one embodiment, with respect to formulae 3-23, the subscript \( n_2 \) is 0; and each \( R_3 \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkanethio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklylcarbonyl, amino, aryl, substituted aryalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfonfyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aminosulfonfyl, substituted or unsubstituted arylsulfonic acid, substituted or unsubstituted dihydroxyaryl, or substituted or unsubstituted aminodiarylsulfonic acid, substituted or unsubstituted carbamoyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylthio, substituted or unsubstituted carboxylic acid, or substituted or unsubstituted halogen.

In one embodiment, with respect to formulae 3-23, the subscript \( n_2 \) is 0; and each \( R_3 \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkanethio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklylcarbonyl, amino, aryl, substituted aryalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfonfyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aminosulfonfyl, substituted or unsubstituted arylsulfonic acid, substituted or unsubstituted dihydroxyaryl, or substituted or unsubstituted aminodiarylsulfonic acid, substituted or unsubstituted carbamoyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylthio, substituted or unsubstituted carboxylic acid, or substituted or unsubstituted halogen.

In one embodiment, with respect to formulae 3-23, the subscript \( n_2 \) is 0; and each \( R_3 \) is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkanethio, substituted or unsubstituted alkylcarbonylamino, substituted or unsubstituted alklylcarbonyl, amino, aryl, substituted aryalkyl, substituted or unsubstituted aryalkyl, or substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfanyl, substituted or unsubstituted arylsulfonfyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aminosulfonfyl, substituted or unsubstituted arylsulfonic acid, substituted or unsubstituted dihydroxyaryl, or substituted or unsubstituted aminodiarylsulfonic acid, substituted or unsubstituted carbamoyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylthio, substituted or unsubstituted carboxylic acid, or substituted or unsubstituted halogen.
[0638] 3”-Dimethylamino-4-methyl-[1,1’;3,1”]-terphenyl-5’-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0639] 4”-Cyano-4-methyl-[1,1’;3,1”]-terphenyl-5’-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0640] 3”4”-Difluoro-4-methyl-[1,1’;3,1”]-terphenyl-5’-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0641] 4”-Hydroxymethyl-4’-methyl-[1,1’;3,1”]-terphenyl-5’-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0642] 2”-Cyano-4-methyl-[1,1’;3,1”]-terphenyl-5’-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0643] 2”-Dimethylaminomethyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0644] 3,5-Bis-(5-methyl-pyridin-2-yl)-N-(2-methyl-pyrimidin-5-ylmethyl)benzamide;
[0645] 4-Methyl-2”-trifluoromethyl-[1,1’;3,1”]-terophenyl-5’-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0646] 2”-Cyano-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0647] 3-(5-Methyl-pyridin-2-yl)-N-(6-methyl-pyridin-3-ylmethyl)-pyridin-2-yl-benzamide;
[0648] 2”3”-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0649] 2”-Hydroxymethyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0650] 2”-Cyano-4”-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0651] 2”3”-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0652] 4”-Methyl-5-(2-oxo-piperidin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0653] 4”-Methyl-5-(2-oxo-piperidin-1-yl)-biphenyl-3-carboxylic acid (2-methyl-pyrimidin-5-ylmethyl)-amide;
[0654] 4”-Methyl-5-(2-oxo-piperidin-1-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0655] 4”-Methyl-5-(2-oxo-piperidin-1-yl)-biphenyl-3-carboxylic acid [(R)-1-(6-methyl-pyrimidin-3-yl)-ethyl]amide;
[0656] 3-(5-Amino-pyrazin-2-yl)-5-(5-methyl-pyridin-2-yl)-N-(6-methyl-pyridin-3-yl)-benzamide;
[0657] 3-(2-Cyano-pyridin-3-yl)-5-(5-methyl-pyridin-2-yl)-N-(6-methyl-pyridin-3-ylmethyl)-benzamide;
[0658] 2”-Cyano-5-pyridin-2-yl-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0659] 2”-Hydroxymethyl-5-pyridin-2-yl-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0660] 2”-Methoxymethyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0661] 3-(4-Cyano-pyridin-3-yl)-5-(5-methyl-pyridin-2-yl)-N-(6-methyl-pyridin-3-ylmethyl)-benzamide;
[0662] 5”-(5-Methyl-pyridin-2-yl)-biphenyl-2,3”-dicarboxylic acid 2-amide 3”-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0663] 4”-Methyl-5-(2-oxo-pyridin-1-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0664] 4”-Methyl-5-(2-oxo-pyridin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0665] 4”-Methyl-5-(2-oxo-pyridin-1-yl)-biphenyl-3-carboxylic acid (2-methyl-pyrimidin-5-ylmethyl)-amide;
[0666] 4”-Methyl-5-(2-oxo-pyridin-1-yl)-biphenyl-3-carboxylic acid [(R)-1-(6-methyl-pyridin-3-yl)-ethyl]amide;
[0667] 2”-Cyano-3”-fluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0668] 2”-Methoxymethyl-5-pyridin-2-yl-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0669] 5”-(5-Methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid 2-dimethylamido 3”-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]amide;
[0670] 3”-(4-Cyano-pyridin-3-yl)-5-(5-methyl-pyridin-2-yl)-N-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]benzamide;
[0671] 3-(5-Methyl-pyridin-2-yl)-N-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-5-(2-oxo-piperidin-1-yl)-benzamide;
[0672] 3-(5-Methyl-pyridin-2-yl)-N-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-5-(5-oxo-morpholin-4-yl)-benzamide;
[0673] 3-(5-Methyl-pyridin-2-yl)-N-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-5-(2-oxo-pyridinol-1-1)-benzamide;
[0674] 5-(S)-2-Hydroxymethyl-pyridinol-1-yl)-4”-methyl-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-yl-ethyl)amide;
[0675] 4”-Methyl-5-(2-oxo-pyridinol-1-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl)amide;
[0676] 4”-Methyl-5-(2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0677] 5”-(5-R)-2-Hydroxymethyl-pyridinol-1-yl)-4”-methyl-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-yl-ethyl)amide;
[0678] 3”-(2-R)-2-Hydroxymethyl-pyridinol-1-yl)-5-(5-methyl-pyridin-2-yl)-N-(6-methyl-pyrimidin-3-yl)-benzamide;
[0679] 2”-Cyano-4”-methyl-5-(3-oxo-morpholin-4-yl)-biphenyl-3-carboxylic acid (2-methyl-pyrimidin-5-yl-ethyl)amide;
[0680] 2”-Cyano-4”-methyl-5-(2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyrimidin-3-ylmethyl)-amide;
[0681] 2”-Cyano-4”-methyl-5-(2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (2-methyl-pyrimidin-5-yl-ethyl)amide;
[0682] 2”-Cyano-4”-methyl-5-(4-methyl-2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyrimidin-3-ylmethyl)-amide;
[0683] 4”-Methyl-5-(4-methyl-2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyrimidin-3-yl-ethyl)amide;
[0684] 2”3”-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (1-methoxymethyl-propyl)amide;
[0685] 2”3”-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl)amide;
[0686] 2”-Cyano-5”-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl)amide;
[0687] 6'-Cyano-2'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0688] 8'-Cyano-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide;
[0689] 2'-Cyano-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (2-hydroxy-1-methoxymethyl-ethyl)-amide;
[0690] 2'-Cyano-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (1-methoxymethyl-propyl)-amide;
[0691] 4'-Cyano-2'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0692] 2'3'-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide;
[0693] 2'3'-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (2-hydroxy-1-methoxymethyl-ethyl)-amide;
[0694] 2'-Cyano-5-(5-methyl-pyridin-2-yl)-5'-trifluoromethyl-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0695] 2'-Cyano-5-(5-methyl-pyridin-2-yl)-5'-trifluoromethyl-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide;
[0696] N-(S)-2-Hydroxy-1-methyl-ethyl)-3-(5-methyl-pyridin-2-yl)-5-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
[0697] 2'-Hydroxymethyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0698] 2'-Fluoro-5-(5-methyl-pyridin-2-yl)-6'-trifluoromethyl-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide;
[0699] 3-(4-Cyano-pyridin-3-yl)-N-(S)-2-hydroxy-1-methyl-ethyl)-5-(5-methyl-pyridin-2-yl)-benzamide;
[0700] 2'-Cyano-2'3'-difluoro-4-methyl-[1',1',3',3',1']terphenyl-5-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0701] 2'-Cyano-5-(4-cyano-pyridin-3-yl)-4'-methyl-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0702] 2'-Cyano-5-(4-cyano-pyridin-3-yl)-4'-methyl-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide; and
[0703] 2'-Cyano-2'-hydroxymethyl-4-methyl-[1',1',3',1']terphenyl-5'-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0704] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomor or isotope variant thereof.
[0705] With regard to formula 1, in certain embodiments, the compound is selected from (R')-heterocycloalkyl:
[0706] 2'-Cyano-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide;
[0707] 2'3'-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide;
[0708] 2'-Cyano-5-(5-methyl-pyridin-2-yl)-5'-trifluoromethyl-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide;
[0709] 2'-Fluoro-5-(5-methyl-pyridin-2-yl)-6'-trifluoromethyl-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide; and
[0710] 2'-Cyano-5-(4-cyano-pyridin-3-yl)-4'-methyl-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide;
[0711] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotope variant thereof;
[0712] With regard to formula 1, in certain embodiments, the compound is selected from (R')-alkyl:
[0713] 4'-Methyl-5-(2-oxo-pyrrolidin-1-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0714] 2',3'-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (1-methoxymethyl-propyl)-amide;
[0715] 2',3'-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0716] 2'-Cyano-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0717] 6'-Cyano-2'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0718] 2'-Cyano-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (2-hydroxy-1-methoxymethyl-ethyl)-amide;
[0719] 2'-Cyano-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (1-methoxymethyl-propyl)-amide;
[0720] 4'-Cyano-2'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0721] 2',3'-Difluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (2-hydroxy-1-methoxymethyl-ethyl)-amide;
[0722] 2'-Cyano-5-(5-methyl-pyridin-2-yl)-5'-trifluoromethyl-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0723] 2'-Cyano-5-(5-methyl-pyridin-2-yl)-5'-trifluoromethyl-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0724] 2'-Cyano-5-(5-methyl-pyridin-2-yl)-5'-trifluoromethyl-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0725] 3-(4-Cyano-pyridin-3-yl)-N-(S)-2-hydroxy-1-methyl-ethyl)-5-(5-methyl-pyridin-2-yl)-benzamide;
[0726] 2'-Cyano-2',3'-difluoro-4-methyl-[1',1',3',3',1']terphenyl-5'-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0727] 2'-Cyano-5-(4-cyano-pyridin-3-yl)-4'-methyl-biphenyl-3-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide; and
[0728] 2'-Cyano-2'-hydroxymethyl-4-methyl-[1',1',3',3',1']terphenyl-5'-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide;
[0729] or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotope variant thereof.
[0730] With regard to formula 1, in certain embodiments, the compound is selected from (R')-heterocycloalkyl:
[0731] 4'-ethyl-5-(2-oxo-piperidin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0732] 4'-Methyl-5-(2-oxo-piperidin-1-yl)-biphenyl-3-carboxylic acid (2-methyl-pyrimidin-5-ylmethyl)-amide;
[0733] 4'-Methyl-5-(2-oxo-piperidin-1-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
[0734] 4'-Methyl-5-(2-oxo-piperidin-1-yl)-biphenyl-3-carboxylic acid [(R)-1-(6-methyl-pyridin-3-yl)-ethyl]-amide;
[0735] 4'-Methyl-5-(2-oxo-pyridolin-1-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-amide;
[0736] 4'-Methyl-5-(2-oxo-pyridolin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0737] 4'-Methyl-5-(2-oxo-pyridolin-1-yl)-biphenyl-3-carboxylic acid (2-methyl-pyrimidin-5-ylmethyl)-amide;
[0738] 4'-Methyl-5-(2-oxo-pyridolin-1-yl)-biphenyl-3-carboxylic acid [(R)-1-(6-methyl-pyridin-3-yl)-ethyl]-amide;
[0739] 3-(5-Methyl-pyridin-2-yl)-N-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-5-(2-oxo-piperidin-1-yl)-benzamide;
[0740] 3-(5-Methyl-pyridin-2-yl)-N-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-5-(3-oxo-morpholin-4-yl)-benzamide;
[0741] 3-(5-Methyl-pyridin-2-yl)-N-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-5-(2-oxo-pyridolin-1-yl)-benzamide;
[0742] 5-[(S)-2-Hydroxymethyl-pyridolin-1-yl]-4'-methyl-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0743] 4'-Methyl-5-(2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0744] 5-[(R)-2-Hydroxymethyl-pyridolin-1-yl]-4'-methyl-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0745] 3-(5-Methyl-pyridin-2-yl)-N-[(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-5-(5-methyl-pyridin-2-yl)-benzamide;
[0746] 2'-Cyano-4'-methyl-5-(3-oxo-morpholin-4-yl)-biphenyl-3-carboxylic acid (2-methyl-pyridin-5-ylmethyl)-amide;
[0747] 2'-Cyano-4'-methyl-5-(2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0748] 2'-Cyano-4'-methyl-5-(2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (2-methyl-pyridin-5-ylmethyl)-amide;
[0749] 2'-Cyano-4'-methyl-5-(4-methyl-2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;
[0750] 4'-Methyl-5-(4-methyl-2-oxo-piperazin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

[0751] Additional embodiments within the scope provided herein are set forth in non-limiting fashion elsewhere herein and in the examples. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting in any manner.

[0752] In certain aspects, provided herein are prodrugs and derivatives of the compounds according to the formulae above. Prodrugs are derivatives of the compounds provided herein, which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds provided herein, which are pharmaceutically active, in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0753] Certain compounds provided herein have activity in both their acid and acid derivative forms, but the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds provided herein are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or (alkoxy carbonyloxy) alkyl esters. Preferred are the C1 to C6 alkyl, C2 to C6 alkenyl, aryl, C7 to C12 substituted aryl, and C7 to C12 arylalkyl esters of the compounds provided herein.

Pharmaceutical Compositions

[0754] When employed as pharmaceuticals, the compounds provided herein are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

[0755] Generally, the compounds provided herein are administered in a therapeutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient’s symptoms, and the like.

[0756] The pharmaceutical compositions provided herein can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds provided herein are preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[0757] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term “unit dosage forms” refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include pre-filled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the fumaric acid compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[0758] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispersing agents, colorants, flavors and the like. Solid forms may include, for example, any of the
following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0759] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[0760] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as an ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope provided herein.

[0761] The compounds provided herein can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[0762] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington’s Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pa., which is incorporated herein by reference.

[0763] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington’s The Science and Practice of Pharmacy, 21st edition, 2005. Publisher: Lippincott Williams & Wilkins, which is incorporated herein by reference.

[0764] The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington’s Pharmaceutical Sciences.

[0765] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1
Tablets

[0766] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active amide compound per tablet) in a tablet press.

Formulation 2
Capsules

[0767] A compound of the invention may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture may be filled into 250 mg capsules (125 mg of active amide compound per capsule).

Formulation 3
Liquid

[0768] A compound of the invention (125 mg), sucrose (1.75 g) and xanthan gum (4 mg) may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 ml.

Formulation 4
Tablets

[0769] A compound of the invention may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active amide compound) in a tablet press.

Formulation 5
Injection

[0770] A compound of the invention may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Formulation 6
Topical

[0771] Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of a compound of the invention (50 g) methylparaben (0.25 g), propylparaben (0.15 g), sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) is added and the resulting mixture is stirred until it coagulates.

Methods of Treatment

[0772] The present compounds are used as therapeutic agents for the treatment of conditions in mammals. Accordingly, the compounds and pharmaceutical compositions provided herein find use as therapeutics for preventing and/or treating neurodegenerative, autoimmune and inflammatory conditions in mammals including humans and non-human mammals. Thus, and as stated earlier, the present invention includes within its scope, and extends to, the recited methods of treatment, as well as to the compounds for such methods,
and to the use of such compounds for the preparation of medicaments useful for such methods.

[0773] In a method of treatment aspect, provided herein is a method of treating a mammal susceptible to or afflicted with a condition associated with arthritis, asthma, myocardial infarction, inflammatory bowel disease and autoimmune disorders, which method comprises administering an effective amount of one or more of the pharmaceutical compositions just described.

[0774] In yet another method of treatment aspect, provided herein is a method of treating a mammal susceptible to or afflicted with a condition that gives rise to pain responses or that relates to imbalances in the maintenance of basal activity of sensory nerves. The present compounds have use as analgesics for the treatment of pain of various genuses or etiology, for example acute, inflammatory pain (such as pain associated with osteoarthritis and rheumatoid arthritis); various neuropathic pain syndromes (such as post-herpetic neuralgia, trigeminal neuralgia, reflex sympathetic dystrophy, diabetic neuropathy, Guillain Barre syndrome, fibromyalgia, phantom limb pain, post-mastectomy pain, peripheral neuropathy, HIV neuropathy, and chemotherapy-induced and other iatrogenic neuropathies); visceral pain, (such as that associated with gastrointestinal reflex disease, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, and various gynecological and urological disorders), dental pain and headache (such as migraine, cluster headache and tension headache).

