Title: 2,3,5 TRISUBSTITUTED ARYL AND HETEROARYL AMINO DERIVATIVES, COMPOSITIONS, AND METHODS OF USE

Abstract: Compounds are disclosed that have a formula represented by the following (1) wherein Cy, L_1 R_1, R_2, R_3 R_4, n, and L_2 are as described herein. These compounds may be prepared as a pharmaceutical composition, and may be used for the prevention and treatment of a variety of conditions in mammals including humans, including by way of non-limiting example addictive disorders, Alzheimer's Disease, anxiety disorders, ascites, autism, bipolar disorder, cancer, depression, endothelial cornal dystrophy, edema, epilepsy, glaucoma, Huntington's Disease, inflammatory pain, insomnia, ischemia, migraine, migraine with aura, migraine without aura, neuropathic pain, nociceptive neuralgia, nociceptive pain, ocular diseases, pain, itch, excessive itch, Pruritis, neuropathic pruritis, Parkinson's disease, personality disorders, postherpetic neuralgia, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.
2,3,5-TRISUBSTITUTED ARYL AND HETEROARYL AMINO DERIVATIVES,
COMPOSITIONS, AND METHODS OF USE

Field of the Invention

[0001] This international patent application claims benefit of U.S. Provisional Patent Application No. 61/550,254, filed October 21, 2011, the disclosure of which is hereby incorporated by reference in its entirety.

[0002] The present invention relates to 2,3,5-trisubstituted aryl amino derivatives, positional isomers, and prodrugs thereof, compositions comprising the same and methods of making and using the same. The present invention also relates to pharmaceutical compositions comprising these compounds and methods for using these compounds. Compounds described herein are particularly useful for the treatment and/or prophylaxis of diseases, disorders, and conditions that involve the Na⁺K⁺Cl⁻ co-transporters (NKCC1 or NKCC2 or combinations thereof) including but not limited to addictive disorders, anxiety disorders, ascites, bipolar disorder, cancer, depression, edema, endothelial corneal dystrophy, epilepsy, glaucoma, ischemia, migraine, neuropathic pain, nociceptive neuralgia, ocular diseases, pain, postherpetic neuralgia, and schizophrenia. Compounds described herein are also particularly useful for the treatment and/or prophylaxis of diseases, disorders, and conditions that involve GABA₆ receptors including but not limited to Alzheimer's Disease, addictive disorders, anxiety disorders, autism, bipolar disorder, depression, epilepsy, Huntington's Disease, inflammatory pain, insomnia, migraine, migraine with aura, migraine without aura, neuropathic pain, nociceptive pain, pain, itch, excessive itch, pruritis, neuropathic pruritis, Parkinson's disease, personality disorders, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.

Background of the Invention

Na⁺K⁺Cl⁻ Co-Transporters

[0003] In absorptive and secretory epithelia, transcellular ion transport depends on specific plasma membrane proteins for mediating ion entry and exit from cells. In basolateral membrane of almost all epithelia (with exception of choroidal plexus), sodium exit and potassium entrance occur through Na⁺K⁺-ATPase, generating electrochemical gradients that constitute a driving force for Na⁺ influx and K⁺ efflux. Transport of these ions following their gradients can be accomplished by specific ion channels, allowing membrane passage of ions alone or by transporters in which Na⁺ or K⁺ transport is accompanied by other ions or solutes by means of several different solute transporters. These membrane proteins are known as secondary transporters because ion translocation is not dependent on ATP hydrolysis but rather on gradients generated by primary transporters. A secondary transport mechanism for transcellular ion transport in epithelial cells involves cations (Na⁺ or K⁺) coupled with chloride (Cl⁻), with a stoichiometry of 1:1, and, therefore, the ion translocation produces no change in transmembrane potential. For this reason, these transporters are known as electroneutral cation-chloride coupled cotransporters. In addition
to being heavily implicated in ion absorptive and secretory mechanisms, electroneutral cation-chloride coupled cotransporters play a key role in maintenance and regulation of cell volume in both epithelial and nonepithelial cells. Because Na\(^+\) influx and K\(^+\) efflux by electroneutral cotransporters are rapidly corrected by Na\(^+\)K\(^+\)-ATPases, the net effect of its activity is Cl\(^-\) movement inside or outside cells. The change in intracellular chloride concentration is known to be accompanied by changes in cell volume. Finally, a variety of new physiological roles for electroneutral cotransporters are emerging (e.g., regulation of intraneuronal Cl\(^-\) concentration and thus modulation of neurotransmission). Gamba (2005) Physiol. Rev. 85: 423-493.