[0775] In additional method of treatment aspects, provided herein are methods of treating a mammal susceptible to or afflicted with neurodegenerative diseases and disorders such as, for example Parkinson’s disease, Alzheimer’s disease and multiple sclerosis; diseases and disorders which are mediated by or result in neuroinflammation such as, for example encephalitis; centrally-mediated neuropsychiatric diseases and disorders such as, for example depression mania, bipolar disease, anxiety, schizophrenia, eating disorders, sleep disorders and cognition disorders; epilepsy and seizure disorders; prostate, bladder and bowel dysfunction such as, for example urinary incontinence, urinary hesitancy, rectal hypersensitivity, fecal incontinence, benign prostatic hypertrophy and inflammatory bowel disease; respiratory and airway disease and disorders such as, for example, allergic rhinitis, asthma and reactive airway disease and chronic obstructive pulmonary disease; diseases and disorders which are mediated by or result in inflammation such as, for example rheumatoid arthritis and osteoarthritis, myocardial infarction, various autoimmune diseases and disorders; itch/pruritus such as, for example psoriasis; obesity; lipid disorders; cancer; and renal disorders method comprises administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions just described.

[0776] As a further aspect there is provided the present compounds for use as a pharmaceutical especially in the treatment or prevention of the aforementioned conditions and diseases. We also provide the use of the present compounds in the manufacture of a medicament for the treatment or prevention of one of the aforementioned conditions and diseases.

[0777] Injection dose levels range from about 0.1 mg/kg/hour to at least 10 mg/kg/hour, all for from about 1 to about 120 hours and especially 24 to 96 hours. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[0778] For the prevention and/or treatment of long-term conditions, such as neurodegenerative and autoimmune conditions, the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.05 to about 20 mg/kg of the compound provided herein, with preferred doses each providing from about 0.1 to about 10 mg/kg and especially about 1 to about 5 mg/kg.

[0779] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[0780] When used to prevent the onset of a neurodegenerative, autoimmune or inflammatory condition, the compounds provided herein will be administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[0781] The compounds provided herein can be administered as the sole active agent or they can be administered in combination with other agents, including other active amines and derivatives. Administration in combination can proceed by any technic, but not limited to those of skill in the art including, for example, separate, sequential, concurrent, and alternating administration.

General Synthetic Procedures

[0782] The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. See, e.g., FIG. 1 and Synthetic Schemes 1-10 below. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0783] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and P. G. M. Wuts, Protecting Groups in Organic Synthesis, Second Edition, Wiley, New York, 1991, and references cited therein.

[0784] The compounds provided herein, for example, may be prepared by the reaction of a chloro derivative with an appropriately substituted amine and the product isolated and purified by known standard procedures. Such procedures include (but are not limited to) recrystallization, column chromatography or HPLC. The following schemes are presented with details as to the preparation of representative fused heterocycles that have been listed hereinabove. The compounds provided herein may be prepared from known or commer-
cially available starting materials and reagents by one skilled in the art of organic synthesis.


In certain embodiments, an enantiomerically pure compound of formula 1 may be obtained by reaction of the racemate with a suitable optically active acid or base. Suitable acids or bases include those described in Bighley et al., 1995, Salt Forms of Drugs and Adsorption, in Encyclopedia of Pharmaceutical Technology, vol. 13, Swarbrick & Boylan, eds., Marcel Dekker, New York; ten Hoeve & H. Wynberg, 1985, Journal of Organic Chemistry 50:4508-4514; Dale & Mosher, 1973, J. Am. Chem. Soc. 95:512 and CRC Handbook of Optical Resolution via Diastereomeric Salt Formation, the contents of which are hereby incorporated by reference in their entireties.

Enantiomerically pure compounds can also be recovered either from the crystallized diastereomer or from the mother liquor, depending on the solubility properties of the particular acid resolving agent employed and the particular acid enantiodimer used. The identity and optical purity of the particular compound so recovered can be determined by polarimetry or other analytical methods known in the art. The diastereoisomers can then be separated, for example, by chromatography or fractional crystallization, and the desired enantiomer regenerated by treatment with an appropriate base or acid. The other enantiomer may be obtained from the racemate in a similar manner or worked up from the liquors of the first separation.

In certain embodiments, enantiomerically pure compound can be separated from racemic compound by chiral chromatography. Various chiral columns and eluents for use in the separation of the enantiomers are available and suitable conditions for the separation can be empirically determined by methods known to one of skill in the art. Exemplary chiral columns available for use in the separation of the enantiomers provided herein include, but are not limited to CHIRALCEL® OB, CHIRALCEL® OB-H, CHIRALCEL® OD, CHIRALCEL® OD-H, CHIRALCEL® OF, CHIRALCEL® OJ, CHIRALCEL® OJ and CHIRALCEL® OK.

Various compounds of the invention can be prepared using a general procedures or synthetic schemes described below.
Scheme 5

-continued

Scheme 6

-continued
[0790] In Schemes 1-11 above, each of $X^1$ and $X^2$ is independently selected from F, Cl, Br, I, and OTf; R is selected from H, C$_1$-C$_6$ alkyl, and benzyl; n=0, 1, or 2; Q—Substituted or unsubstituted C, N, O, S(O)$_2$; and A, B, W, X', L, R', R$^1$, R$^2$, R$^3$, L$'$, and m$'$ as described herein.

SYNTHESIS OF INTERMEDIATES

Intermediate A

5-Bromo-4'-methylbiphenyl-3-carboxylic acid

[0791] A pressure vial was charged with 3-bromo-5-iodobenzoic acid (7.60 g, 23.2 mmol), p-tolylboronic acid (3.16 g, 23.2 mmol), tetrakis(triphenylphosphine)palladium(0) (1.34 g, 1.16 mmol), cesium carbonate (8.33 g, 25.6 mmol), toluene (99.0 mL, 930 mmol), ethanol (27.1 mL, 465 mmol) and water (12.6 mL, 697 mmol) and the reaction stirred at 85°C over nights. The reaction mixture was filtered over celite and the solvent removed to get the crude product as a brown solid.

[0793] LC/MS m/z 289.7 (M-H$^-$)
A) Methyl 3-iodo-5-nitrobenzoate

[0795] To a stirred solution of 3-iodo-5-nitrobenzoic acid (15.1 g, 0.049 mol) in methanol (151 mL, 3.73 mol) was added thionyl chloride (15.1 mL, 0.205 mol) dropwise at 0°C. The mixture was heated to reflux for 2 hours. The solvent was removed in vacuo. The residue was purified by flash chromatography (0-100% EtOAc/hexane) to afford an white solid.

B) Methyl 4'-methyl-5-nitrophenyl-3-carboxylate

[0796] To a stirred solution of methyl 3-iodo-5-nitrobenzoate (7.76 g, 24 mmol) and p-tolylboronic acid (3.94 g, 28 mmol) in toluene (576 mL) was added cesium carbonate (9.4 g, 28 mmol) in water (7.8 mL). The mixture was purged with nitrogen, and then tetrakis(triphenylphosphine)palladium(0) (860 mg, 0.74 mmol) was added at room temperature. The reaction mixture was heated to reflux for 3 days. After cooling, the mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by flash chromatography to afford a white solid.

C) Methyl 5-amino-4'-methylbiphenyl-3-carboxylate

[0797] To a stirred solution methyl 4'-methyl-5-nitrobiphenyl-3-carboxylate (4.58 g, 16 mmol) in methanol (130 mL) was added oxalyl chloride (12.56 g, 64.2 mmol) at room temperature. The mixture was heated under reflux for 3 hours. After cooling, the mixture was concentrated in vacuo. The residue was washed with water, basified to pH 9-9 by addition of Na2CO3, and extracted with CH2Cl2. The organic layer was dried over MgSO4, filtered and concentrated to afford a white solid.

[0798] 1H NMR (300 MHz, CDCl3): 7.85 (t, 1H, J=1.5 Hz), 7.57 (t, 1H, J=1.8 Hz), 7.48 (d, 2H, J=8.4 Hz), 7.35 (t, 1H, J=2.0 Hz), 7.22 (d, 2H, J=8.1 Hz), 3.90 (s, 3H), 2.37 (s, 3H).

D) 4'-Methyl-5-(2-oxopiperidin-1-yl)biphenyl-3-carboxylic acid

[0799] To a stirred solution of methyl 5-amino-4'-methylbiphenyl-3-carboxylate (410 mg, 1.7 mmol) in CH2Cl2 (30 mL) and N,N-diisopropylethylamine (0.44 mL, 2.5 mmol) at 0°C, was added 5-bromopentanoyl chloride (370 mg, 1.9 mmol). The mixture was stirred at room temperature overnight and then washed with sat. Na2CO3 solution and brine, dried (Na2SO4), and concentrated. The residue was dissolved in THF (30 mL) and cooled to 0°C. Sodium tert-butoxide (200 mg, 2.0 mmol) was added and the mixture was stirred at room temperature for 3 h. LC-MS indicated the cyclization reaction was complete. MeOH (20 mL) and water (10 mL) were added followed by lithium hydroxide (120 mg, 5.1 mmol). The mixture was stirred at room temperature for another 3 h, and LC-MS indicated the saponification was complete. The mixture was concentrated in vacuo. The residue was treated with water and acidified to pH 2-3 with 1N HCl, extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried (Na2SO4), and concentrated to afford a white solid. LC-MS: 310.1 [M+1]+.

Intermediate C

3-(5-Methylpyridin-2-yl)-5-(3-oxomorpholino)benzoic acid

[0800]
A) Methyl 3-bromo-5-(5-methylpyridin-2-yl)benzoate

[0801] A microwave vial was charged with methyl 3-bromo-5-iodobenzoate (2.00 g, 5.87 mmol), 5-methyl-2-(tributylstannyl)pyridine (2.24 g, 5.87 mmol), tetrakis(triphenylphosphine)palladium(0) (0.59 mg, 0.29 mmol) and 1,4-dioxane (30 mL). The reaction mixture was subjected to microwave irradiation at 120°C for 1 hour. The reaction was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to afford the product as a white solid.

[0802] 1H NMR (400 Hz, DMSO-d6): 8.64 (t, J=1.51 Hz, 1H), 8.55 (m, 1H), 8.52 (t, J=1.89 Hz, 1H), 8.07 (t, J=1.89 Hz, 1H), 8.03 (d, J=8.31 Hz, 1H), 7.75 (dd, J=8.31 & 2.27 Hz, 1H), 3.91 (s, 1H), 2.36 (s, 1H).

B) Methyl 3-(5-methylpyridin-2-yl)-5-(3-oxomorpholino)benzoate

[0803] A microwave vial was charged with methyl 3-bromo-5-(5-methylpyridin-2-yl)benzoate (100 mg, 0.33 mmol), morpholin-3-one (42 mg, 0.41 mmol), palladium-acetate (4 mg), cesium carbonate (169 mg, 0.52 mmol), xantphos (3 mg), and 1,4-dioxane (1 mL). The reaction mixture was subjected to microwave irradiation at 110°C for 15 min. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resultant residue was purified by preparative HPLC to get the product as a yellow solid.

C) 3-(5-Methylpyridin-2-yl)-5-(3-oxomorpholino)benzoic acid

[0804] A round bottom flask was charged with methyl 3-(5-methylpyridin-2-yl)-5-(3-oxomorpholino)benzoate (50 mg, 0.15 mmol), methanol (1.2 mL) and lithium hydroxide (11 mg, 0.46 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was acidified to pH=5 and concentrated under reduced pressure to get the title compound-LiCl mixture as a white solid.

Intermediate D
3-Bromo-5-(5-methylpyridin-2-yl)benzoic acid

[0805]

[0806] A round bottom flask was charged with methyl 3-bromo-5-(5-methylpyridin-2-yl)benzoate (300 mg, 0.98 mmol), tetrahydrofuran (15 mL) and lithium hydroxide (70 mg, 2.94 mmol) and the reaction mixture was stirred at 50°C overnight. After cooling, the reaction mixture was acidified to pH=5 and concentrated under reduced pressure to get the title compound-LiCl mixture.

Intermediate E
2',3'-difluoro-5-(5-methylpyridin-2-yl)biphenyl-3-carboxylic acid

[0807]
To a mixture of methyl 3-bromo-5-(5-methylpyridin-2-yl)benzoate (901 mg, 2.94 mmol), bis(pinacolato)diboron (1.1 g, 4.4 mmol), potassium acetate (1.445 g, 14.72 mmol), and N,N-dimethylformamide (0.63 mL, 8.1 mmol) under argon was added [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (216 mg, 0.26 mmol). The mixture was heated under argon at 80°C overnight, and then cooled to rt. Water (50 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried (Na2SO4), and evaporated. The residue was purified by silica gel column (0-50% EtOAc-hexane) to yield a light green solid.

B) Methyl 2',3'-difluoro-5-(5-methylpyridin-2-yl)biphenyl-3-carboxylate

Into a 5 mL microwave vial were charged with methyl 3-(5-methylpyridin-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (250 mg, 0.71 mmol), 1-bromo-2,3-difluorobenzene (273 mg, 1.42 mmol), cesium carbonate (1.15 g, 3.54 mmol), tetra-n-butylammonium iodide (261 mg, 0.71 mmol), POPDI (35 mg, 0.071 mmol), water (0.5 mL) and N,N-dimethylformamide (3 mL). The reaction mixture was subjected to microwave irradiation at 150°C for 10 mins. After cooling, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated under reduced pressure to give the residue which was purified by silica gel column to yield the title compound.

C) 2',3'-Difluoro-5-(5-methylpyridin-2-yl)biphenyl-3-carboxylic acid

A round bottom flask was charged with methyl 2',3'-difluoro-5-(5-methylpyridin-2-yl)biphenyl-3-carboxylate (297 mg, 0.87 mmol), potassium carbonate (303 mg, 2.19 mmol) and methanol (5 mL) and few drops of water. The reaction was stirred at room temperature for 24 hours, then acidified to pH 5 and concentrated under reduced pressure to afford the title compound LiCl mixture.

Intermediate F

2'-Cyano-5-(5-methylpyridin-2-yl)-5'-(trifluoromethyl)biphenyl-3-carboxylic acid

A) Methyl 2'-cyano-5-(5-methylpyridin-2-yl)-5'-(trifluoromethyl)biphenyl-3-carboxylate

Into a 5 mL microwave vial were charged with methyl 3-(5-methylpyridin-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (250 mg, 0.71 mmol), 1-bromo-2,3-difluorobenzene (273 mg, 1.42 mmol), cesium carbonate (1.15 g, 3.54 mmol), tetra-n-butylammonium iodide (261 mg, 0.71 mmol), POPDI (35 mg, 0.071 mmol), water (0.5 mL) and N,N-dimethylformamide (3 mL). The reaction mixture was subjected to microwave irradiation at 150°C for 10 mins. After cooling, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated under reduced pressure to give the residue which was purified by silica gel column to yield the title compound.
aborolan-2-yl)benzoate (300 mg, 0.85 mmol), 2-bromo-4-(trifluoromethyl)benzonitrile (425 mg, 1.70 mmol), cesium carbonate (1.38 g, 4.25 mmol), tetra-n-butylammonium iodide (314 mg, 0.85 mmol), POPd (43 mg, 0.085 mmol), water (0.6 mL) and N,N-dimethylformamide (3 mL). The reaction mixture was subjected to microwave irradiation at 150°C for 10 mins. After cooling, the reaction mixture was extracted with ethylacetate. The organic layer was washed with brine, dried, and concentrated under reduced pressure to afford the residue which was purified by silica gel column to yield the title compound.

B) 2'-Cyano-5-(5-methylpyridin-2-yl)-5'-[(trifluoromethyl)benzoyl]biphenyl-3-carboxylic acid

[0813] A round bottom flask was charged with methyl 2'-cyano-5-(5-methylpyridin-2-yl)-5'(trifluoromethyl)benzoyl)biphenyl-3-carboxylate (106 mg, 0.27 mmol), lithium hydroxide (19 mg, 0.81 mmol), methanol (4.0 mL) and a few drops of water. The reaction was stirred at room temperature for 1 day, and then acidified to pH=5 and concentrated under reduced pressure to afford the title compound-LiCl mixture.

Intermediate G

2'-Cyano-5-(5-methylpyridin-2-yl)-5'-(trifluoromethyl)biphenyl-3-carboxylic acid

[0814]

A) Methyl 5-bromo-2'-cyano-4'-methylbiphenyl-3-carboxylate

[0815] Into a microwave vial were charged methyl 3-bromo-5-iodobenzoate (1.3 g, 3.8 mmol), 5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.1 g, 4.6 mmol), cesium carbonate (3.1 g, 9.5 mmol), and tetrakis(triphenylphosphine)palladium(0) (44 mg, 0.08 mmol), water (3 mL) and toluene (8 mL). The reaction mixture was subjected to microwave irradiation at 100°C for 1 h. After cooling, the reaction was filtered and concentrated. The residue was purified by reversed phase HPLC (acetonitrile:water gradient) to the title compound as a white solid. LC-MS: 331.1 [M+1]+; 1H NMR (400 MHz, CDCl3): 8.16 (s, 1H), 8.03 (t, J=1.3 Hz, 1H), 7.76 (t, J=1.8 Hz, 1H), 7.53 (s, 1H), 7.33 (dd, J=1.6, 9.4 Hz, 1H), 7.25 (d, J=8.1 Hz, 1H), 3.93 (s, 3H), 2.43 (s, 3H).

B) Methyl 2'-cyano-4'-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-carboxylate

[0816] To a mixture of methyl 5-bromo-2'-cyano-4'-methylbiphenyl-3-carboxylate (1.0 g, 3.0 mol), bis(pinacolato) diboron (1.1 g, 4.5 mmol), potassium acetate (1.48 g, 15.1 mmol), and N,N-dimethylformamide (12 mL) under argon was added [1,1'-Bis(diphenylphosphino)ferrocene][dichloropalladium(II)], complex with dichloromethane (1:1) (223 mg, 0.27 mmol). The mixture was heated under argon at 80°C overnight, and then cooled to rt. Water (50 mL) was added and the mixture was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine, dried (Na2SO4), and evaporated. The residue was purified by silica gel column (0-50% EtOAc-hexane) to give a white solid.

C) 2'-Cyano-5-(4-cyanopyridin-3-yl)-4'-methylbiphenyl-3-carboxylic acid

[0817] Into a 5 mL microwave vial were charged methyl 2'-cyano-4'-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)biphenyl-3-carboxylate (150 mg, 0.36 mmol), 3-bromoisonicotinonitrile (131 mg, 0.72 mmol), cesium carbonate (583 mg, 1.79 mmol), tetra-n-butylammonium iodide (132 mg, 0.36 mmol), POPd (18 mg, 0.036 mmol), water (0.5 mL) and N,N-dimethylformamide (1 mL). The reaction mixture was subjected to microwave irradiation at 150°C for 10 mins. The reaction mixture was purified by HPLC to afford the title compound.
Intermediate H
2-Cyano-2'-hydroxymethyl-4-methyl-1,1':3',1" terphenyl-3-carboxylic acid methyl ester

Into a 5 mL microwave vial were charged methyl 5-bromo-2'-cyano-4'-methylbiphenyl-3-carboxylate (95 mg, 0.29 mmol), 2-(hydroxymethyl)phenylboronic acid (87 mg, 0.57 mmol), cesium carbonate (466 mg, 1.43 mmol), tetra-n-butylammonium iodide (106 mg, 0.29 mmol), Pd(PPh₃)₂Cl₂ (14 mg, 0.029 mmol), water (0.2 mL) and N,N-dimethylformamide (1 mL). The reaction mixture was subjected to microwave irradiation for 10 mins at 150°C. After cooling, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated under reduced pressure to give the residue which was purified by HPLC to yield the title compound.

Intermediate J
(2-Methylpyrimidin-5-yl)methanamine

A solution of 2-methylpyrimidine-5-carbaldehyde (7.5 g, 0.058 mol) in methanol (270 mL, 9.1 mol) was cooled to 0°C. and treated with sodium tetrahydroborate (11.7 g, 0.29 mol). After 30 min, the reaction was quenched with eq H₂O (200 mL) and extracted with ethyl acetate. The organic layer was dried over MgSO₄ and concentrated to give the title compound as a yellow solid.

b. 5-(Azidomethyl)-2-methylpyrimidine

A solution of (2-methylpyrimidin-5-yl)methanol (92.8 g, 0.66 mmol) in toluene (30 mL, 300 mmol) and methylene chloride (40 mL, 660 mmol) at 0°C was treated with diphenylphosphino-azole (2.8 mL, 13 mmol) followed by 1,8-diazabicyclo-[5.4.0]-undec-7-ene (2.0 mL, 13 mmol) and stirred for 2 h at 0°C. After being further stirred at rt for 16 h, the reaction mixture was diluted with water (50 mL) and DCM (50 mL). The organic layer was separated and washed with brine; dried (MgSO₄), filtered, and concentrated. The residue was purified by column to give the product as a colorless oil.

Intermediate K
5-Bromo-4'-methyl-N-((2-methylpyrimidin-5-yl)methyl)biphenyl-3-carboxamide

A round bottom flask was charged with 5-bromo-4'-methylbiphenyl-3-carboxylic acid (1.00 g, 2.75 mmol), (2-methylpyrimidin-5-yl)methanamine (0.406 g, 3.30 mmol), N,N,N',N'-tetramethyl-O-(7-azabenzo[d]imidazol-1-yl)uroniumhexafluorophosphate (2.40 g, 6.32 mmol), N,N-disopropylethylamine (1.91 mL, 11.0 mol) and N,N-dimethylformamide (10 mL, 100 mmol) and the reaction stirred for 3 hours. The reaction was then quenched with water and extracted with ethyl acetate and washed with brine. The solvents were removed under reduced pressure and the residue purified by flash chromatography followed by prep HPLC to get the product as light yellow solid.

A solution of 2-methylpyrimidine-5-carboxaldehyde (7.5 g, 0.058 mol) in methanol (370 mL, 9.1 mol) was cooled to 0°C. and treated with sodium tetrahydroborate (5.4 g, 0.090 mmol). After 30 min, the reaction was quenched with eq H₂O (200 mL) and extracted with ethyl acetate. The organic layer was dried over MgSO₄ and concentrated to give the title compound as a yellow solid.

Intermediate L
(2-Methylpyrimidin-5-yl)methanamine
7.98 (t, J=1.84 Hz, 1H), 7.66 (d, J=8.13 Hz, 2H), 7.31 (d, J=8.15 Hz, 2H), 4.47 (d, J=5.69 Hz, 2H), 2.59 (s, 3H), 2.35 (s, 3H).

Synthesis of Representative Compounds

**Compound 1**

4'-Methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (2-methyl-pyrimidin-5-ylmethyl)-amide

A mixture of 5-bromo-4'-methyl-N-((2-methylpyrimidin-5-yl)methyl)biphenyl-3-carboxamide (40.00 mg, 0.09084 mmol), 2-(tributylstanny)pyrimidine (0.1 g, 0.0003 mol), tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.000005 mol) and toluene (1 mL, 0.009 mol) was heated in the microwave at 120°C for 1 hour. LC/MS showed the desired product, LC/MS m/e=396.3. The mixture was cooled to room temperature and the reaction mixture filtered over celite and solvent removed under reduced pressure. The residue was purified by reverse phase prep HPLC to get the product as white solid.

**Compound 2**

4'-Methyl-5-pyrimidin-2-yl-biphenyl-3-carboxylic acid (2-methyl-pyrimidin-5-ylmethyl)-amide

A mixture of 5-bromo-4'-methyl-N-((2-methylpyrimidin-5-yl)methyl)biphenyl-3-carboxamide (100 mg, 0.0002 mol), 2-(tributylstanny)pyrimidine (0.05 g, 0.001 mol), tetrakis(triphenylphosphine)palladium(0) (2 mg, 0.000002 mol) and toluene (0.4 mL, 0.004 mol) was heated in the microwave at 120°C for 1 hour. The mixture was cooled to room temperature and the reaction mixture filtered over celite and solvent removed under reduced pressure. The residue was purified by prep HPLC to get the product as white solid.

**Compound 15**

2'-Fluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide

A round bottom flask was charged with 3-bromo-5-(5-methylpyridin-2-yl)benzoic acid (450.00 mg, 1.5404 mmol), 6-(methylpyridin-3-yl)methanamine (225.83 mg, 1.8485 mmol), N,N,N,N-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (1171.4 mg, 3.0808 mmol), N,N-diisopropylethylamine (0.93910 mL, 5.3915 mmol) and N,N-dimethylformamide (5.00 mL, 64.6 mmol) and the reaction stirred at room temperature for 1 hour. The
reaction was poured into brine and extracted with ethyl acetate to get the product as brown solid

b, 2'-Fluoro-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide

[0836] In a 5 mL microwave vial, 3-bromo-5-(5-methylpyridin-2-yl)-N-((6-methylpyridin-3-yl)methyl)benzamide (20 mg, 0.1012 mmol), 2-fluorophenylboronic acid (14.16 mg, 0.1012 mmol), cesium carbonate (82.42 mg, 0.2530 mmol), tetra-n-butylammonium iodide (18.69 mg, 0.05060 mmol), and PO4 (2.538 mg, 0.005060 mmol) were dissolved in Water (0.04 mL, 2 mmol) and N,N-dimethylformamide (0.2 mL, 2 mmol). The reaction mixture was microwaved for 20 mins at 150 degrees. The reaction was purified directly by reversed phase HPLC (acetonitrile:water gradient) at pH10. The combined pure fractions were reduced invacuo to afford the title compound as colorless oil.

[0837] 'H NMR (DMSO-d6): 9.28 (t, J=5.77 Hz, 1H), 8.58 (t, J=1.91 Hz, 1H), 8.55 (bs, 1H), 8.45 (9 bs, 1H), 8.37 (q, J=1.76 Hz, 1H), 8.07 (q, J=1.76 Hz, 1H), 8.02 (d, J=8.34 Hz, 1H), 7.75 (dd, J=7.85 & 2.02 Hz, 1H), 7.70-7.63 (m, 2H), 7.51-7.46 (m, 1H), 7.39-7.34 (m, 2H), 7.22 (d, J=7.96 Hz, 1H), 4.50 (d, J=5.66 Hz, 2H), 2.44 (s, 3H), 2.36 (s, 3H)

Compound 18
2'-Methoxy-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide

[0838]

[0839] In a 5 mL microwave vial, 3-bromo-5-(5-methylpyridin-2-yl)-N-((6-methylpyridin-3-yl)methyl)benzamide (20 mg, 0.05 mmol), 2-methoxyphenylboronic acid (15.38 mg, 0.1012 mmol), cesium carbonate (82.42 mg, 0.2530 mmol), tetra-n-butylammonium iodide (18.69 mg, 0.05060 mmol), and PO4 (2.538 mg, 0.005060 mmol) were dissolved in Water (0.04 mL, 2 mmol) and N,N-dimethylformamide (0.2 mL, 2 mmol). The reaction mixture was microwaved for 20 mins at 150 degrees. The reaction was purified directly by reversed phase HPLC (acetonitrile:water gradient) at pH10. The combined pure fractions were reduced invacuo to afford the title compound as colorless oil.

Compound 22
4'-Methyl-5-pyridin-4-yl-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide

[0840]

[0841] In a 5 mL microwave vial, 5-Bromo-4'-methyl-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide (20 mg, 0.05 mmol), Pyridine-4-boronic acid (12.44 mg, 0.1012 mmol), cesium carbonate (82.42 mg, 0.2530 mmol), tetra-n-butylammonium iodide (18.69 mg, 0.05060 mmol), and PO4 (2.538 mg, 0.005060 mmol) were dissolved in Water (0.04 mL, 2 mmol) and N,N-dimethylformamide (0.2 mL, 2 mmol). The reaction mixture was microwaved for 20 mins at 150 degrees. The reaction was purified directly by reversed phase HPLC (acetonitrile:water gradient) at pH10. The combined pure fractions were reduced invacuo to afford the title compound as a white solid.

Compound 28
2'-Dimethylaminomethyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide

[0842]

[0843] In a 5 mL microwave vial, 3-bromo-5-(5-methylpyridin-2-yl)-N-((6-methylpyridin-3-yl)methyl)benzamide (15.00 mg, 0.03785 mmol), Unnamed (13.55 mg, 0.07570 mmol), cesium carbonate (61.66 mg, 0.1892 mmol), tetra-n-butylammonium iodide (13.98 mg, 0.03785 mmol), and PO4 (1.899 mg, 0.003785 mmol) were dissolved in Water (0.05 mL, 2 mmol) and N,N-dimethylformamide (0.1 mL, 2 mmol). The reaction mixture was microwaved for 20 mins at 150 degrees. The reaction was purified directly by reversed
phase HPLC (acetonitrile:water gradient) at pH 10. The combined pure fractions were reduced in vacuo to afford the title compound as a colorless oil.

In DMSO-d6: 9.21 (t, J = 5.83 Hz, 1H), 8.57 (7.12 Hz, 1H), 8.54 (d, J = 2.12 Hz, 1H), 8.44 (d, J = 2.12 Hz, 1H), 8.28 (d, J = 1.55 Hz, 1H), 7.97 (d, J = 8.22 Hz, 1H), 7.93 (t, J = 1.55 Hz, 1H), 7.74 (dd, J = 8.06 & 2.02 Hz, 1H), 7.64 (dd, J = 8.06 & 2.24 Hz, 1H), 7.52 (d, J = 6.94 Hz, 1H), 7.43-7.34 (m, 3H), 7.21 (d, J = 8.06 Hz, 1H), 4.48 (d, J = 6.22 Hz, 2H), 2.43 (s, d3H), 2.55 (s, 3H), 2.07 (s, 6H).

In a 5 mL microwave vial, (R)-3-bromo-5-(5-methylpyridin-2-yl)-N-(1-(2-methylpyrimidin-5-yl)ethyl)benzamide (50.00 mg, 0.1216 mmol), 2-cyanophenylboronic acid (35.72 mg, 0.2431 mmol), cesium carbonate (198.0 mg, 0.6078 mmol) and N,N-dimethylformamide (0.4 mL, 6 mmol). The reaction mixture was microwaved for 20 mins at 150 degrees. The reaction was purified directly by reversed phase HPLC (acetonitrile:water gradient) at pH 10. The combined pure fractions were reduced in vacuo to afford the title compound as white solid.

In 1H NMR (DMSO-d6): 9.13 (d, J = 7.43 Hz, 1H), 8.74 (s, 2H), 8.64 (t, J = 1.75 Hz, 1H), 8.56 (d, J = 2.18 Hz, 1H), 8.42 (t, J = 1.44 Hz, 1H), 8.09 (t, J = 1.60 Hz, 1H), 8.02 (t, J = 8.17 Hz, 2H), 7.86 (t, J = 7.64 Hz, 1H), 7.80-7.76 (m, 2H), 7.65 (t, J = 7.81 Hz, 1H), 5.26-5.19 (m, 1H), 2.59 (s, 3H), 2.36 (s, 3H), 1.56 (d, J = 7.02 Hz, 3H).

In a 5 mL microwave vial, 5-Bromo-4'-methyl-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)amide (30.00 mg, 0.07589 mmol), 2-(trifluoromethyl)phenylboronic acid (28.83 mg, 0.1518 mmol), cesium carbonate (123.6 mg, 0.3795 mmol), tetra-n-butylammonium iodide (28.03 mg, 0.07589 mmol), and PO4 (3.808 mg, 0.007589 mmol) were dissolved in Water (0.06 mL, 3 mmol) and N,N-dimethylformamide (0.3 mL, 4 mmol). The reaction mixture was microwaved for 20 mins at 150 degrees. The reaction was purified directly by reversed phase chromatography.

In 2'-Cyano-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid [(R)-1-(2-methyl-pyrimidin-5-yl)-ethyl]-amide

In LC-MS: 414.5 [M+H]+; 1H NMR (400 MHz, DMSO-d6): 9.19 (t, J = 6.0 Hz, 1H), 8.43 (d, J = 2.4 Hz, 8.03 (t, J = 1.6 Hz, 7.72 (d, J = 1.6 Hz, 7.65-7.60 (m, 3H), 7.30 (d, J = 8.0 Hz, 7.21 (d, J = 7.6 Hz, 4.47 (d, J = 5.6 Hz, 3.69 (t, J = 5.6 Hz, 2.44 (s, 3H), 2.41 (t, J = 6.0 Hz, 2.36 (s, 3H), 1.94-1.80 (m, 4H).
Compound 38
4'-Methyl-N-(2-methylpyrimidin-5-yl)methyl)-5-(2-oxopiperidin-1-yl)biphenyl-3-carboxamide

[0853]

The residue was purified by preparative HPLC (100×20.2 mm, C18 column; 30-80% CH3CN-water[10 mM Et3NH]) to afford a white foam.

[0858] LC-MS: 429.1 [M+1]⁺; ¹H NMR (400 MHz, DMSO-d6): 8.99 (d, 1H, J=7.6 Hz), 8.72 (s, 2H), 8.01 (s, 1H, J=1.6 Hz), 7.72 (s, 1H, J=1.6 Hz), 7.70 (t, 1H, J=1.6 Hz), 7.65 (d, 2H, J=8.4 Hz), 7.31 (d, 2H, J=8.0 Hz), 5.20 (m, 1H), 3.69 (t, 2H, J=5.6 Hz), 2.59 (s, 3H), 2.42 (t, 2H, J=6.0 Hz), 2.36 (s, 3H), 1.95-1.80 (m, 4H), 1.55 (d, 3H, J=7.2 Hz).

Compound 40
(R)-4'-Methyl-N-(1-(6-methylpyrimidin-3-yl)ethyl)-5-(2-oxopiperidin-1-yl)biphenyl-3-carboxamide

[0859]

Compound 39
(R)-4'-Methyl-N-(1-(2-methylpyrimidin-5-yl)ethyl)-5-(2-oxopiperidin-1-yl)biphenyl-3-carboxamide

[0856]

The residue was stirred at room temperature overnight and then concentrated.

[0860] To a mixture of 4'-methyl-5-(2-oxopiperidin-1-yl)biphenyl-3-carboxylic acid (45 mg, 0.14 mmol), N-(3-dimethylaminopropyl)-N'-ethylenediisocarbodiimide hydrochloride (56 mg, 0.29 mmol), 1-hydroxybenzotriazole hydrate (22 mg, 0.14 mmol), and CH3Cl2 (3 mL) were added R)-1-(6-methylpyrimidin-3-yl)ethanamine (27 mg, 0.22 mmol) and N,N-disopropylethylamine (51 µL, 0.29 mmol). The mixture was stirred at room temperature overnight and then concentrated. The residue was purified by preparative HPLC (100×20.2 mm, C18 column; 30-80% CH3CN-water[10 mM Et3NH]) to afford a white foam.