[0004] Four groups of electroneutral cotransporter systems (also known as "symporters") have been functionally identified based on cation(s) coupled with chloride, stoichiometry of transport process, and sensitivity to inhibitors. These systems include: (1) the benzothiadiazine (or thiazide)-sensitive Na\(^+\)Cl\(^-\) cotransporter; (2) the sulfamoylbenzoic (or bumetanide) sensitive Na\(^+\)K\(^+\)2Cl\(^-\) cotransporters; (3) the sulfamoylbenzoic (or bumetanide) sensitive Na\(^+\)Cl\(^-\) cotransporters; and (4) the dihydroindenyloxy-alkanoic acid (DIOA)-sensitive K\(^+\)Cl\(^-\) cotransporter. Some overlap exists in sensitivity to inhibitors in the last two groups because Na\(^+\)K\(^+\)2Cl\(^-\) and K\(^+\)Cl\(^-\) cotransporters can be inhibited by high concentration of DIOA or loop diuretics, respectively; however, affinity for inhibitor and the cation coupled with chloride clearly differentiate between both groups of transporters. Gamba (2005) "Molecular Physiology and Pathophysiology of Electroneutral Cation-Chloride Cotransporters." Physiol. Rev, 85: 423-493. Loop diuretics (e.g., bumetanide, furosemide, piretanide, azosemide, and torsemide) are antagonists of the Na\(^+\)K\(^+\)Cl\(^-\) cotransporter (e.g., NKCC2) in the thick ascending limb of the loop of Henle and act to inhibit sodium and chloride reabsorption by competing for the Cl\(^-\) binding site. See also Russell (January 2000) Physiolocal Reviews 80(1): 211-275.

[0005] Major advances have been made in the past decade in molecular identification and characterization of solute carriers. As of 2005, the Human Genome Organization (HUGO) Nomenclature Committee Database recognizes 43 solute carries (SLC) families, which include a total of 298 transporter genes encoding for uniporters (passive transporters), cotransporters (coupled transporters), antiporters (exchangers), vesicular transporters, and mitochondrial transporters. This amount of solute carrier genes represents ~1% of the total pool of genes that have been calculated to compose human genome. Gamba (2005) Physiol. Rev. 85: 423-493.

[0006] One isoform of the Na\(^+\)K\(^+\)Cl\(^-\) cotransporter (NKCC) NKCC1 is widely distributed throughout the body. NKCC1 transports sodium, potassium, and chloride into the cell. NKCC1 is also found throughout the nervous system where it is expressed on astrocytes, oligodendrocytes, and Schwann cells. Lenart, et al, (2004) The Journal of Neuroscience 24(43): 9585-9597. Another isoform, NKCC2, is found primarily in the kidney, where it serves to extract sodium, potassium, and chloride from the urine. Haas (1994) Am J Physiol Celt Physiol 267: C869-C885.

[0007] The mediators of transcellular Cl\(^-\) cotransport (Na-Cl cotransporter, NKCC1, NKCC2, KCC1,
and KCC2) are all related members of the SLC12A family of cation/Cl⁻ cotransporters; each takes advantage of inward Na⁺ or outward K⁺ gradients to move Cl⁻ into or out of cells, respectively. The importance of this family of transporters is underscored by their use as pharmacologic targets (thiazide diuretics act at NKCC, and loop diuretics act at NKCC2), and that their mutation results in diverse diseases. For example, disruption of NKCC1 in mice leads to hearing loss, altered pain perception, neuronal excitability, and altered blood pressure. Kahle, et al. (2004) Proc. Natl. Acad. Sci. USA 102(46): 16783-1 6788.

[0008] The regulation of Cl⁻ transport into and out of cells also plays a critical role in the maintenance of intracellular volume and the excitability of GABA responsive neurons regulated by at least two ion cotransporters: CP influx is mediated by the NKCC1 which mediates the Cl⁻ influx and KCC1 or KCC2 which mediates the Cl⁻ efflux. Kahle, et al. (2004) Proc. Natl. Acad. Sci. USA 102(46): 16783-16788. The maintenance of intra- and extracellular electrolyte homeostasis are required for a wide range of essential physiologic processes, including general functions (e.g., maintenance of proper cell volume), specialized cell functions (e.g., control of neuronal excitability), and global functions (e.g., regulation of blood pressure). This homeostasis is achieved via the regulated movement of Na⁺, K⁺, and Cl⁻ across cell membranes by ion channels, cotransporters, exchangers, and pumps that execute transmembrane electrolyte flux. Kahle, et al. (2004) Proc. Natl. Acad. Sci. USA 102(46): 16783-16788.

[0009] The predominant mechanism by which intracellular volume is maintained in cells in response to changes in extracellular tonicity is the raising or lowering of intracellular Cl⁻ concentration ([Cl⁻]), thereby minimizing transmembrane water flux. [Cl⁻] is modulated by altering the balance between Cl⁻ entry and exit. The major mediator of Cl⁻ entry is NKCC1 and Cl⁻ exit is largely mediated by KCC1. These cotransporters are both regulated by extracellular tonicity: hypertonicity activates NKCC1 and inhibits KCC1, whereas hypotonicity has the opposite effect. Kahle, et al. (2004) Proc. Natl. Acad. Sci. USA 102(46): 16783-16788.


GABA Receptors

[0011] Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system (CNS) where approximately 30% of all synapses use GABA as a transmitter. There are three classes of GABA receptors: GABA_A (ligand-gated ion channel), GABA_B (G protein-coupled receptor), and GABA_C (ligand-gated ion channel). Chloride flux into the cell results from the activation of GABA_A receptors by the binding of GABA molecules, hyperpolarizing the resting membrane potential, and decreasing the chances of the post-synaptic neuron propagating an action potential.

[0012] GABA_A receptors are pentameric and approximately 19 GABA receptor subunits have been
cloned from mammals (6 α, 3 β, 3 γ, 1 δ, 1 ε, 1 θ, 1 π, and 3 ρ subunits). The heterogeneity of GABA subunits are further increased by alternate splicing (e.g., γ2 short and γ2 long are the two major splice variants of the γ2). In general, a functional GABA_A receptor requires 2 α subunits, 2 β subunits and a third "regulatory" subunit (usually γ or δ). WO 2009/100040. The specific subunit combination determines the pharmacological and ligand binding properties of the GABA_A receptor. The most abundant subunit combination found in the CNS are αβγδ. This subtype represents approximately 40% of GABA_A receptors in the brain and it is expressed throughout the CNS and is located on post-synaptic cells. WO 2007/002359.

[0013] The importance of [Cl]_i regulation has been recognized with the discovery that GABA neurotransmission is not uniformly inhibitory (e.g., it is predominantly excitatory in the neonatal period.) If [Cl]_i is below its equilibrium potential, Cl⁻ enters the cell, resulting in hyperpolarization and inhibition. If [Cl]_i is above its equilibrium potential, GABA induces Cl⁻ efflux, depolarization, and neuronal excitation. Similarly, neurons of the suprachiasmatic nucleus show circadian variation in their response to GABA, demonstrating the ability to dynamically regulate [CP]_i. Finally, GABA neurotransmission in the peripheral nervous system is predominantly excitatory.

[0014] GABA_A receptors are the targets of a wide range of therapeutic and clinically relevant compounds including benzodiazepines, barbiturates, neurosteroids, ethanol, certain intravenous anesthetics, and subtype specific modulators (e.g., Zolpidem.) These compounds serve as anxiolytics, sedative/hypnotics, anti-epileptic drugs (AED), and memory enhancers. Many of these therapeutics show efficacy but cause side effects due to unwanted effects at α , and/or αβ GABA_A variants or due to low therapeutic index. For example, benzodiazepines such as diazepam (VALIUM) are excellent anxiolytics but cause unwanted sedative effects. WO 2007/002359.

[0015] At a cellular level, GABA_A receptors are expressed both pre-synaptic, post-synaptic, and extrasynaptic sites (pre-synaptic and extrasynaptic being defined herein as parasynaptic to distinguish from post-synaptic) where they respond to large changes in GABA concentration caused by release of the neurotransmitter into the synaptic space, and extra-synaptically where the receptors respond to lower concentrations of GABA that "leak" from synaptic junctions. The post-synaptic receptors respond to acute changes in neuronal firing, pre-synaptic receptors are responsible for inhibition of GABA release in the setting of high GABA levels, whereas the extrasynaptic receptors are responsible for maintaining overall tone of neuronal networks. WO 2009/100040. Tonic inhibition is generated by the persistent activation of extrasynaptic (perisynaptic) GABA_A receptors and regulates the excitability of individual neurons and neural networks. Jia, et al. (2008) The Journal of Pharmacology and Experimental Therapeutics 326(2): 475-482.

[0016] Presynaptic GABA_A receptors situated at extrasynaptic sites may comprise αδβδ and αδβδ isoforms. The extrasynaptic αδβδ and αδβδ GABA_A receptor isoforms show marked sensitivity to GABA, alcohol, and anesthetics, suggesting that receptors may present a critical site for regulating synaptic
function in the developing brain in both physiological and pathological situations. Xiao, et al. (2007) J Physiol. 580(Pt.3):731^13. For example, temporal lobe epilepsy (TLE), Parkinson's disease (PD) and Huntington's disease (HD) are neurodegenerative disorders that involve disruptions in GABA signaling. TLE seizures reflect excess excitation, which may result from local inhibitory circuit dysfunction. PD devastates the input to striatal GABAergic neurones and HD destroys striatal GABAergic neurones. Directing GABA synthesis, degradation, release, transport or receptors may be useful in controlling GABA signaling in specific brain areas should benefit each of these diseases. The presynaptic localization of certain GABA receptor subtypes may also allow GABA receptor inhibitors with novel modes of action to serve as presynaptic-specific agents. Thus, new drugs targeting GABA synthesis, release, and binding may be useful for improved therapeutic treatments for epilepsy and both Parkinson's and Huntington's disease. Kleppner and Tobin (2001) Expert Opin Ther Targets. 5(2):219–39. See also Shumate, et al. (1998) Epilepsy Research (32): 114-128; Frielsch (2008) Frontiers in Molecular Neuroscience 1(5): 1-5; Roberts, et al. (2006) The Journal of Biological Chemistry 281(40): 29431-29435; and Roberts, et al. PNAS 102(33): 11894-1 1899.