[0861] LC-MS: 428.0 [M+1]⁺; ¹H NMR (400 MHz, DMSO-d6): 8.95 (d, 1H, J=8.0 Hz), 8.48 (d, 1H, J=2.4 Hz), 8.02 (t, 1H, J=1.6 Hz), 7.71 (d, 2H, J=1.2 Hz), 7.68 (dd, 1H, J=8.0, 2.4 Hz), 7.63 (d, 2H, J=8.4 Hz), 7.31 (d, 2H, J=7.6 Hz), 7.21 (d, 1H, J=8.0 Hz), 5.20 (m, 1H), 3.69 (t, 2H, J=5.6 Hz), 2.43 (s, 3H), 2.42 (t, 2H, J=6.4 Hz), 2.36 (s, 3H), 1.95-1.80 (m, 4H), 1.52 (d, 3H, J=7.2 Hz).

Compound 45
2'-Methoxymethyl-5-(5-methylpyridin-2-yl)biphenyl-3-carboxylic acid [(R)-1-(2-methylpyrimidin-5-yl)ethyl]amide

[0862]
[0863] In a 5 mL microwave vial, (R)-3-bromo-5-(5-methylpyridin-2-yl)-N-(1-(2-methylpyrimidin-5-yl)ethyl)benzamide (50.00 mg, 0.1216 mmol), 2-(methoxyimino)phenylboronic acid (40.36 mg, 0.2431 mmol), cesium carbonate (198.0 mg, 0.6078 mmol), tetra-n-butylammonium iodide (44.90 mg, 0.1216 mmol), and Pd(PPh3)4 (6.100 mg, 0.01216 mmol) were dissolved in Water (0.09 mL, 5 mmol) and N,N-dimethylformamide (0.4 mL, 6 mmol). The reaction mixture was microwaved for 20 mins at 150 degrees. The reaction was purified directly by reversed phase HPLC (acetonitrile:water gradient) at pH10. The combined pure fractions were reduced in vacuo to afford the title compound as white solid.

[0864] 1H NMR (DMSO-d6): 9.06 (d, J=7.66 Hz, 1H), 8.73 (s, 2H), 8.56-8.54 (m, 2H), 8.22 (t, J=1.49 Hz, 1H), 8.01 (d, J=8.06 Hz, 1H), 7.93 (t, J=1.49 Hz, 1H), 7.74 (td, J=8.36 & 2.39 Hz, 1H), 7.55-7.52 (m, 1H), 7.45-7.40 (m, 3H), 5.22 (qt, J=8.24 Hz, 1H), 4.29 (s, 2H), 3.22 (s, 3H), 2.59 (s, 3H), 2.35 (s, 3H), 1.55 (d, J=7.29 Hz, 3H).

Compound 46
3-(4-Cyano-pyridin-3-yl)-5-(5-methyl-pyridin-2-yl)-N-(6-methyl-pyridin-3-ylmethyl)-benzamide

[0865] Intos a 5 mL microwave vial was combined 3-bromo-5-(5-methyl-pyridin-2-yl)-N-((6-methyl-pyridin-3-yl)methyl)benzamide (25.00 mg, 0.06309 mmol) 3-(5,5-Dimethyl-[1,3,2]dioxaborinanyl-2-yl)-isonicotinonitrile (20.4 mg, 0.0946 mmol), potassium carbonate (26.2 mg, 0.189 mmol) PO et (3.16 mg, 0.06631 mmol) and isopropanol alcohol (0.483 mL, 6.31 mmol) The mixture was heated via microwave irradiation for 10 min at 150 degrees. The mixture was purified directly by reversed phase HPLC (acetonitrile:water gradient) at pH 10. The combined pure fractions were reduced in vacuo to afford the title compound.

Compound 48
4'-Methyl-5-(2-oxo-pyridin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide

[0867] To a solution of 4'-methyl-5-(2-oxopyridin-1-yl) biphenyl-3-carboxylic acid (5.00 mg, 0.0001747 mol) in N,N-dimethylformamide (1 mL, 0.01 mol) was added (R)-1-(2-methylpyrimidin-5-yl)ethanamine (50.00 mg, 0.000364 mol), N,N,N',N'-tetramethyl-O-(7-azabenztiazol-1-yl)uronium hexafluorophosphate (150.0 mg, 0.0003945 mol) and N,N-disopropylethylamine (150.0 ul, 0.000882 mg). The reaction mixture was stirred for 16 hours at 25° C. Checked LC/MS, the reaction was completed. The DMF reaction solution was directly applied to prep. HPLC. The final product was yield a light yellow foam.

[0868] 1H NMR (400 MHz, DMSO-d6): 9.18 (d, J=1.0 Hz, 8.44 (d, 1H, J=2.0 Hz), 8.15 (t, 1H, J=1.7 Hz), 8.00 (d, 1H, J=1.6 Hz), 7.90 (s, 1H), 7.65-7.60 (m, 3H), 7.31 (d, 2H, J=8.0 Hz), 7.22 (d, 1H, J=8.0 Hz), 4.48 (d, 2HI, J=5.8 Hz), 3.94 (t, 2H, J=6.9 Hz), 2.53 (m, 2H), 2.44 (s, 3H), 2.36 (s, 3H), 2.09 (m, 2H).

Compound 49
4'-Methyl-5-(2-oxo-pyridin-1-yl)-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide
A) Methyl 3-bromo-5-iodobenzoate

A round bottom flask was charged with 3-bromo-5-iodobenzoic acid (8.00 g, 24.5 mmol) and methanol (50 mL). Thiouyl chloride (5.36 mL, 73.4 mmol) was slowly added and the reaction mixture was heated at 65°C for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and washed with sat. NaHCO₃. Removal of the solvent under reduced pressure gave the product as a white solid.

B) Methyl 3-bromo-5-(5-methylpyridin-2-yl)benzoate

A microwave vial was charged with methyl 3-bromo-5-iodobenzoate (2.00 g, 5.87 mmol), 5-methyl-2-(tributylstannyl)pyridine (2.24 g, 5.87 mmol), tetrais(triphenylphosphine)palladium(0) (340 mg, 0.30 mmol) and 1,4-dioxane (30 mL). The reaction mixture was subjected to microwave irradiation at 120°C for 1 hour. After cooling, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to afford the product as a white solid. 

C) 3-Bromo-5-(5-methylpyridin-2-yl)benzoic acid

A round bottom flask was charged with methyl 3-bromo-5-(5-methylpyridin-2-yl)benzoate (500 mg, 0.98 mmol), tetrahydrofuran (15 mL) and lithium hydroxide (70 mg, 2.94 mmol). The reaction mixture was stirred at 50°C overnight, and then filtered through sodium sulfate. The filtrate was concentrated under reduced pressure to afford the product as a white solid.

D) (R)-3-Bromo-5-(5-methylpyridin-2-yl)-N-(1-(2-methylpyrimidin-5-yl)ethyl)benzamide

A round bottom flask was charged with 3-bromo-5-(5-methylpyridin-2-yl)benzoic acid (250 mg, 0.86 mmol), (R)-1-(2-methylpyrimidin-5-yl)ethanamine (141 mg, 1.03 mmol), N,N,N,N'-tetramethyl-O-(7-azabenotriazol-1-yl)urium hexahlorophosphate (651 mg, 1.71 mmol), N,N-disopropylethylamine (0.60 mL, 3.42 mmol), and N,N-dimethylformamide (6 mL). The reaction mixture was stirred at room temperature overnight, and then washed with brine and extracted with ethyl acetate. The organic layer was dried and concentrated under reduced pressure to afford a light brown oil.

E) (R)-3-(5-Methylpyridin-2-yl)-N-(1-(2-methylpyrimidin-5-yl)ethyl)-5-(2-oxopyrrolidin-1-yl)benzamide

Into a 5 mL microwave vial was charged (R)-3-bromo-5-(5-methylpyridin-2-yl)-N-(1-(2-methylpyrimidin-5-yl)ethyl)benzamide (20 mg, 0.05 mmol), 2-pyrrolidinone (7 mg, 0.08 mmol) xantphos (3 mg, 0.005 mmol), tris(dibenzylideneacetone)dipalladium(0) (2 mg, 0.002 mmol), cesium carbonate (50 mg, 0.1 mmol), and 1,4-dioxane (0.8 mL). The mixture was subjected to microwave irradiation at 130°C for
10 min. The cooled mixture was diluted with 3 mL of methanol and purified by reverse phase HPLC to afford the title compound.

**Compound 59**

(S)-5-(2-(Hydroxymethyl)pyrrolidin-1-yl)-4'-methyl-N-((6-methylpyridin-3-yl)methyl)biphenyl-3-carboxamide

![Chemical Structure](image)

**[0879]**

**A)** 3-Bromo-5-iodo-N-((6-methylpyridin-3-yl)methyl)benzamide

To a stirred mixture of 3-bromo-5-iodo-benzoic acid (1.4 g, 4.4 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.7 g, 8.8 mmol), 1-hydroxybenzotriazole hydrate (0.20 g, 1.3 mmol), and CH$_3$Cl (50 mL) were added (6-methylpyridin-3-yl)ethanamine (0.65 g, 5.3 mmol) and N,N-diisopropylethylamine (1.5 mL, 8.8 mmol). The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo. The precipitated solid was washed with water and ethyl ether and dried to afford the product as a white solid. LC-MS: 432.7 [M+H]+.

**[0880]**

**B)** (S)-3-Bromo-5-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-((6-methylpyridin-3-yl)methyl)benzamide

A mixture of 3-bromo-5-iodo-N-((6-methylpyridin-3-yl)methyl)benzamide (250 mg, 0.58 mmol), L-proline (13 mg, 0.12 mmol), and copper(I) iodide (11 mg, 0.058 mmol) in dimethyl sulfoxide (2 mL) under nitrogen was stirred at 90°C for 10 h. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by silica gel column (EtOAc/hexane: 0-100%) to afford a white foam.

**[0881]**

**C)** (S)-5-(2-(Hydroxymethyl)pyrrolidin-1-yl)-4'-methyl-N-((6-methylpyridin-3-yl)methyl)biphenyl-3-carboxamide

To a mixture of (S)-3-bromo-5-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-((6-methylpyridin-3-yl)methyl)benzamide (65 mg, 0.16 mmol), p-tolylboronic acid (24 mg, 0.18 mmol), toluene (4 mL), cesium carbonate (57 mg, 0.18 mmol), and water (0.2 mL) under argon was added tetrakis (triphenylphosphine)palladium(0) (9.2 mg, 0.0080 mmol). The reaction mixture was heated under reflux for 5 h. After cooling, the mixture was filtered through Celite and the filter cake was washed with EtOAc. The filtrate was washed with brine, dried (Na$_2$SO$_4$), and concentrated. The residue was purified by preparative HPLC (100×21.2 mm C18 column, 30-80% CH$_3$CN/water(10 mM Et$_3$N)) to afford a white foam.

**[0882]**

**[0883]**

To a mixture of (S)-3-bromo-5-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-((6-methylpyridin-3-yl)methyl)benzamide (88 mg, 0.87 mmol), potassium carbonate (160 mg, 1.2 mmol), L-proline (13 mg, 0.12 mmol), and copper(I) iodide (11 mg, 0.058 mmol) in dimethyl sulfoxide (2 mL) under nitrogen was stirred at 90°C for 10 h. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by silica gel column (EtOAc/hexane: 0-100%) to afford a white foam.

**[0884]**

**[0885]**

5-((R)-2-Hydroxymethyl-pyrrolidin-1-yl)-4'-methyl-biphenyl-3-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide

**[0886]**

To a mixture of (R)-3-bromo-5-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-((6-methylpyridin-3-yl)methyl)benzamide (45 mg, 0.11 mmol), p-tolylboronic acid (16 mg, 0.12
(4.0E1 mg, 0.12 mmol), and Water (0.2 mL, 8 mmol) under argon was added to the mixture. The mixture was stirred for 5 h. After cooling, the mixture was filtered through Celite and the filter cake was washed with EtOAc. The filtrate was washed with brine, dried (Na2SO4), and concentrated. The residue was purified by preparative HPLC (100×21.2 mm C18 column, 30-80% CH3CN/water/10 mM Et2N) to afford a white foam. LC-MS: 2.09 min, 416.5 [M+1]+; HPLC: 9.12 min.

**Compound 63**

3-((R)-2-Hydroxymethyl-pyrrolidin-1-yl)-5-(5-methyl-pyridin-2-yl)-N-(6-methyl-pyridin-3-ylmethyl)-benzamide

**[0887]**

A mixture of (R)-3-bromo-5-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(5-methyl-pyridin-3-ylmethyl)benzamide (55 mg, 0.14 mmol), 5-methyl-2-(tributylstanny1)pyridine (65 mg, 0.16 mmol), Tetrakis(triphenylphosphine) palladium(0) (7.8 mg, 0.0068 mmol) and Toluene (1.5 mL, 14 mmol) under argon was subjected to microwave irradiation at 160°C for 1 hour. The mixture was cooled to room temperature. Solvent was removed in vacuo and the residue was rinsed with hexane and then dissolved in MeOH and filtered. The filtrate was purified by preparative HPLC (100×21.2 mm C18 column, 20-70% CH3CN/water/10 mM Et2N) to afford a white foam. LC-MS: 1.64 min, 417.3 [M+1]+; HPLC: 6.76 min.

**[0889]** A mixture of (R)-3-bromo-5-(2-(hydroxymethyl)pyrrolidin-1-yl)-N-(5-methyl-pyridin-3-ylmethyl)benzamide (30.0 mg, 0.09222 mmol), (2S)-2-Aminopropan-1-ol (8.3119 mg, 0.11066 mmol), N,N,N',N'-tetramethyl-1-(7-azabenzotriadizol-1'-yl)uronium hexafluorophosphate (0.087662 g, 0.23055 mmol), N,N-diisopropylethylamine (0.064252 mL, 0.36888 mmol), N,N-dimethylformamide (0.157 mL, 2.03 mmol) and the reaction stirred over night at room temperature. The solvent was removed under reduced pressure and the residue purified by preparative HPLC to give compound as white solid.

**[0893]** A round bottom flask was charged with 2',3'-difluoro-5-(5-methyl-pyridin-2-yl)benzyl-1-carboxylic acid (50.0 mg, 0.09222 mmol), (2S)-2-Aminopropan-1-ol (8.3119 mg, 0.11066 mmol), N,N,N',N'-tetramethyl-1-(7-azabenzo triadizol-1'-yl)uronium hexafluorophosphate (0.087662 g, 0.23055 mmol), N,N-diisopropylethylamine (0.064252 mL, 0.36888 mmol), N,N-dimethylformamide (0.157 mL, 2.03 mmol) and the reaction stirred over night at room temperature. The solvent was removed under reduced pressure and the residue purified by preparative HPLC to give compound as white solid.

**[0894]** 1H NMR (DMSO-d6): 8.58 (t, J=1.670 Hz, 1H), 8.56 (d, J=1.87 Hz, 1H), 8.38-8.36 (m, 2H), 8.06 (d, J=1.47 Hz, 1H), 8.03 (d, J=8.25 Hz, 1H), 7.76 (dd, J=8.27 Hz & 2.23 Hz, 1H), 7.55-7.48 (m, 2H), 7.40-7.34 (m, 1H), 7.48 (t, J=6.75 Hz, 1H), 4.12-4.02 (m, 1H), 3.52-3.47 (m, 1H), 3.41-3.35 (m, 1H), 2.36 (s, 3H), 2.18 (s, 3H), 1.16 (d, J=6.67 Hz, 3H).
Compound 71

2'-Cyanoo-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid ((S)-2-hydroxy-1-methyl-ethyl)-amide

[0895]

H3C
O

CH3
N

H3C
O

[0896] A round bottom flask was charged with 2'-cyanoo-5'-methyl-5-(5-methyl-pyridin-2-yl)-biphenyl-3-carboxylic acid (30.0 mg, 0.0914 mmol), (2S)-2-Aminopropan-1-ol (13.724 mg, 0.18272 mmol), N,N,N',N'-tetramethyl-O-(7-azabenzo-triazol-1-yl)uronium hexafluorophosphate (0.14474 g, 0.38068 mmol), N,N-diisopropylethylamine (0.10609 mL, 0.60908 mmol), N,N-dimethylformamide (0.260 mL, 3.35 mmol) and the reaction stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue purified by prep HPLC to get the compound as a white solid.

[0897] 1H NMR (DMSO-d6): 8.61 (d, J=1.67 Hz, 1H), 8.56 (d, J=2.57 Hz, 1H), 8.38-8.36 (m, 2H), 8.05-8.02 (m, 2H) 8.16 (d, J=1.40 Hz, 1H), 8.03 (d, J=7.69 Hz, 1H), 7.86 (t, J=1.62 Hz, 1H), 7.81 (d, J=7.96 Hz, 1H), 7.76 (dd, J=8.44 Hz, 2.17 Hz, 1H), 7.71 (d, J=7.72 Hz, 1H), 4.76 (t, J=6.75 Hz, 1H), 4.12-4.02 (m, 1H), 3.52-3.47 (m, 1H), 3.41-3.35 (m, 1H), 2.36 (s, 3H), 2.18 (s, 3H), 1.16 (d, J=6.75 Hz, 3H).