[0017] Sulfonamide derivatives are well known GABA\textsubscript{A} inhibitors and/or NKCC co-transporters.

[0018] Accordingly, GABA\textsubscript{A} inhibitors and/or NKCC co-transporters are widely sought. For example, certain GABA\textsubscript{A} inhibitors and/or NKCC co-transporters, including sulfonamide substituted benzoic acids are reported in a PCT publication, WO2010/085352.

[0019] Thus, new or improved agents which are GABAA inhibitors and/or NKCC co-transporters are continually needed for developing new and more effective pharmaceuticals that are useful for treatment and/or prophylaxis of diseases, disorders, and conditions that involve the Na+K+Cl- co-transporters (e.g., NKCC1 and NKCC2) including but not limited to addictive disorders, anxiety disorders, ascites, bipolar disorder, cancer, endothelial corneal dystrophy, edema, depression, epilepsy, glaucoma, ischemia, migraine, neuropathic pain, nociceptive neuralgia, ocular diseases, pain, postherpetic neuralgia, and schizophrenia. Additionally, there is a continuing need for compositions and methods for treatment and/or prophylaxis of diseases, disorders, and conditions that involve the GABA\textsubscript{A} receptors including but not limited to Alzheimer's Disease, addictive disorders, anxiety disorders, autism, bipolar disorder, depression, epilepsy, Huntington's Disease, inflammatory pain, insomnia, migraine, neuropathic pain, nociceptive pain, pain, Parkinson's disease, personality disorders, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes. The compounds of the invention, as well as their compositions and methods for use described herein are directed toward these and other needs.

Summary of the Invention

[0020] The present invention relates to novel compounds that are GABA\textsubscript{A} inhibitors and/or NKCC co-transporters useful for the treatment of anxiety disorders, ascites, bipolar disorder, cancer, endothelial corneal dystrophy, edema, depression, epilepsy, glaucoma, ischemia, migraine, neuropathic pain, nociceptive neuralgia, ocular diseases, pain, postherpetic neuralgia, and schizophrenia.
Additionally, the compounds are useful for the treatment of Alzheimer's Disease, addictive disorders, anxiety disorders, autism, bipolar disorder, depression, epilepsy, Huntington's Disease, inflammatory pain, itch, excessive itch, pruritis, neuropathic pruritis, insomnia, migraine, neuropathic pain, nociceptive pain, pain, Parkinson's disease, personality disorders, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.

Accordingly, in a first aspect of the invention, a compound of the invention is disclosed having a formula I:

wherein:
- Cy is aryl or heteroaryl;
- L^1 is substituted or unsubstituted alkylene, or -C(=0)-;
- L^2 is a single bond, or -O-;
- R^1 is selected from the group consisting of hydroxy, amino, substituted or unsubstituted amino, substituted or unsubstituted N containing heterocycloalkyl, and substituted or unsubstituted alkoxy;
  - or L^1 is a single bond or substituted or unsubstituted alkyene, and R^1 is selected from the group consisting of H, halo, CN, substituted or unsubstituted 5-12 membered heteroaryl, and substituted or unsubstituted 4-8 membered heterocycloalkyl;
- R^{2a} is H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, or substituted or unsubstituted heteroarylalkyl;
- R^{2b} is substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, or substituted or unsubstituted heteroarylalkyl;
  - or R^{2a} and R^{2b} may join together to form a 4-7 membered heterocycloalkyl ring;
- R^3 is selected from the group consisting of halo, alkyl, substituted or unsubstituted haloalkyl, CN, and S(0)_x-R^{3b};
  - the subscript x is 0, 1, or 2;
- R^{3b} is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, aryl or heteroaryl;
  - or
R₃ is substituted or unsubstituted amino, or substituted or unsubstituted N- containing heterocycloalkyl, and wherein the N of the heterocycle is bonded to S via a single bond; provided that L¹ is other than -C(=0)-;
or

R₃ is substituted or unsubstituted amino, or substituted or unsubstituted N- containing heterocycloalkyl, and wherein the N of the heterocycle is bonded to S via a single bond; provided that R₃ is other than H; and the subscript n is other than 0;

each R₄ is independently selected from the group consisting of 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 alkoxycarbonyl, substituted or unsubstituted alkylarylthio, substituted or unsubstituted amino, substituted or unsubstituted aryloxy, substituted or unsubstituted arylamide, substituted or unsubstituted aryloxy, substituted or unsubstituted arylaminocarbonyl, substituted or unsubstituted arylaminocarbonyl, substituted or unsubstituted aryloxy, substituted or unsubstituted arylaminocarbonyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, substituted or unsubstituted dialkylamino, halo, nitro, and thiol; or two adjacent R₄'s may join together to form cycloalkyl or heterocycloalkyl; and the subscript n is 0, 1, 2, or 3;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

i) when R³ is S(0)ₓ-R²ₓ, x is 2, L¹ is -C(=0)-, R¹ is OH, R³ is unsubstituted alkyl, L² is -O-. R² is H, and R³ is unsubstituted benzyl; then n is other than 0; and

ii) when R³ is S(0)ₓ-R²ₓ, x is 2, L¹ is -C(=0)-, R¹ is OH, R³ is unsubstituted alkyl, L² is -O-. one of R² and R³ is n-Bu, and the other is H, unsubstituted alkyl, unsubstituted aralkyl, or unsubstituted heteroarylalkyl; then n is other than 0; and

iii) when L¹ is -CH₂-, R¹ is OH, R³ is Br, L² is a single bond, and R² is Me; then R² is other than Me;

iv) when R³ is S(0)ₓ-R²ₓ, x is 2, L¹ is -C(=0)-, R¹ is OH, R³ is methoxymethyl, L² is -O-. one of R² and R³ is n-Bu, and the other is H; then n is other than 0;

v) when R³ is S(0)ₓ-R²ₓ, x is 2, L¹ is -C(=0)-, R¹ is OH, R³ is Me, L² is -O-. the NR³ₓ₋₂ₓ group is unsubstituted pyrrolidin-1-yl; then n is other than 0;

vi) when R³ is S(0)ₓ-R²ₓ, x is 2, L¹ is a single bond, R¹ is tetrazolyl, and L² is -O-. then n is other than 0;

vii) when L¹ is a single bond or alkylene, R¹ is CI, R² is H or Me, and R² is Me; then R³ is other
than Cl;

viii) when \( L^1 \) is a single bond or alkylene, \( R^1 \) is H, and \( R^3 \) is Cl; then \( R^{2a} \) is other than H;

ix) when \( R^{2b} \) is substituted or unsubstituted acyl, \( L' \) is -C(=O)-, and \( R^1 \) is OH; then \( R^3 \) is selected from the group consisting of halo, alkyl, substituted or unsubstituted haloalkyl, CN, and \( S(0)_x \cdot R^{2a} \); the subscript \( x \) is 0, 1, or 2; and \( R^{2b} \) is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, aryl or heteroaryl; and

x) the compound is other than

\[
\begin{align*}
\text{[0023]} & \quad \text{In another aspect, the present invention provides compounds according to formula I:} \\
\end{align*}
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\begin{align*}
\text{wherein:} \\
\text{Cy is aryl or heteroaryl;} \\
\text{L'} \text{ is substituted or unsubstituted alkylene;} \\
\text{L}^2 \text{ is a single bond, or -O-;} \\
\text{R}^1 \text{ is selected from the group consisting of hydroxy, amino, substituted or unsubstituted amino,} \\
\text{substituted or unsubstituted N containing heterocycloalkyl, and substituted or unsubstituted alkoxy;} \\
\text{or L}^1 \text{ is a single bond or substituted or unsubstituted alkylene, and R}^1 \text{ is selected from the group} \\
\text{consisting of H, halo, CN, substituted or unsubstituted 5-12 membered heteroaryl, and substituted or} \\
\text{unsubstituted 4-8 membered heterocycloalkyl;} \\
\text{R}^{2b} \text{ is H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, or substituted or} \\
\text{unsubstituted heteroarylalkyl;} \\
\text{R}^{2b} \text{ is substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted} \\
\text{arylalkyl, or substituted or unsubstituted heteroarylalkyl;} \\
\end{align*}
\]
or $R^{2a}$ and $R^{2b}$ may join together to form a 4-7 membered heterocycloalkyi ring;

$$R^3$$ is $S(0)\_x\cdot R^{3a}$;

the subscript $x$ is 0, 1, or 2;

$R^{3a}$ is substituted or unsubstituted amino, or substituted or unsubstituted N- containing heterocycloalkyi, and wherein the N of the heterocycle is bonded to S via a single bond;

each $R^4$ is independently selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted alkylarylamino, substituted or unsubstituted amino, substituted or unsubstituted arylalkyl, hydroxy, substituted or unsubstituted alkoxy, substituted sulfonyl, substituted sulfanyl, substituted sulfanyl, 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 heterocycloalkyi, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, substituted or unsubstituted dialkylamino, halo, nitro, and thiol; or two adjacent $R^5$s may join together to form cycloalkyi or heterocycloalkyi; and the subscript $n$ is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

i) when $R^3$ is $S(0)\_x\cdot R^{3a}$, $x$ is 2, $L^1$ is a single bond, $R^1$ is tetrazolyl, and $L^2$ is -0-; then $n$ is other than 0.

[0024] In one particular embodiment, with respect to the compound of formula I, $L^1$ is -C(=0)-.

[0025] In one particular embodiment, with respect to the compound of formula I, $R'$ is OH.

[0026] In one particular embodiment, with respect to the compound of formula I, $R^1$ is heteroaryl.

[0027] In one particular embodiment, with respect to the compound of formula I, $R^{2a}$ is alkyl. In another embodiment, $R^{2a}$ is substituted alkyl.

[0028] In another particular embodiment, with respect to the compound of formula I, $R^{2a}$ is H.

[0029] In one particular embodiment, with respect to the compound of formula I, $R^{2b}$ is alkyl. In another embodiment, $R^{2b}$ is substituted alkyl.