Compound 80

(R)-2'-difluoro-5-(5-methyl-pyridin-2-yl)-N-(1-morpholinopropan-2-yl)-5'-trifluoromethyl)biphenyl-3-carboxamide

[0901]
A round bottom flask was charged with 2'-cyano-5-(5-methylpyridin-2-yl)-5'-(trifluoromethyl)biphenyl-3-carboxylic acid (30 mg, 0.078 mmol), (R)-1-morpholinopropan-2-amine hydrochloride (33 mg, 0.18 mmol), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (145 mg, 0.38 mmol), N,N-diisopropylethylamine (106 μL, 0.61 mmol), N,N-dimethylformamide (0.5 mL) and the reaction was stirred overnight at room temperature. The mixture was purified by HPLC to afford the title compound as a light orange solid.

LC-MS: 509.2 [M+1]⁺; ¹H NMR (400 MHz, DMSO-d₆): 8.65 (d, J=1.62 Hz, 1H), 8.57 (d, J=2.56 Hz, 1H), 8.46 (t, J=2.13 Hz, 1H), 8.40 (d, J=8.10 Hz, 1H), 8.28 (d, J=8.10 Hz, 1H), 8.14 (s, 1H), 8.10 (t, J=1.67 Hz, 1H), 8.06-8.02 (m, 1H), 7.78 (dd, J=8.07 & 2.31 Hz, 1H), 4.32-4.24 (m, 1H), 3.55 (t, J=4.37 Hz, 4H), 3.18-3.13 (m, 1H), 2.43-2.42 (m, 4H), 2.37 (s, 3H), 2.35-2.30 (m, 1H), 1.19 (d, J=6.44 Hz, 3H).

Compound 83
2'-Fluoro-5-(5-methyl-2-yl)-6'-(trifluoromethyl)-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide

A. Methyl 2'-fluoro-5-(5-methyl-pyridin-2-yl)-6'-(trifluoromethyl)biphenyl-3-carboxylate

In a 5 mL microwave vial, methyl 3-(5-methyl-pyridin-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (300 mg, 0.8493 mmol), 2-bromo-1-fluoro-5-(trifluoromethyl)benzene (412.8 mg, 1.699 mmol), cesium carbonate (1384 mg, 4.247 mmol), tetra-n-butylammonium iodide (313.7 mg, 0.8493 mmol), and Pd(PPh₃)₄ (42.61 mg, 0.08493 mmol) were dissolved in Water (0.6 mL, 40 mmol) and N,N-dimethylformamide (3 mL, 40 mmol). The reaction mixture was microwaved for 10 mins at 150 degrees. The reaction mixture was extracted with ethyl acetate and washed repeatedly with brine. The solvent was removed under reduced pressure (yellow oil) and used in the next reaction without further purification.

B. 2'-Fluoro-5-(5-methylpyridin-2-yl)-6'-(trifluoromethyl)biphenyl-3-carboxylic acid

A round bottom flask was charged with 2'-cyano-5-(5-methyl-pyridin-2-yl)-6'-(trifluoromethyl)biphenyl-3-carboxylic acid (200.00 mg, 0.51368 mmol), Tetrahydrofuran (7.8 mL, 97 mmol) and Lithium hydroxide (36.906 mg, 1.5410 mmol) and the reaction stirred at room temperature overnight and at 50°C for two days. The reaction mixture was filtered over Sodium sulfate and the solvent removed under reduced pressure to get the acid as brown solid.

C. 2'-Fluoro-5-(5-methyl-pyridin-2-yl)-6'-(trifluoromethyl)-biphenyl-3-carboxylic acid (R)-1-methyl-2-morpholin-4-yl-ethyl-amide

A round bottom flask was charged with 2'-fluoro-5-(5-methyl-pyridin-2-yl)-6'-(trifluoromethyl)biphenyl-3-carboxylic acid (100.00 mg, 0.26644 mmol), N,N,N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.49150 g, 1.2926 mmol), N,N-diisopropylethylamine (0.56025 mL, 2.0682 mmol), N,N-dimethylformamide (0.882 mL, 11.4 mmol) and the reaction stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue purified by prep HPLC to get the compound as white solid.

1H NMR (DMSO-d₆): 8.60 (bs, 1H), 8.54 (d, J=2.35 Hz, 1H), 8.38 (d, J=8.63 Hz, 1H), 8.16 (bs, 1H), 7.98 (d, J=7.97 Hz, 1H), 7.82 (bs, 1H), 7.77-7.72 (m, 3H), 4.30-4.22 (m, 1H), 3.54 (m, 3H), 2.40 (m, 3H), 2.35 (s, 3H), 1.17 (d, J=6.20 Hz, 3H).

Compound 87
(R)-2'-Cyano-5-(4-cyanopyridin-3-yl)-4'-methyl-N-(1-morpholinopropan-2-yl)biphenyl-3-carboxamide

A round bottom flask was charged with 2'-cyano-5-(5-methyl-pyridin-2-yl)-6'-trifluoromethyl-biphenyl-3-carboxylic acid (20 mg, 0.059 mmol), N,N,N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (49 mg, 0.13 mmol), N,N-diisopropylethylamine (360 μL, 2.1 mmol), N,N-dimethylformamide (0.555 mL) and the
reaction was stirred overnight at room temperature. The mixture was purified by HPLC to get the title compound as a light yellow solid.

**[0911]** LC-MS: 466.1 [M+1]+; 1H NMR (400 MHz, DMSO-d6) δ 9.06 (d, J=0.7 Hz, 1H), 8.90 (d, J=5.0 Hz, 1H), 8.39 (d, J=8.2 Hz, 1H), 8.20 (d, J=10.7, 1.6 Hz, 2H), 8.08-8.01 (m, 2H), 7.86 (s, 1H), 7.73-7.65 (m, 2H), 4.27 (dt, J=14.1, 6.9 Hz, 1H), 3.54 (t, J=4.6 Hz, 4H), 2.47-2.36 (m, 8H), 2.31 (dd, J=12.5, 6.6 Hz, 1H), 1.18 (d, J=6.6 Hz, 3H).

**Compound 88**

2-Cyano-2'-hydroxymethyl-4-methyl-[1,1',3,1']terphenyl-5'-carboxylic acid (S)-2-hydroxy-1-methyl-ethyl-amide

A reaction vial was charged with 2-Cyano-2'-hydroxymethyl-4-methyl-[1,1',3,1']terphenyl-5'-carboxylic acid (50.00 mg, 0.1456 mmol), (2S)-2-aminopropan-1-ol (13.12 mg, 0.1747 mmol), N,N,N',N'-tetramethyl-O-(7-aza-benzotriazol-1-yl)uronium hexafluorophosphate (110.7 mg, 0.2912 mmol), N,N-disopropylethylamine (0.06341 ml, 0.3640 mmol) and N,N-dimethylformamide (5.0 ml, 64 mmol) and the reaction stirred at room temperature over night. The reaction mixture was then purified by prep HPLC to get the compound as white solid.

**[0914]** 1H NMR (DMSO-d6): 8.27 (d, J=7.44 Hz, 1H), 8.01 (t, J=1.64 Hz, 1H), 7.90 (t, J=1.64 Hz, 1H), 7.81 (s, 1H), 7.72 (t, J=1.64 Hz, 1H), 7.65-7.59 (m, 3H), 7.46-7.32 (m, 3H), 5.17 (t, J=5.65 Hz, 1H), 4.74 (t, J=5.65 Hz, 1H), 4.45 (d, J=5.12 Hz, 1H), 4.05 (q, J=7.32 Hz, 1H), 3.50-3.43 (m, 1H), 3.10-3.03 (m, 1H), 2.41 (s, 3H), 1.13 (d, J=6.56 Hz, 3H).

**[0915]** The syntheses of representative compounds of this invention can be carried out in accordance with the methods set forth above and using the appropriate reagents, starting materials, and purification methods known to those skilled in the art.

**Assays**

**[0916]** Compounds provided herein can be evaluated using cell-based assays, such as calcium influx or electrophysiological assays, using biochemical assays, such as binding assays to P2X and P2Y receptors, or can be evaluated in animal models of pain or urinary function. Examples of assays are described below.

**[0917]** The purinergic receptors P2X and P2Y are expressed in a variety of tissues including various sensory and sympathetic ganglia, such as the dorsal root (DRG), nodose (ND), trigeminal (TG), and superior cervical ganglia (SCG) and also in smooth muscle cells (Burnstock, Trends Pharmacol. Sci. 27:166-76, 2006). In several regions, P2X2, and P2X3 receptors are coexpressed and functional studies have demonstrated the presence of heteromeric P2X2/3 receptors whose properties differ from those of either homomeric receptor. In addition, chimeric P2X2/3 receptors, containing the N-terminal cytoplasmic domain of P2X2 fused to the first transmembrane domain of P2X3, have been described; these chimeric channels retain the pharmacological profile of homomeric P2X3 receptors, while gaining the non-desensitizing phenotype of the homomeric P2X2 receptor (Neelands et al., Br. J. Pharmacol. 140:202-10, 2003). The non-desensitizing behavior of the chimeric receptor is especially useful for screening.

**[0918]** Members of the P2X family are ligand-gated non-selective cation channels whose activity can be characterized by using electrophysiological methods, or by measuring calcium ion influx using calcium-sensitive fluorescent dyes. Applications of agonists such as ATP, or an ATP analog such as α,β-Methylxenadenosine 5′-triphosphate (αβMeATP, Sigma-Aldrich), causes channel opening, resulting in current flow and calcium influx (Bianchi et al., Eur. J. Pharmacol. 376:127-38, 1999).

**[0919]** The compounds provided herein can be tested for antagonist activity at P2X2, and P2X3 receptors by measuring their ability to affect channel opening by ATP, αβMeATP, or other agonists. Functional tests of receptor activity include but are not limited to: (i) calcium ion influx measured by fluorescence of a calcium-sensitive dye and; (ii) ion flux resulting from channel opening measured by electrophysiological methods. These methods can be used to evaluate channel function when the relevant receptor is heterologously expressed in mammalian or amphibian cells. These methods can also be used to evaluate compounds provided herein in rodent primary neurons and other mammalian primary cells and cell lines that normally express the receptor of interest.

**[0920]** Compounds can further be evaluated for their ability to bind P2X3 and P2X2/3 receptors using biochemical approaches.

**[0921]** Compounds can also be evaluated for their ability to modify sensory and autonomic nervous system signaling where the receptors are known to have a role (e.g., urinary bladder afferent signaling, sensory nerve pain transmission). Finally, compounds provided herein can be tested in vivo in relevant animal models known to one skilled in the art, such as, for example, models of neuropathic, inflammatory, or visceral pain, or models of urinary incontinence.

**[0922]** The following biological examples are offered to illustrate the compounds, pharmaceutical compositions and methods provided herein and are not to be construed in any way as limiting the scope thereof.

**Calcium Uptake Assay**

**[0923]** Human P2X3 (Accession no. NM_000255), P2X2 (Accession no. NM_170682) and Rat P2X3 (Accession no. NM_031075) and P2X2 (Accession no. NM_053656) are cloned into a mammalian expression vector (e.g., pcDNA5/TO or pcDNA3 Invitrogen). The human P2X2/3 chimera clone is created as described by Neelands et al, and then cloned into an expression vector as above. Receptors are expressed in cells (e.g., HEK293 or 1321N1 (obtained from the ECACC)) via transient transfection using standard lipid
mediated transfection, or by creation of stable transfectants for each receptor. For expression of the P2X<sub>2,3</sub> heteromeric receptor, the P2X<sub>3</sub> expression vector is stably transfected into a cell line already stably expressing P2X<sub>2</sub>. P2X<sub>2,3</sub> heteromer function is isolated using pharmacological methods. Cell lines are maintained in DMEM plus 5% Glutamax, the appropriate level of selective antibiotic, and 10% heat inactivated FBS.

P2X Antagonist Assay:

[0924] Functional activity of compounds at the P2X receptor is determined by measuring their ability to inhibit agonist-induced calcium influx. Compounds are tested for antagonist activity against the P2X<sub>2,3</sub> chimer, the P2X<sub>3</sub> homomer, or the P2X<sub>2,3</sub> heteromer. At the start of each screening day, the agonist IC<sub>50</sub> is determined. Compound % inhibition or IC<sub>50</sub>s are subsequently determined using a pre-determined agonist concentration (IC<sub>50-90</sub> depending on cell line) as a stimulus. The agonists used are cdpMeATP, ATP, or other ATP analogs. Compounds may be tested at concentrations ranging from 1 μM to 10 μM.

[0925] To test for antagonist activity, cells expressing the appropriate receptor are seeded onto 96 or 384 well plates 18-24 hours prior to assay. On the day of the assay, cells are loaded with calcium-sensitive fluorescent dye (e.g., Fura-2 no wash reagent Invitrogen cat# F36206, or the BD<sup>TM</sup> PBX Calcium Assay Kit-BD cat# 640175) in Hank’s Buffered Salt Solution (HBSS) with up to 10 mM supplemental CaCl<sub>2</sub>. Plates are incubated at 37°C and then equilibrated at room temperature. Antagonism of agonist-induced calcium influx is measured using a fluorescent imaging plate reader (e.g., FLIPE<sup>Z</sup>TRA, Molecular Devices, Sunnyvale, Calif.). The assay comprises two stages: a pre-treatment phase followed by a treatment phase. Compounds may be tested as follows: For the pre-treatment phase, 50 μL of 3x concentration of test compound in HBSS is added to cells containing 100 μL of dye loading media to achieve a final concentration of 1x test compound. For the treatment phase, at a set interval after pre-treatment (1-30 minutes), 50 μL of 1x test compound plus 4x agonist solution is added, resulting in a final concentration of 1x compound and 1x agonist. Fluorescence is measured at 0.1-3 second intervals—with an excitation wavelength of 494 nM and an emission wavelength of 515 nM. Responses are measured as (peak fluorescence after agonist addition) minus (baseline fluorescence prior to treatment). Percent inhibition is calculated as follows:

\[
\text{Percentage inhibition} = \frac{(\text{Compound Response} - \text{Control Response})}{(\text{Agonist Response} - \text{Control Response})} \times 100
\]

IC<sub>50</sub> values are determined by analyzing dose response data in a 4 parameter logistic fit using GraphPad Prizm.

Electrophysiological Experiments

Whole Cell Patch Clamp:
[0926] Whole cell recordings are made using the Multiclamp700A patch-clamp amplifier and Clampex acquisition program (Molecular Devices Corporation). Whole-cell recordings are obtained from 1321N1 or HEK cells stably or transiently transfected with P2X<sub>3</sub> and/or P2X<sub>2</sub> expression vectors. Solutions are either applied for periods of 1 to 3s by a gravity flow, 8-valve delivery system, or for periods of milliseconds using the quick-change Dynaflow perfusion system (Celsisetron Inc.). The internal pipette solution may include 140 mM CsCl, 10 mM EGTA, and 5 mM Hepes at pH 7.2; normal external solution is 140 mM NaCl, 5 mM KCl, 1 mM CaCl<sub>2</sub>, 2 mM MgCl<sub>2</sub>, 25 mM Hepes, and 10 mM glucose. Concentration-response curves are obtained by recording currents in response to brief applications of agonist at 1-3 min intervals where regular external solution is perfused during the intervals. To obtain inhibition curves, antagonists are pre-applied to the cells for a defined time period before a short application of the agonist+antagonist. The periods of antagonist pre-application and agonist+antagonist applications are constant for the entire test concentration series. Agonist evoked currents are measured in cells that are voltage clamped at -60 or -80 millivolts. IC<sub>50</sub> values are determined by analyzing dose response data in a 4 parameter logistic fit using GraphPad Prizm or Origin.

Automated Two-Electrode Voltage Clamp Recording:
[0927] *Xenopus* oocytes (Nalco) are isolated by enzymatic dissociation using collagenase (Worthington, 2 mg/ml). Oocytes are then individually injected with P2X<sub>3</sub>, P2X<sub>2</sub>, or a combination of P2X<sub>3</sub> and P2X<sub>2</sub> mRNA. Each oocyte receives ~64 nL of RNA solution in water at a concentration of ~0.01 μg/μL. Injected oocytes are stored in standard oocyte incubation solution, ND96, containing (in mM) 96 NaCl, 2 KCl, 1 MgCl<sub>2</sub>, 1.5 CaCl<sub>2</sub> and 50 μg/ml Gentamicin at 16°C. Agonist-induced current caused by P2X channel opening is observed in oocytes 1-3 days after injection. For automated recordings, 8 oocytes are placed in the recording chambers. Each oocyte is impaled by 2 glass electrodes having resistances of 0.5 to 1 MOhm when filled with a 3 M KCl solution. Electrode advancement and oocyte impalement are under software control (OPUSXPRESS 1.1, Molecular devices Corporation). The solutions are prepared in 96 well plates and robotically pipetted into the oocyte recording chambers by an 8 channel pipettor. Inhibition by antagonists is determined by calculating % current remaining when oocytes are stimulated with agonist in the presence of test compound compared to the peak current in the presence of agonist alone. The sequence of solution application to the oocyte is as follows: a specific concentration (e.g., IC<sub>50</sub>, IC<sub>90</sub>, or IC<sub>95</sub>) of the agonist is added first to elicit the maximal response. After the pulse, oocytes are washed for several minutes with ND96. The test compound is then added at a particular concentration, followed by the compound at the same concentration along with the agonist. Concentrations for the compounds may range from 0.3 to 10,000 mM. IC<sub>50</sub> values are determined by analyzing dose response data using a 4 parameter logistic fit using GraphPad Prizm or Origin software.