[0030] In one particular embodiment, with respect to the compound of formula I, $L^2$ is -0-.

[0031] In one particular embodiment, with respect to the compound of formula I, Cy is phenyl. In another embodiment, Cy is substituted phenyl.

[0032] In one particular embodiment, with respect to the compound of formula I, $R^3$ is CF$_3$.

[0033] In one particular embodiment, with respect to the compound of formula I, $R^3$ is halo. In another embodiment, $R^3$ is Cl.

[0034] In one particular embodiment, with respect to the compound of formula I, $R^3$ is $S(0)\_x\cdot R^{3a}$. In
one embodiment, x is 0. In another embodiment, x is 1. In yet another embodiment x is 2. In one particular embodiment, $R^{2b}$ is alkyl.

[0035] In a particular embodiment, the compound according to formula Va-Vg:

![Chemical structures](attachment:chemical_structures.png)

and wherein $R^{2a}$, $R^{2b}$, $R^4$, n, and $L^2$ are as described for formula I; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof; provided that

i) when the compound is according to formula Vd or Ve, $L^2$ is -O-, $R^{2a}$ is H, and $R^{2b}$ is unsubstituted benzyl, then n is other than 0; and

ii) when the compound is according to formula Vd or Ve, $L^2$ is -O-, and one of $R^{2a}$ and $R^{2b}$ is n-Bu, and the other is H, unsubstituted alkyl, unsubstituted aralkyl, or unsubstituted heteroarylalkyl; then n is other than 0.

[0036] In one particular embodiment, with respect to the compound of formula I, the compound is according to formula Via, VIb, Vic, VId, Vie, Vlf, or VIg:
and wherein $R^{2a}$, $R^{2b}$, $R^4$, $n$, and $L^2$ are as described for formula I; and $R^1$ is CN, substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof; provided that when the compound is according to formula VIg, $L^2$ is -0-, $R^1$ is tetrazolyl, then $n$ is other than 0.

[0037] In a further aspect of the invention, a compound of the invention is disclosed having a formula XVIII:

wherein:
each R¹ and R² is independently unsubstituted C¹-C⁴ alkyl or unsubstituted benzyl;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and
tautomers thereof;
provided that when R¹ is Me, and R² is n-Bu at the same time; then the compound is in a form of a
sodium, potassium, calcium, ammonium or magnesium salt.

[0038] In a further aspect, the present invention provides compounds according to formula:

![Chemical Structure]

or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers
thereof.

[0039] In a further aspect, the present invention provides pharmaceutical compositions comprising a
compound of the invention, and a pharmaceutical carrier, excipient or diluent. Moreover, a compound of
the present invention useful in the pharmaceutical compositions and treatment methods disclosed herein,
is pharmaceutically acceptable as prepared and used. In this aspect of the invention, the pharmaceutical
composition may additionally comprise further active ingredients suitable for use in combination with a
compound of the invention.

[0040] In another aspect of the invention, this invention provides novel compounds of the invention
for use in therapy.

[0041] Embodiments of the present invention provide a pharmaceutical composition comprising a
compound of formula I, a pharmaceutically acceptable salt, solvate, tautomer, hydrate, or combination
thereof and a pharmaceutically acceptable carrier, excipient, or diluent.

[0042] In one embodiment of the invention, the compounds described herein may be formulated into
compositions. Preferably, the composition will comprise a carrier, excipient, stabilizer, and/or solubilizer.
In a preferred embodiment, the composition may be a pharmaceutical composition.

[0043] In one embodiment of the invention, the compounds described herein may have little or no
diuretic effect. Particularly, the compounds described herein may have little or no diuretic effect as
compared a diuretic compound, such as bumetanide, furosemide, azosemide, torsemide, or piretanide. In
a particular embodiment, the compounds described herein may have less than 1, 5, 10, 20, 30, 40, or 50%
of the diuretic activity of a diuretic compound, such as bumetanide, furosemide, azosemide, torsemide, or
piretanide.

[0044] In another embodiment, the invention relates to a method for treating addictive disorders,
Alzheimer’s Disease, anxiety disorders, ascites, autism, bipolar disorder, cancer, depression, edema,
endothelial corneal dystrophy, epilepsy, glaucoma, Huntington’s Disease, inflammatory pain, insomnia,
ischemia, migraine with aura, migraine, migraine without aura, neuropathic pain, nociceptive neuralgia,
nociceptive pain, itch, excessive itch, pruritis, neuropathic pruritis, ocular diseases, pain, Parkinson's disease, personality disorders, postherpetic neuralgia, psychosis, schizophrenia, seizure disorders, tinnitus, or withdrawal syndromes comprising administering an effective amount of a compound of invention.

In another aspect, the invention relates to a method of inhibiting the Na⁺K⁺Cl⁻ cotransporters comprising administering an effective amount of a compound of the present invention.

The present invention also provides methods of using the compounds of invention for treating disorders involving the Na⁺K⁺Cl⁻ co-transporters including but not limited to addictive disorders (e.g., compulsive disorders, eating disorders (e.g., obesity), addiction to narcotics/physical dependence, alcohol addiction, narcotic addiction, cocaine addiction, heroin addiction, opiate addiction, alcoholism, and smoking); anxiety disorders (e.g., anxiety, acute anxiety, panic disorder, social anxiety disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), generalized anxiety disorder, and specific phobia); ascites (e.g., peritoneal cavity fluid, peritoneal fluid excess, hydroperitoneum, abdominal dropsy, cancer related to ascites, tumors related to ascites); bipolar disorder (e.g., manic-depressive illness, manic phase, depressive phase, mixed bipolar state, bipolar I disorder, bipolar II disorder, rapid-cycling bipolar disorder); cancer (e.g., tumors, cancer related to ascites, tumors related to ascites); depression (e.g., psychotic depression, postpartum depression, seasonal affective disorder (SAD), cortical spreading depression, dysthymia (mild depression)); edema (e.g., central nervous system edema); endothelial corneal dystrophy (e.g., post-chamber ocular diseases); epilepsy (e.g., seizures, epileptic seizures, a seizure cluster, an acute seizure (e.g., status epilepticus), seizure disorder, and other neurological disorders involving seizures (e.g., cerebral palsy, Ohtahara Syndrome)); glaucoma (e.g., increased intraocular pressure, angle-closure glaucoma, neovascular glaucoma, open-angle glaucoma); ischemia (e.g., cardiac ischemia (myocardial ischemia), intestinal ischemia, mesenteric artery ischemia (acute mesenteric ischemia), hepatic ischemia, and cerebral ischemia (brain ischemia)); migraine (e.g., migraine including headache, migraine variant, migraine headache, cervical migraine syndrome, acute confusional migraine, migraine with aura, migraine without aura); neuropathic pain (e.g., diabetic neuropathy, nerve injury, nerve tract injury, neuropathic pain associated with visceral and/or somatic pain, peripheral neuropathy, chemotherapy-induced neuropathy, chemotheraphy-induced peripheral neuropathy, neuralgia, polyneuropathy, mononeuropathy, mononeuritis multiplex, autonomic neuropathy, symmetrical peripheral neuropathy, radiculopathy, large fiber peripheral neuropathy, small fiber peripheral neuropathy, idiopathic neuropathic pain); nociceptive neuralgia; itch, excessive itch, pruritis, neuropathic pruritis, ocular diseases (e.g., diseases of retina-retinal detachment and injury response; diseases of electrical transmission between various retinal elements such as rods, cones, amacrine and horizontal cells, activity of retinal ganglion cells, dysfunction of Müller (glial) cells, abnormal function of the retinal pigment epithelium; dysfunction of formation of the retina in development and the appropriate maintenance of neural connections following maturation and development; regulation of normal electrolyte homeostasis in various chorioretinal and vitreoretinal diseases; abnormal function of Müller cells in diabetic...
retinopathy; loss of normal electrical activity in degenerative diseases of retina, inherited and those of unknown etiology; inflammatory diseases and conditions of the eye such as chorioretinitis, multiple sclerosis; infectious processes in the eye with abnormal inflammatory and injury responses; uveitis; abnormal function of Muller cells of retina and disease thereof; dysfunction of RPE-retinal pigment epithelium (e.g., diseases of RPE); endothelial (posterior) corneal dystrophies, which result from primary endothelial dysfunction. (e.g., Fuchs endothelial corneal dystrophy (FECD), posterior polymorphous corneal dystrophy (PPCD) and congenital hereditary endothelial dystrophy (CHED)); retinitis pigmentosa; age-related macular degeneration (e.g., dry age-related macular degeneration, exudative age-related macular degeneration, and myopic degeneration); retinopathy (e.g., diabetic retinopathy, proliferative vitreoretinopathy, and toxic retinopathy) and diseases of aqueous humor formation (e.g., glaucoma); pain (e.g., chronic inflammatory pain, pain associated with arthritis, fibromyalgia, back pain, cancer-associated pain, chemotherapy-induced neuropathy, chemotherapy-induced peripheral neuropathy, HIV-treatment induced neuropathy, HIV-treatment induced neuralgia, pain associated with digestive disease, pain associated with Crohn's disease, pain associated with autoimmune disease, pain associated with endocrine disease, pain associated with diabetic neuropathy, pain associated with shingles or herpes zoster, phantom limb pain, spontaneous pain, chronic post-surgical pain, chronic temporomandibular pain, causalgia, postherpetic neuralgia, AIDS-related pain, complex regional pain syndromes type I and II, trigeminal neuralgia, chronic back pain, pain associated with spinal cord injury and/or recurrent acute pain); postherpetic neuralgia (e.g., shingles, herpes zoster); and schizophrenia. In a preferred embodiment, these compounds are selective antagonists of NKCC1.