Manual Two-Electrode Voltage Clamp:
[0928] Individual oocytes are impaled manually with 2 electrodes and agonist evoked current are measured using an Oocyte clamp amplifier (Warner Instruments Corp.) and Clampex (Molecular Devices Corporation) acquisition software. Solutions are delivered using gravity flow and applied as above. The agonist induced current is measured in the absence and presence of antagonist. Antagonists are tested in a concentration series to obtain an inhibition curve as described above.

Selectivity Screens:
[0929] Compounds that inhibit P2X<sub>3</sub> and/or P2X<sub>2,3</sub> activation will be tested for activity against other P2X receptors to
determine their selectivity for specific P2X family members. The list of receptors to be assayed includes, but is not restricted to P2X1, P2X2, P2X4, P2X5, P2X6, and P2X7. The types of assay used for selectivity determination may include: 1) Agonist-induced Calcium influx in cells heterologously expressing the relevant receptor, 2) Electrophysiological determination of receptor inhibition in either mammalian cells or Xenopus oocytes heterologously expressing the receptor of interest. Methods and data analysis are similar to those described above for P2X4 and P2X2/3.

Radioligand Binding:

**[0930]** Radioligand experiments are done to determine the affinity of test compounds for P2X3 homeric and P2X2/3 heteromeric receptors. These studies also provide valuable insights into the mechanism of action of antagonism. The general methodologies used for radioligand binding experiments for P2X3 and P2X2/3 receptors are described by Jarvis et al., *J. Pharmacol. Exp. Ther.* 10:407-16, 2004.

**[0931]** Briefly, cell membranes are prepared from cells transiently or stably expressing P2X3 or P2X2/3 receptors. Cells are grown to confluence, washed, isolated, and stored as pellets at −80°C until use. Some studies may require the addition of APyrase or hexokinase (Sigma-Aldrich) during membrane preparation to minimize ATP-mediated receptor desensitization during membrane preparation. Membranes are prepared by resuspending the cell pellet in homogenization buffer, homogenizing, and centrifuging to obtain a membrane pellet. Total protein concentrations are determined using standard methods.

**[0932]** Displacement binding studies are conducted using procedures adapted from Jarvis et al. Under optimized conditions, ligand competition experiments are conducted using radioligand ([3H]A-317491, Abbott), or other high affinity radioligands and a range of different concentrations of test compounds in binding buffer. Ligand saturation studies are conducted using a range of concentrations of radioligand. All binding reactions are terminated by rapid filtration through a glass fiber filter. Membranes are washed, incubated in scintillant, and counted in a scintillation counter. IC_{50} values are determined using a four-parameter logistic Hill equation.

**Drug Metabolism and Pharmacokinetics**

**[0933]** Caco-2 permeability:

Caco-2 permeability is measured according to the method described in Yee, *Pharm. Res.* 14:763-6, 1997. Caco-2 cells are grown on filter supports (Falcon ITIS multiwell insert system) for 14 days. Culture medium is removed from both the apical and basolateral compartments and the monolayers are preincubated with pre-warmed 0.3 ml apical buffer and 1.0 ml basolateral buffer for 0.75 hour at 37°C in a shaker water bath at 50 cycles/min. The apical buffer consists of Hanks Balanced Salt Solution, 25 mM D-glucose monohydrate, 20 mM MES Biological Buffer, 1.25 mM CaCl2 and 0.5 in M MgCl2 (pH 6.5). The basolateral buffer consists of Hanks Balanced Salt Solution, 25 mM D-glucose monohydrate, 20 mM HEPES Biological Buffer, 1.25 mM CaCl2 and 0.5 mM MgCl2 (pH 7.4). At the end of the preincubation, the media is removed and test compound solution (10 μM) in buffer is added to the apical compartment. The inserts are moved to wells containing fresh basolateral buffer and incubated for 1 hr. Drug concentration in the buffer is measured by LC/MS analysis.

**[0934]** Flux rate (F, mass/time) is calculated from the slope of cumulative appearance of substrate on the receiver side and apparent permeability coefficient (P_{app}) is calculated from the following equation:

\[ P_{app} (\text{cm/sec}) = \frac{F}{(S \cdot D) / (A \cdot M \cdot D)} \]

where SA is surface area for transport (0.3 cm²), VD is the donor volume (0.3 ml), MD is the total amount of drug on the donor side at t=0. All data represent the mean of 2 inserts. Monolayer integrity is determined by Lucifer Yellow transport.

**Human Dofetilide Binding:**

**[0935]** Cell paste of HEK-293 cells expressing the HERG product can be suspended in 10-fold volume of 50 mM Tris buffer adjusted at pH 7.5 at 25°C with 2 M HCl containing 1 mM MgCl2, 10 mM KCl. The cells are homogenized using a Polytron homogenizer (at the maximum power for 20 seconds) and centrifuged at 48,000 g for 20 minutes at 4°C. The pellet is resuspended, homogenized, and centrifuged once more in the same manner. The resultant supernatant is discarded and the final pellet was resuspended (10-fold volume of 50 mM Tris buffer) and homogenized at the maximum power for 20 seconds. The membrane homogenate is aliquoted and stored at −80°C until use. An aliquot is used for protein concentration determination using a Protein Assay Rapid Kit and ARVO SX plate reader (Wallac). All the manipulation, stock solution and equipment are kept on ice at all time. For saturation assays, experiments are conducted in a total volume of 200 μl. Saturation is determined by incubating 20 μl of [3H]-dofetilide and 160 μl of membrane homogenates (20-30 μg protein well) for 60 min at room temperature in the absence or presence of 100 μM dofetilide at final concentrations (20 μl) for total or nonspecific binding, respectively. All incubations are terminated by rapid vacuum filtration over polyethylenimide (PEI) coated glass fiber filter papers using Skatron cell harvester followed by two washes with 50 mM Tris buffer (pH 7.5 at 25°C). Receptor-bound radioactivity is quantified by liquid scintillation counting using Packard LS counter.

**[0936]** For the competition assay, compounds are diluted in 96 well polypropylene plates as 4-point dilutions in semi-log format. All dilutions are performed in DMSO first and then transferred into 50 mM Tris buffer (pH 7.5 at 25°C) containing 1 mM MgCl2, 10 mM KCl so that the final DMSO concentration became equal to 1%. Compounds are dispensed in triplicate in assay plates (4 μl). Total binding and nonspecific binding wells are set up in 6 wells as vehicle and 10 μM dofetilide at final concentration, respectively. The radioligand was prepared at 5.6x final concentration and this solution is added to each well (36 μl). The assay is initiated by addition of YSi poly-L-lysine Scintillation Proximity Assay (SPA) beads (50 μl, 1 mg/well) and membranes (110 μA, 20 μg/well). Incubation is continued for 60 min at room temperature. Plates are incubated for a further 3 hours at room temperature for beads to settle. Receptor-bound radioactivity is quantified by counting WALLAC MICROBETA plate counter.

**HERG Assay:**

**[0937]** HEK 293 cells which stably express the HERG potassium channel are used for electrophysiological study. The methodology for stable transfection of this channel in HEK cells can be found elsewhere (Zhou et al., *Bioph. J.*
Before the day of experimentation, the cells are harvested from culture flasks and plated onto glass coverslips in a standard Minimum Essential Medium (MEM) medium with 10% Fetal Calve Serum (FCS). The plated cells are stored in an incubator at 37°C, maintained in an atmosphere of 95% O2/5% CO2. Cells are studied between 15-28 h after harvest.

**HEPG2** currents are studied using standard patch clamp techniques in the whole-cell mode. During the experiment, the cells are superfused with a standard external solution of the following composition (mM): NaCl 150; KCl 4; CaCl2 2; MgCl2 1; Glucose, 10; HEPES, 5; pH 7.4 with NaOH. Whole-cell recordings are made using a patch clamp amplifier and patch pipettes which have a resistance of 1-3 MΩm when filled with the standard internal solution of the following composition (mM): KCl 130; MgATP 5; MgCl2 1.0; HEPES 10; EGTA 5; pH 7.2 with KOH. Only those cells with access resistances below 15 MΩm and seal resistances >1 GΩm are accepted for further experimentation. Series resistance compensation was applied up to a maximum of 80%. No leak subtraction is done. However, acceptable access resistance depended on the size of the recorded currents and the level of series resistance compensation that can safely be used. Following the achievement of whole cell configuration and sufficient time for cell dialysis with pipette solution (∼5 min), a standard voltage protocol is applied to the cell to evoke membrane currents. The voltage protocol is as follows. The membrane is depolarized from a holding potential of −80 mV to +40 mV for 1000 ms. This was followed by a descending voltage ramp (rate 0.5 mV msec−1) back to the holding potential. The voltage protocol is applied to a cell continuously throughout the experiment every 4 seconds (0.25 Hz). The amplitude of the peak current elicited around −40 mV during the ramp is measured. Once stable evoked current responses are obtained in the external solution, vehicle (0.5% DMSO in the standard external solution) is applied for 10-20 min by a peristaltic pump. Provided there were minimal changes in the amplitude of the evoked current response in the vehicle control condition, the test compound of either 0.3, 1, 3, or 10 mM is applied for a 10 min period. The 10 min period included the time which supplying solution was passing through the tube from solution reservoir to the recording chamber via the pump. Exposing time of cells to the compound solution was more than 5 min after the drug concentration in the chamber well reached the attempting concentration. There is a subsequent wash period of a 10-20 min to assess reversibility. Finally, the cells are exposed to high dose of dofetilide (5 mM), a specific IKr blocker, to evaluate the insensitive endogenous current.

**Formalin Model:**
Test compounds are administered at various times prior to intraplantar administration of formalin. A dilute solution of formalin (25-50 μL of 1-2% formaldehyde/saline) is administered s.c. into the plantar surface of the left hind paw under light restraint. Immediately following injection, animals are placed on a mesh stand inside a clear observation chamber large enough to allow for free movement of the animals during the study. Behaviors are scored using manual scoring or automated scoring.

In Vivo Efficacy Assays

**P2X3, P2X2,3 antagonists** may be tested in various animal models of human diseases, including models of neuropathic, inflammatory, and visceral pain, and models of bladder function. P2X3 antagonists may be administered prior to or post-induction of the model depending upon the specific model and the compound PK characteristics. The route of administration may include intraperitoneal (i.p.), subcutaneous (s.c.), oral (p.o.), intravenous (i.v.), intrathecal (i.t.), or intraplantar. The endpoints for these studies may include mechanical alldynia, thermal hyperalgesia, cold allodynia, decreased formalin-induced pain responses, decreased writhing and contractions or altered bladder mechanosensation as appropriate for the model as described below.

**Half-life**
In human liver microsomes (HLM):

**Test compounds (1 μM)** are incubated with 3.3 mM MgCl2 and 0.76 mg/mL HLM (HLM101) in 100 mM potassium phosphate buffer (pH 7.4) at 37°C on the 96-deep well plate. The reaction mixture is split into two groups, a non-P450 and a P450 group. NADPH is only added to the reaction mixture of the P450 group. An aliquot of samples of P450 group is collected at 0, 10, 30, and 60 min time point, where 0 min time point indicated the time when NADPH was added into the reaction mixture of P450 group. An aliquot of samples of non-P450 group is collected at −10 and 65 min time point. Collected aliquots are extracted with acetonitrile solution containing an internal standard. The precipitated protein is spun down in centrifuge (2000 rpm, 15 min). The compound concentration in supernatant is measured by LC/MS/MS system. The half-life value is obtained by plotting the natural logarithm of the peak area ratio of compounds/internal standard versus time. The slope of the line of best fit through the points yields the rate of metabolism (k). This is converted to a half-life value using following equation:

**In Vivo Efficacy Assays**

**P2X3, P2X2,3 antagonists** may be tested in various animal models of human diseases, including models of neuropathic, inflammatory, and visceral pain, and models of bladder function. P2X3 antagonists may be administered prior to or post-induction of the model depending upon the specific model and the compound PK characteristics. The route of administration may include intraperitoneal (i.p.), subcutaneous (s.c.), oral (p.o.), intravenous (i.v.), intrathecal (i.t.), or intraplantar. The endpoints for these studies may include mechanical alldynia, thermal hyperalgesia, cold allodynia, decreased formalin-induced pain responses, decreased writhing and contractions or altered bladder mechanosensation as appropriate for the model as described below.

**Formalin Model:**
Test compounds are administered at various times prior to intraplantar administration of formalin. A dilute solution of formalin (25-50 μL of 1-2% formaldehyde/saline) is administered s.c. into the plantar surface of the left hind paw under light restraint. Immediately following injection, animals are placed on a mesh stand inside a clear observation chamber large enough to allow for free movement of the animals during the study. Behaviors are scored using manual scoring or automated scoring.

**Manual scoring:** Using a three channel timer, the observer records the times (t in seconds) of decreased weight-bearing (t₁), paw lifting (t₂), and licking/biting/shaking (t₃). Results are weighted according to the method of Dubuisson and Dennis, *Pain* 4:161-174, 1977, using the formula t₁ + t₂ + t₃ / 180 where 180 s is the evaluation time for each increment. Behaviors are acquired in alternating 3 min increments starting at time=0 min (i.e. 0-3 min, 6-9 min etc.) and ending at 60 min.

**Automated scoring:** A small metal band weighing 0.5 g is placed on the left paw. Formalin is administered and the animal placed unrestrained inside an observation chamber over an electromagnetic detector system (Automated Nociception Analyzer, University of California, San Diego). The number of paw flinches is electronically recorded. ATP and αβ-Methylene ATP (αβ meATP)-Induced Inflammatory Pain:

**Rats are administered up to 1 μMol c-fmeATP, ATP, adenosine, or PBS in a volume up to 100 μL subcutaneously into the dorsal surface of the hindpaw. Immediately after injection, animals are placed on a stand inside a clear obser-
vation chamber large enough to allow for free movement of the animals. The duration of flinching and licking are recorded over a 20 minute interval to evaluate nociceptive behavior. Responses are measured using either the manual or automated methods described above for the Formalin test. Additional behavioral testing may include assessment of mechanical allodynia and thermal hyperalgesia. For testing, compounds are administered prior to agonist injection.

Complete Freund’s Adjuvant Model (CFA):

[0947] Animals receive an s.c. injection of 100 µL complete Freund’s adjuvant containing 100 µg Mycobacterium tuberculosis strain H37Ra into the plantar surface of the right hind paw under isoflurane anesthesia. Swelling and inflammation are visible within 1 h after administration. Nociceptive testing may begin 24 h post CFA administration. Compounds are generally administered 0.5-12 hrs before testing.

Carrageenan Induced Acute Pain:

[0948] Animals receive a subcutaneous injection of 100 µL of 2% carrageenan into the plantar surface of the right hind paw under isoflurane anesthesia. Swelling and inflammation are visible within 1 h after administration. Nociceptive testing may start 3-24 h post carrageenan administration (Hargreaves et al., Pain, 32:77-88, 1988). Compounds are generally administered 0.5-12 hrs before testing.

Chronic Constriction Injury Model (CCI or Bennett model):

[0949] The CCI model is performed according to the method described by Bennett and Xie, Pain, 33:87-107, 1988. Briefly, under isoflurane anesthesia, the right sciatic nerve is exposed at mid-thigh level via blunt dissection through the biceps femoris. Proximal to the bifurcation of the sciatic nerve, about 7 mm of nerve is freed of adhering tissue and 4 loose ligatures of 4.0 chromic gut are tied around the nerve. Spaces between ligatures is approximately 1 mm. The wound is closed in layers, and the skin closed with staples or non-silk sutures. Sham operated animals are treated identically with the exception that the sciatic nerve will not be ligated. Nociceptive testing can be done 7-21 days post surgery. Compounds are generally administered 0.5-12 hrs before testing.

Spinal Nerve Transection (SNT or Chung model):

[0950] Under anesthesia, rats are placed in a prone position on a flat, sterile surface. A midline incision from L4-S2 is made and the left paraspinal muscles are separated from the spinous processes. The L5 and L6 spinal nerves are tightly ligated with a 4-0 silicon-treated silk suture, according to the method described by Kim and Chung, Pain, 50:355-363, 1992. The L4 spinal nerve is carefully preserved from being surgically injured. The skin is closed with wound clips and animals are returned to their home cages. Rats exhibiting prolonged postoperative neurological deficits or poor grooming are excluded from the experiments. The animals are assessed for nociceptive responses prior to surgery (baseline), then at various timepoints after administration of test compounds. Nociceptive testing can be done 7-21 days post surgery. Compounds are generally administered 0.5-12 hrs before testing.

Chemotherapy-Induced Painful Neuropathy:

[0951] Chemotherapy neuropathy is induced by i.p. administration of 1 mg/kg taxol administered once/day on 4 alternating days (total dose=4 mg/kg) (Polomano et al., Pain, 94:293-304, 2001). Nociceptive testing can be done 9-30 days after the start of Taxol administration. Compounds are generally administered 0.5-12 hrs before testing.

Nociceptive Testing:

[0952] Mechanical Allodynia: Mechanical allodynia testing is performed using the up-down method of Dixon, Ann. Rev. Pharmacol. Toxicol. 20:441-462, 1980, modified for mechanical thresholds by Chapman et al., J. Neurosci. Methods 53:55-63, 1994. To assess tactile allodynia, rats are placed in clear, plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at least 15 minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the left (operated) foot of each rat. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses. The 50% withdrawal threshold will be calculated using the method described by Chapman et al., J. Neurosci. Methods 53:55-63, 1994

[0953] Thermal Hyperalgesia: Hind paw withdrawal latencies to a noxious thermal stimulus are determined using a plantar test apparatus (Ugo Basile) following the technique described by Hargreaves et al., Pain 32: 77-88, 1988. The radiant heat source is focused onto the plantar surface of the ipsilateral paw, and the paw withdrawal latency is determined. An increase latency of paw withdrawal demonstrates reversal of hyperalgesia.

[0954] Mechanical Hyperalgesia: The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analogymeter (Ugo Basile) as described in Stein et al., Pharmaco. Biochem. Behav. 31:451-455, 1988. The maximum weight that can be applied to the hind paw is set at 250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point.

[0955] Cold allodynia: To measure cold allodynia, a drop of acetone is applied to the plantar surface of the paw through the underside of the grating on which the animals are standing using a 50 Hamilton syringe. The process is performed 5 times with a 3 min interval between each time. Vigorous shaking will be recorded as a positive response, and the time spent shaking is recorded. Alternatively, cold allodynia may be tested using the cold water bath method in which animals are placed into a cold water bath with water at a depth of 1.5-2.0 cm and at a temperature of 3-4 degrees centigrade and the number of paw lifts counted.

Colo-Rectal Distension (CRD):

[0956] Prior to induction of the model, animals are deprived of food but allowed access to water ad libitum for 16 h prior to the induction of the model. A 5 cm latex balloon is attached to a barostat system composed of a flow meter and pressure control program by a length of tubing. Under isoflurane anesthesia, the balloon is inserted into the distal colon via the anus at a distance of 5 cm from the anus and taped to the base of the tail. Post-anesthesia, the animal is placed unrestrained into a clean polypropylene cage and allowed to acclimate for 30 mins. The balloon is progressively inflated from 0-75 mm Hg in 5 mm increments every 30 s. The colonic reaction threshold is defined as the pressure inducing the first abdominal contraction. Abdominal contraction indicative of visceral pain correlates with hunching, hump-backed position, licking of the lower abdomen, repeated waves of contraction of the ipsilateral oblique musculature with inward turning of the ipsilateral hindlimb, stretching, squashing of
the lower abdomen against the floor (Wesselman, Neurosci. Lett., 246:73-76, 1998). Alternatively, electrodes may be placed into the external oblique musculature for electromyographic recordings of abdominal contractions. In this case, EMG activity is quantified during colonic balloon inflation. Compounds are generally administered 0.5-12 hrs before testing.

Acetic Acid Wringing Test:

A 0.6% solution of acetic acid (10 ml/kg) is administered i.p. to rats and the number of abdominal constrictions within 30 min are counted. Compounds are generally administered 0.5-12 hrs before testing.

Bladder Afferent Nerve Recordings:

In order to determine the precise role of inhibition of P2X<sub>3</sub> and P2X<sub>2,3</sub> receptors in the micturition response, test compounds will be examined for their ability to modulate afferent signaling from the bladder. Compounds are evaluated in the urinary bladder/pelvic nerve preparation described by Vlaskovska et al., J. Neuroscience, 21:5670-7, 2001, and Cockayne et al., J. Physiol. 567:621-39, 2005. Briefly, the entire urinary tract attached to the lower vertebral and surrounding tissues is isolated en bloc and superfused in a recording chamber with oxygenated (5% CO<sub>2</sub> and 95% O<sub>2</sub>) Krebs solution. The bladder is catheterized through the urethra for intraluminal infusion. A second double lumen catheter is inserted into the bladder to measure intraluminal pressure and to drain the bladder. After the bladder is prepared, the pelvic nerve exiting the vertebrae is dissected and impaled with a suction glass electrode. Nerve activity is measured using standard electrophysiological methods. Following a 60 min stabilization period, repeated ramp distensions are performed until the afferent response stabilizes. This stabilized afferent response was used for comparing mechanosensitivity of bladder afferents between different treatment groups.

Isovolumetric Bladder Contraction Assay:

Female Sprague dawley rats are anesthetized, tracheotomized, and cannulated in the carotid artery and femoral vein. The urinary bladder is accessed via an abdominal incision, and the ureters ligated and transected. For fluid infusion and pressure measurements, the urinary bladder is cannulated.

Post surgery, the bladder is infused with saline until stable volume-induced bladder contractions are elicited. Once stable threshold volumes and contraction frequencies are obtained, the animal is dosed with compound and contraction frequency is measured.

Refill and Cystitis Models of Bladder Function:

Animals are anaesthetized, and transurethral closed cystometry was conducted as previously described (Dmitrieva et al., Neuroscience 78:449-59, 1997; Cockayne et al., Nature 407:1011-5, 2000). The bladder is catheterized transurethrally with a PE-10 polypropylene catheter. Each cystometrogram consists of slowly filling the bladder with normal saline via the transurethral catheter, and then recording the pressure associated with filling via a pressure transducer. Contractions greater than a predetermined threshold value are interpreted as micturition contractions. For each cystometrogram, the volume at which active contractions occurred (micturition threshold) and the number of contractions per cystometrogram are recorded. The effects of compounds are then determined.

Cystometrograms may also be obtained in animals cystitis models in which bladders are irritated by injection of cyclophosphamide (150 mg/kg, i.p.) 24 hrs prior to cystometry, or by infusion of up to 1% acetic acid during cystometry.

The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions and methods provided herein and are not to be construed in any way as limiting their scope. In the examples, all temperatures are in degrees Celsius (unless otherwise indicated). Compounds that can be prepared in accordance with the methods provided herein along with their biological activity data are presented in the following Table. The syntheses of these representative compounds are carried out in accordance with the methods set forth above.

Exemplary Compounds Provided Herein

The following compounds have been or can be prepared according to the synthetic methods described herein. A calcium uptake assay was performed as described above and the activity of each compound is expressed as follows:

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt; (nM)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;2,3&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>408.5</td>
<td>409.2</td>
<td>87.6</td>
<td>58.8</td>
</tr>
</tbody>
</table>

TABLE 1
### TABLE 1-continued

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;1A&lt;/sub&gt; (nM)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>395.46</td>
<td>396.3</td>
<td>406.6</td>
<td>78.5</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>406.53</td>
<td>406.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>422.53</td>
<td>423.2</td>
<td>1062.0</td>
<td>305.6</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>428.48</td>
<td>428.8</td>
<td>8305.0</td>
<td>1960.0</td>
</tr>
</tbody>
</table>
TABLE 1-continued

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC₅₀ hP₂X₃,H (nM)</th>
<th>IC₅₀ hP₂X₃ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>410.49</td>
<td>411</td>
<td>417.6</td>
<td>341.6</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>422.53</td>
<td>423.2</td>
<td>9197.0</td>
<td>2456.0</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>422.53</td>
<td>423.2</td>
<td>115.8</td>
<td>182.4</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9.png" alt="Structure 9" /></td>
<td>452.55</td>
<td>453.2</td>
<td>415.4</td>
<td>483.8</td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;1A&lt;/sub&gt;H</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3A&lt;/sub&gt;</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>10</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>452.55</td>
<td>453.2</td>
<td>1269.1</td>
<td>759.1</td>
</tr>
<tr>
<td>11</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>422.53</td>
<td>423.8</td>
<td>1062.0</td>
<td>484.9</td>
</tr>
<tr>
<td>12</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>424.5</td>
<td>424.9</td>
<td>291.0</td>
<td>291.6</td>
</tr>
<tr>
<td>13</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>423.51</td>
<td>424.2</td>
<td>12.9</td>
<td>9.0</td>
</tr>
</tbody>
</table>

**TABLE 1-continued**

Ca Influx IC<sub>50</sub> of Exemplary Compounds
TABLE 1-continued

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;2a&lt;/sub&gt; (nM)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td><img src="image1.png" alt="Structure 14" /></td>
<td>477.48</td>
<td>478.2</td>
<td>171.9</td>
<td>317.9</td>
</tr>
<tr>
<td>15</td>
<td><img src="image2.png" alt="Structure 15" /></td>
<td>411.48</td>
<td>412.2</td>
<td>54.9</td>
<td>73.2</td>
</tr>
<tr>
<td>16</td>
<td><img src="image3.png" alt="Structure 16" /></td>
<td>425.49</td>
<td>426.2</td>
<td>268.7</td>
<td>95.6</td>
</tr>
<tr>
<td>17</td>
<td><img src="image4.png" alt="Structure 17" /></td>
<td>418.5</td>
<td>419.2</td>
<td>24.5</td>
<td>21.6</td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;H&lt;/sub&gt; (nM)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>-----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>18</td>
<td><img src="image1.png" alt="Structure 18" /></td>
<td>423.51</td>
<td>424.3</td>
<td>70.9</td>
<td>53.5</td>
</tr>
<tr>
<td>19</td>
<td><img src="image2.png" alt="Structure 19" /></td>
<td>394.48</td>
<td>395.4</td>
<td>238.0</td>
<td>61.4</td>
</tr>
<tr>
<td>20</td>
<td><img src="image3.png" alt="Structure 20" /></td>
<td>394.48</td>
<td>395.4</td>
<td>70.5</td>
<td>38.5</td>
</tr>
<tr>
<td>21</td>
<td><img src="image4.png" alt="Structure 21" /></td>
<td>393.49</td>
<td>394.2</td>
<td>913.6</td>
<td>192.4</td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC$<em>{50}$ hP2X$</em>{1A}$H (nM)</td>
<td>IC$<em>{50}$ hP2X$</em>{4}$ (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>----------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>22</td>
<td><img src="structure22.png" alt="Structure 22" /></td>
<td>393.49</td>
<td>394.2</td>
<td>142.6</td>
<td>191.1</td>
</tr>
<tr>
<td>23</td>
<td><img src="structure23.png" alt="Structure 23" /></td>
<td>435.57</td>
<td>435.8</td>
<td>416.1</td>
<td>430.8</td>
</tr>
<tr>
<td>24</td>
<td><img src="structure24.png" alt="Structure 24" /></td>
<td>417.51</td>
<td>417.2</td>
<td>625.8</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td><img src="structure25.png" alt="Structure 25" /></td>
<td>428.48</td>
<td>429.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;H&lt;/sub&gt; (nM)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;X4&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>-----------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>26</td>
<td><img src="image" alt="Structure 26" /></td>
<td>422.53</td>
<td>423.2</td>
<td>503.2</td>
<td>309.2</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Structure 27" /></td>
<td>417.51</td>
<td>416.4</td>
<td>142.3</td>
<td>195.3</td>
</tr>
<tr>
<td>28</td>
<td><img src="image" alt="Structure 28" /></td>
<td>450.58</td>
<td>410.3</td>
<td>219.3</td>
<td>25.8</td>
</tr>
<tr>
<td>29</td>
<td><img src="image" alt="Structure 29" /></td>
<td>409.49</td>
<td>410.3</td>
<td>219.3</td>
<td>25.8</td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;H&lt;/sub&gt; (nM)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;4&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>30</td>
<td><img src="image30.png" alt="Structure 30" /></td>
<td>460.5</td>
<td>461.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td><img src="image31.png" alt="Structure 31" /></td>
<td>433.51</td>
<td>434.4</td>
<td>17.6</td>
<td>14.2</td>
</tr>
<tr>
<td>32</td>
<td><img src="image32.png" alt="Structure 32" /></td>
<td>394.48</td>
<td>395.4</td>
<td>96.6</td>
<td>58.0</td>
</tr>
<tr>
<td>33</td>
<td><img src="image33.png" alt="Structure 33" /></td>
<td>420.47</td>
<td>430.3</td>
<td>98.7</td>
<td>122.0</td>
</tr>
</tbody>
</table>
### Ca Influx $IC_{50}$ of Exemplary Compounds

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>$IC_{50}$ hP2X$_{xH}$ (nM)</th>
<th>$IC_{50}$ hP2X$_{xA}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Chiral 438.53</td>
<td>439.3</td>
<td>18.4</td>
<td>21.1</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Chiral 432.52</td>
<td>433.3</td>
<td>35.6</td>
<td>50.8</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Chiral 444.48</td>
<td>445.2</td>
<td>32.8</td>
<td>65.4</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Chiral 413.52</td>
<td>414.5</td>
<td>122.1</td>
<td>48.6</td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC_{50} hP2X_{1A} (nM)</td>
<td>IC_{50} hP2X_{3} (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>38</td>
<td><img src="image" alt="Structure 38" /></td>
<td>414.51</td>
<td>415.2</td>
<td>226.2</td>
<td>80.7</td>
</tr>
<tr>
<td>39</td>
<td><img src="image" alt="Structure 39" /></td>
<td>Chiral 428.53</td>
<td>429.1</td>
<td>82.0</td>
<td>38.8</td>
</tr>
<tr>
<td>40</td>
<td><img src="image" alt="Structure 40" /></td>
<td>Chiral 427.55</td>
<td>428</td>
<td>52.7</td>
<td>26.3</td>
</tr>
<tr>
<td>41</td>
<td><img src="image" alt="Structure 41" /></td>
<td>410.48</td>
<td>411.1</td>
<td>169.4</td>
<td>23.8</td>
</tr>
</tbody>
</table>

TABLE 1-continued

Ca Influx IC_{50} of Exemplary Compounds
### TABLE 1-continued

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC_{50}^{hP2X_{1A}} (nM)</th>
<th>IC_{50}^{hP2X_3} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td><img src="image" alt="Structure 42" /></td>
<td>419.49</td>
<td>420.1</td>
<td>50.5</td>
<td>15.1</td>
</tr>
<tr>
<td>43</td>
<td><img src="image" alt="Structure 43" /></td>
<td>419.49</td>
<td>420.1</td>
<td>126.5</td>
<td>24.1</td>
</tr>
<tr>
<td>44</td>
<td><img src="image" alt="Structure 44" /></td>
<td>424.5</td>
<td>425.2</td>
<td>292.6</td>
<td>91.6</td>
</tr>
<tr>
<td>45</td>
<td><img src="image" alt="Structure 45" /></td>
<td>452.56</td>
<td>453.2</td>
<td>13.4</td>
<td>14.6</td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;1&lt;/sub&gt; (nM)</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;4&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>46</td>
<td><img src="image1" alt="Structure" /></td>
<td>419.49</td>
<td>420.1</td>
<td>8.8</td>
<td>7.3</td>
</tr>
<tr>
<td>47</td>
<td><img src="image2" alt="Structure" /></td>
<td>451.53</td>
<td>452.3</td>
<td>36.8</td>
<td>29.1</td>
</tr>
<tr>
<td>48</td>
<td><img src="image3" alt="Structure" /></td>
<td>414.51</td>
<td>415.2</td>
<td>33.2</td>
<td>16.5</td>
</tr>
<tr>
<td>49</td>
<td><img src="image4" alt="Structure" /></td>
<td>399.49</td>
<td>400.2</td>
<td>205.4</td>
<td>34.1</td>
</tr>
</tbody>
</table>
### TABLE 1-continued

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC50 hP2X1/2 (nM)</th>
<th>IC50 hP2X3 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td><img src="image50.png" alt="Structure 50" /></td>
<td>400.48</td>
<td>401.4</td>
<td>428.4</td>
<td>25.9</td>
</tr>
<tr>
<td>51</td>
<td><img src="image51.png" alt="Structure 51" /></td>
<td>413.52</td>
<td>414.1</td>
<td>37.0</td>
<td>23.8</td>
</tr>
<tr>
<td>52</td>
<td><img src="image52.png" alt="Structure 52" /></td>
<td>451.5</td>
<td>452.1</td>
<td>37.5</td>
<td>26.2</td>
</tr>
<tr>
<td>53</td>
<td><img src="image53.png" alt="Structure 53" /></td>
<td>438.53</td>
<td>439.3</td>
<td>295.3</td>
<td>62.6</td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC$<em>{50}$ hP2X$</em>{1A}$H (nM)</td>
<td>IC$<em>{50}$ hP2X$</em>{4}$ (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>--------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>54</td>
<td><img src="image" alt="Structure 54" /></td>
<td>479.58</td>
<td>480.2</td>
<td>509.3</td>
<td>55.2</td>
</tr>
<tr>
<td>55</td>
<td><img src="image" alt="Structure 55" /></td>
<td>434.5</td>
<td>435.2</td>
<td>27.5</td>
<td>12.7</td>
</tr>
<tr>
<td>56</td>
<td><img src="image" alt="Structure 56" /></td>
<td>429.52</td>
<td>430.1</td>
<td>418.4</td>
<td>95.9</td>
</tr>
<tr>
<td>57</td>
<td><img src="image" alt="Structure 57" /></td>
<td>431.49</td>
<td>432.1</td>
<td>527.0</td>
<td>89.2</td>
</tr>
</tbody>
</table>
### TABLE 1-continued

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;1/3&lt;/sub&gt;H (nM)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td><img src="image" alt="Structure 58" /></td>
<td>415.49</td>
<td>416.2</td>
<td>193.6</td>
<td>35.3</td>
</tr>
<tr>
<td>59</td>
<td><img src="image" alt="Structure 59" /></td>
<td>415.53</td>
<td>416.2</td>
<td>127.1</td>
<td>65.8</td>
</tr>
<tr>
<td>60</td>
<td><img src="image" alt="Structure 60" /></td>
<td>352.43</td>
<td>353.3</td>
<td>8681.0</td>
<td>206.8</td>
</tr>
<tr>
<td>61</td>
<td><img src="image" alt="Structure 61" /></td>
<td>414.51</td>
<td>415.4</td>
<td>2352.0</td>
<td>268.5</td>
</tr>
</tbody>
</table>
### TABLE 1-continued

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;2,h&lt;/sub&gt; (nM)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td><a href="#">Structure</a></td>
<td>415.53</td>
<td>416.5</td>
<td>47.4</td>
<td>45.7</td>
</tr>
<tr>
<td>63</td>
<td><a href="#">Structure</a></td>
<td>416.52</td>
<td>417.3</td>
<td>25.7</td>
<td>11.8</td>
</tr>
<tr>
<td>64</td>
<td><a href="#">Structure</a></td>
<td>441.49</td>
<td>442.2</td>
<td>254.5</td>
<td>33.2</td>
</tr>
<tr>
<td>65</td>
<td><a href="#">Structure</a></td>
<td>439.32</td>
<td>439.8</td>
<td>1653.0</td>
<td>117.4</td>
</tr>
</tbody>
</table>

*Sep. 29, 2011*
<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;1a&lt;/sub&gt;H</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td><img src="image1" alt="Structure" /></td>
<td>440.5</td>
<td>441.2</td>
<td>728.6</td>
<td>85.8</td>
</tr>
<tr>
<td>67</td>
<td><img src="image2" alt="Structure" /></td>
<td>453.54</td>
<td>454</td>
<td>667.4</td>
<td>101.5</td>
</tr>
<tr>
<td>68</td>
<td><img src="image3" alt="Structure" /></td>
<td>429.53</td>
<td>429</td>
<td>1386.0</td>
<td>370.5</td>
</tr>
<tr>
<td>69</td>
<td><img src="image4" alt="Structure" /></td>
<td>410.46</td>
<td>411.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC50 hP2X, H (nM)</td>
<td>IC50 hP2X, 3H (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>70</td>
<td>Chiral</td>
<td>382.41</td>
<td>383.2</td>
<td>43.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>Chiral</td>
<td>385.46</td>
<td>386.3</td>
<td>240.0</td>
<td>43.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>Chiral</td>
<td>385.46</td>
<td>386.5</td>
<td>59.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>Chiral</td>
<td>454.57</td>
<td>455.4</td>
<td>339.7</td>
<td>103.8</td>
</tr>
</tbody>
</table>

Note: The structures are shown alongside the table entries.
<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC_{50, hP2X_{1A}} (nM)</th>
<th>IC_{50, hP2X_{3A}} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td><img src="image1" alt="Structure 74" /></td>
<td>415.49</td>
<td>416.3</td>
<td>5582.0</td>
<td>138.1</td>
</tr>
<tr>
<td>75</td>
<td><img src="image2" alt="Structure 75" /></td>
<td>413.52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>76</td>
<td><img src="image3" alt="Structure 76" /></td>
<td>385.46</td>
<td>386.4</td>
<td>77.7</td>
<td></td>
</tr>
<tr>
<td>77</td>
<td><img src="image4" alt="Structure 77" /></td>
<td>451.51</td>
<td>452.1</td>
<td>372.9</td>
<td>99.5</td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC &lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;13&lt;/sub&gt;H (nM)</td>
<td>IC &lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>-----------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>78</td>
<td><img src="image1.png" alt="Structure 78" /></td>
<td>412.43</td>
<td>413.2</td>
<td>7169.0</td>
<td>220.9</td>
</tr>
<tr>
<td>79</td>
<td><img src="image2.png" alt="Structure 79" /></td>
<td>439.44</td>
<td>440.3</td>
<td>444.4</td>
<td>71.8</td>
</tr>
<tr>
<td>80</td>
<td><img src="image3.png" alt="Structure 80" /></td>
<td>508.54</td>
<td>509.2</td>
<td>217.9</td>
<td>351.1</td>
</tr>
<tr>
<td>81</td>
<td><img src="image4.png" alt="Structure 81" /></td>
<td>415.41</td>
<td>416.3</td>
<td>1224.0</td>
<td>48.7</td>
</tr>
<tr>
<td>ID</td>
<td>Structure</td>
<td>MW (Calcd)</td>
<td>MW (Obs)</td>
<td>IC₅₀ hP₂X, H</td>
<td>IC₅₀ hP₂X, H</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>82</td>
<td></td>
<td>376.45</td>
<td>377.2</td>
<td>33.2</td>
<td></td>
</tr>
<tr>
<td>83</td>
<td></td>
<td>501.52</td>
<td>502.3</td>
<td>26.0</td>
<td>72.1</td>
</tr>
<tr>
<td>84</td>
<td></td>
<td>372.43</td>
<td>373.2</td>
<td>850.0</td>
<td>10.3</td>
</tr>
<tr>
<td>85</td>
<td></td>
<td>406.43</td>
<td>407.2</td>
<td>1355.0</td>
<td>31.9</td>
</tr>
</tbody>
</table>
From the foregoing description, various modifications and changes in the compositions and methods provided herein will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

At least some of the chemical names of compounds of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing this function include the Lexichem naming tool sold by OpenEye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

Chemical structures shown herein were prepared using ISISDRAW. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure.

<table>
<thead>
<tr>
<th>ID</th>
<th>Structure</th>
<th>MW (Calcd)</th>
<th>MW (Obs)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;2;iH&lt;/sub&gt; (nM)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; hP2X&lt;sub&gt;3&lt;/sub&gt; (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>Chiral</td>
<td>396.45</td>
<td>397.2</td>
<td>28.1</td>
<td>2.2</td>
</tr>
<tr>
<td>87</td>
<td>Chiral</td>
<td>465.55</td>
<td>466.1</td>
<td>18.6</td>
<td>22.2</td>
</tr>
<tr>
<td>88</td>
<td>Chiral</td>
<td>400.48</td>
<td>401.1</td>
<td>7.1</td>
<td></td>
</tr>
</tbody>
</table>

[0965] From the foregoing description, various modifications and changes in the compositions and methods provided herein will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

[0966] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[0967] At least some of the chemical names of compounds of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing this function include the Lexichem naming tool sold by OpenEye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

[0968] Chemical structures shown herein were prepared using ISISDRAW. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure.
I. A compound having a formula 1:

wherein each of A, B, and W are independently selected from CR and N; provided that not all A, B, and W are N at the same time;

X is selected from CR and N;
L is substituted or unsubstituted C1-C9 alkyne or C1-C9 heteroalkylene;
R is selected from substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;
R is substituted or unsubstituted 6-10 membered aryl, or substituted or unsubstituted membered heteroaryl; or
R is substituted or unsubstituted N containing heterocycloalkyl, and the heterocycloalkyl is attached to the core group via the N;

each R is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acyaminino, substituted or unsubstituted alkyaminino, lythyo, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyynyaminino, substituted or unsubstituted alkyynyaminino, substituted or unsubstituted aryalklyyoxy, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted arylalklyloxy, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted alkylosulfonyl, substituted or unsubstituted carbamoyl, carbboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkyaminino, halo, nitro, and thiol;

each R and R is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acyaminino, substituted or unsubstituted alkyaminino, lythyo, substituted or unsubstituted alkoxy, substituted or unsubstituted alkyynyaminino, substituted or unsubstituted alkyynyaminino, substituted or unsubstituted aryalklyyoxy, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted arylalklyloxy, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted alkylosulfonyl, substituted or unsubstituted carbamoyl, carbboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkyaminino, halo, heteroaryloxy, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaryl, hydroxy, nitro, and thiol; and subscript m is selected from 0-4;

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

2. (canceled)

3. (canceled)

4. (canceled)

5. A compound according to claim 1, wherein the compound is according to formula 2:

wherein
X, L, R, R, R, and m are as in claim 1;
or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

6. (canceled)

7. (canceled)

8. (canceled)

9. A compound according to formula 2a:
R² is N containing heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, hydroxalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alkylsulfonfylalkyl, and oxo; and the heterocycloalkyl is attached to the core group via the N; each R⁴a, and R⁴b is independently selected from H, unsubstituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxyalkynyl, substituted or unsubstituted alkoxyalkynyl, substituted or unsubstituted alkoxyalkenyl, substituted or unsubstituted alkylaminosulfonyl, substituted or unsubstituted alkoxyalkyl, or unsubstituted pyridyl, unsubstituted or unsubstituted oxazolyl, unsubstituted or unsubstituted quinolinyl, unsubstituted or unsubstituted indolyl. 13. (canceled) 14. (canceled) 15. A compound according to claim 1, wherein R³ is

![Chemical Structure](image)

and wherein subscript n₁ is selected from 1-5 and each R⁴ is independently selected from hydrogen, unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxyalkenyl, substituted or unsubstituted alkoxyalkynyl, substituted or unsubstituted oxazolyl, unsubstituted or unsubstituted pyridyl, unsubstituted or unsubstituted oxazolyl, unsubstituted or unsubstituted quinolinyl, unsubstituted or unsubstituted indolyl. 16. A compound according to claim 1, of formula 3, 4, or 5:

![Chemical Structure](image)
A compound according to claim 16, wherein the compound is according to formula 6, 7, 8, 9, 10, or 11:

-continued

wherein

- $X'$ is selected from $CR^{4a}$ and $N$;
- $R^1$ is selected from substituted or unsubstituted aryl, and heteroaryl; or
- $R^1$ is substituted or unsubstituted cycloalkyl; or
- $R^1$ is heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminooalkyl, dialkylaminoalkyl, alkyloxynalkyl, and oxo;
- each of $R^{2a}$ and $R^{2b}$ is independently selected from hydrogen, $C_1-C_4$ alkyl, alkoxyalkyl, alkoxy, dialkylamino, alkyloxynalkyl, haloalkyl, and halo; or $R^{2a}$ and $R^{2b}$ join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms;
- each $R^{4a}$ and $R^{4b}$ is independently selected from $H$, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted aminooalkyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted aminosulfanyl, substituted or unsubstituted alkylsulfanyl, substituted or unsubstituted aminosulfanyl, azido, substituted or unsubstituted carbamoyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted dialkylamino, halo, heteroaryl, substituted or unsubstituted heteroaryl, hydroxy, halo, nitro, and thiol; and subscripts $n1$ is selected from 1-5; and the subscript $n2$ is 0 or 1;
- or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof;

provided that

a) when $n2$ is 0, $R^1$ is other than $Me$; or
b) the compound is other than

i) 3-(3-fluoro-2-pyridinyl)-N-[2-hydroxy-1-(3-methyl-1, 2,4-oxadiazol-5-yl)propyl]-5-(5-methyl-2-pyridinyl)-benzamide.

17. (canceled)
18. (canceled)
19. A compound according to claim 16, wherein the compound is according to formula 6, 7, 8, 9, 10, or 11:
wherein

X' is selected from CR₄ⁿ and N;
R₁ is selected from substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;
each of R₂a and R₂b is independently selected from hydrogen, C₁₋₄ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, haloalkyl, and halo; or R₂a and R₂b join together to form a cycloalkyl or heterocycloalkyl ring of 3-7 atoms;
R₃ is N containing heterocycloalkyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, hydroxyalkyl, alkoxyalkyl, aminalkyl, dialkylaminoalkyl, alkyloxymethyl, and oxo; and the heterocycloalkyl is attached to the core group via the N;
each of R₄a and R₄b is independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylaminonitro, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkylaminocarbonyl, substituted or unsubstituted aroylaminomethyl, substituted or unsubstituted aroylamino, substituted or unsubstituted aroylalkyl, substituted or unsubstituted amino, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted aryalkyl, substituted or unsubstituted aryalkylamino, substituted or unsubstituted aryalkylmethyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted diazacyclopentane, substituted or unsubstituted heteroaeryl, substituted or unsubstituted heteroaeryl, substituted or unsubstituted heteroaeryl, substituted or unsubstituted heteroaeryl, substituted or unsubstituted heteroaeryl, substituted or unsubstituted heteroaeryl, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

20. (canceled)
21. (canceled)
22. (canceled)
23. (canceled)
24. (canceled)
25. (canceled)
26. A compound according to claim 1, of formula 2a:

wherein

R₁, R₂a, R₂b, R₃, R₄a, R₄b, n₁ and n₂ are as in claim 16; or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

27. (canceled)
28. (canceled)
29. (canceled)
30. (canceled)
31. (canceled)
32. (canceled)
33. A compound according to claim 26, wherein the compound is according to formula 18, 19, 20, 21, 22, or 23:

![Chemical Structure 18]

![Chemical Structure 19]

![Chemical Structure 20]

![Chemical Structure 21]

wherein X', R', R, R', R; and n2 are as in claim 26; and R^3 is hydrogen, or substituted or unsubstituted alkyl; or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

34. (canceled)
35. (canceled)
36. (canceled)
37. (canceled)
38. (canceled)
39. (canceled)
40. (canceled)
41. A compound according to claim 16, wherein each of R^{20} and R^{20} is hydrogen; or one of R^{20} and R^{20} is methyl, hydroxymethyl or hydroxy-ethyl; or each of R^{20} and R^{20} is methyl; or R^{20} and R^{20} join together to form a cycloalkyl ring.
42. (canceled)
43. (canceled)
44. (canceled)
45. (canceled)
46. (canceled)
47. (canceled)
48. (canceled)
49. (canceled)
50. (canceled)
51. A compound according to claim 1, wherein R^1 is selected from unsubstituted pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, piperazinyl, and azepinyl.
52. A compound according to claim 1, wherein R^1 is selected from pyrrolidinyl, piperidinyl, morpholinyl, thio-
morpholinyl, piperazinyl, and azepinyl, unsubstituted or substituted with one or more groups selected from alkyl, halo, haloalkyl, alkoxyalkyl, aminoalkyl, dialkylaminoalkyl, alkylsulfonylalkyl, and oxo.

53. A compound according to claim 1, wherein R² is selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, and azepinyl, substituted with oxo.

54. A compound according to claim 1, wherein R² is selected from morpholinyl, and 1,1-dioxo-thiomorpholinyl.

55. A compound according to claim 1, wherein R² is Et, i-Pr, or t-Bu.

56. (canceled)
57. (canceled)
58. (canceled)
59. (canceled)
60. (canceled)

61. A compound according to claim 1, wherein R¹ is

\[
\begin{align*}
\text{and wherein subscript } n & \text{ is selected from 1-5 and each } R^5 & \\
& \text{is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylation, substituted or unsubstituted alkylthio, substituted or unsubstituted alkoxy, aryl, alkoxyalkeny, substituted alkoxyalkeny, substituted or unsubstituted alkylarylamino, aryalkylamino, substituted aryalkylamino, amino, aryl, substituted aryl, aryalkyl, sulfo, substituted sulfo, substituted sulfanyl, substituted sulfonyl, substituted sulfinyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, azido, substituted or unsubstituted carbamoyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted diazolyl, halo, heteroaryloxy, substituted or unsubstituted heteroaryl, hydroxy, nitro, and thiol.}
\end{align*}
\]

62. (canceled)
63. (canceled)
64. (canceled)
65. (canceled)
66. (canceled)
67. (canceled)

68. A compound according to claim 1, selected from compounds exemplified in Table 1; or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, tautomer or isotopic variant thereof.

69. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of claim 1.

70. (canceled)
71. (canceled)
72. (canceled)
73. A method for preventing or treating in a mammalian disease or condition which comprises administering to the mammal an effective disease-treating or condition-treating amount of a compound according to claim 1.

74. (canceled)
75. (canceled)
76. (canceled)
77. (canceled)
78. (canceled)
79. (canceled)
80. (canceled)
81. (canceled)
82. (canceled)

83. A method of treating a mammalian suffering from at least one symptom selected from the group consisting of symptoms of exposure to capsaicin, symptoms of burns or irritation due to exposure to heat, symptoms of burns or irritation due to exposure to light, symptoms of burns, bronchoconstriction or irritation due to exposure to tear gas, and symptoms of burns or irritation due to exposure to acid (which comprises administering to the mammal an effective symptom-treating amount of a compound according to claim 1).

84. (canceled)
85. The method of claim 73, wherein the disease or condition is selected from: pain including acute, inflammatory and neuropathic pain, chronic pain, dental pain and headache including migraine, cluster headache and tension headache, Parkinson’s disease, Alzheimer’s disease and multiple sclerosis; diseases and disorders which are mediated by or result in neuroinflammation, encephalitis; centrally-mediated neuropsychiatric diseases and disorders, depression mania, bipolar disease, anxiety, schizophrenia, eating disorders, sleep disorders and cognition disorders; neurological and neurodegenerative diseases and disorders; epilepsy and seizure disorders; prostate, bladder and bowel dysfunction, urinary incontinence, urinary hesitancy, rectal hypersensitivity, fecal incontinence, benign prostatic hyperplasia and inflammatory bowel disease; respiratory and airway disease and disorders, allergic rhinitis, asthma and reactive airway disease and chronic obstructive pulmonary disease; diseases and disorders which are mediated by or result in inflammation, arthritis, rheumatoid arthritis and osteoarthritis, myocardial infarction, autoimmune diseases and disorders, tics/pruritus, psoriasis; obesity; lipid disorders; cancer; and renal disorders.

* * * * *