[0047] The present invention also provides methods of using the compounds of invention for treating disorders involving a GABA_A receptor in which a presynaptic-specific action may be desirable including but not limited to Alzheimer's Disease (AD), addictive disorders (e.g., compulsive disorders, eating disorders (e.g., obesity, anorexia nervosa, bulimia), addiction to narcotics/physical dependence, alcohol addiction, narcotic addiction, cocaine addiction, heroin addiction, opiate addiction, alcoholism, and smoking); anxiety disorders (e.g., anxiety, acute anxiety, panic disorder, social anxiety disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), generalized anxiety disorder, and specific phobia); autism (e.g., Autism spectrum disorder (ASD)); bipolar disorder (e.g., manic-depressive illness, manic phase, depressive phase, mixed bipolar state, bipolar I disorder, bipolar II disorder, rapid-cycling bipolar disorder, bipolar I disorder, bipolar II disorder); depression (e.g., psychotic depression, postpartum depression, seasonal affective disorder (SAD), cortical spreading depression, dysthymia (mild depression)); epilepsy (e.g., seizures, epileptic seizures, a seizure cluster, an acute seizure (e.g., status epilepticus), seizure disorder, and other neurological disorders involving seizures (e.g., cerebral palsy, Ohtahara Syndrome)); Huntington's Disease (HD) (e.g., Huntington's chorea); insomnia, migraine (e.g., migraine including headache, migraine variant, migraine headache, cervical migraine syndrome, acute confusional migraine, migraine with aura, migraine without aura, chronic migraine, transformed...
migraine); neuropathic pain (e.g., diabetic neuropathy, cluster headache, nerve injury, nerve tract injury, neuropathic pain associated with visceral and/or somatic pain, peripheral neuropathy, chemotherapy-induced neuropathy, chemotherapy-induced peripheral neuropathy, HIV-treatment induced neuropathy, HIV-treatment induced neuralgia, neuralgia, polyneuropathy, mononeuropathy, mononeuritis multiplex, autonomic neuropathy, symmetrical peripheral neuropathy, radiculopathy, large fiber peripheral neuropathy, small fiber peripheral neuropathy, idiopathic neuropathic pain); nociceptive pain; pain (e.g., acute pain, acute inflammatory pain, chronic inflammatory pain, pain associated with arthritis, fibromyalgia, back pain, cancer-associated pain, chemotherapy-induced neuropathy, chemotherapy-induced peripheral neuropathy, pain associated with digestive disease, pain associated with Crohn's disease, pain associated with autoimmune disease, pain associated with endocrine disease, pain associated with diabetic neuropathy, pain associated with shingles or herpes zoster, phantom limb pain, spontaneous pain, chronic post-surgical pain, chronic temporomandibular pain, causalgia, postherpetic neuralgia, AIDS-related pain, complex regional pain syndromes type I and II, trigeminal neuralgia, chronic back pain, pain associated with spinal cord injury, incisional post operative, trauma associated, burns, recurrent acute pain, head pain, headache, nonmigrainous, specific non-migraine head pains, tic doloureux, postherpetic neuralgia, ice pick headache); Parkinson's disease, personality disorders, psychosis, seizure disorders, personality disorders, schizophrenia, tinnitus, and withdrawal syndromes (e.g., alcohol withdrawal syndrome, nicotine withdrawal syndrome, opioid withdrawal syndrome, benzodiazepine withdrawal syndrome, methadone withdrawal syndrome, SSRI discontinuation syndrome, hydrocodone withdrawal syndrome, cocaine withdrawal syndrome, heroin withdrawal syndrome).

[0048] The present invention further provides methods for treating a patient diagnosed with risk factors for a condition selected from the group consisting of addictive disorders, Alzheimer's Disease, anxiety disorders, ascites, autism, bipolar disorder, cancer, depression, endothelial corneal dystrophy, edema, epilepsy, glaucoma, Huntington's Disease, inflammatory pain, insomnia, ischemia, migraine, migraine with aura, migraine without aura, neuropathic pain, nociceptive neuralgia, nociceptive pain, ocular diseases, pain, Parkinson's disease, personality disorders, postherpetic neuralgia, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes comprising administering an effective amount of a compound of invention.

[0049] Embodiments of the present invention provide kits including the compounds including compounds described herein. These kits may be used in the treatment methods disclosed herein. In another embodiment, the kits may include instructions, directions, labels, warnings, or information pamphlets.

[0050] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed descriptions set forth herein.

**Brief Description of the Drawings**

[0051] FIGURE 1 depicts the results of a marble burying model of anxiety using several compounds
described herein: NTP-8012, NTP-8020, and NTP-8025 as compared to CLOBAZAM (positive control) and vehicle (negative control). A decrease in the number of marbles buried is indicative of a reduction in anxiety. NTP-8012, NTP-8020, and NTP-8025 exhibit anxiolytic effects.

FIGURE 2 depicts the results of an MTLE model of epilepsy using several compounds described herein: NTP-12001, NTP-12002, NTP-16004, NTP-8001, NTP-8009, NTP-8010, NTP-8012, NTP-8014, NTP-8018, NTP-8020, NTP-8023, NTP-8025, NTP-8034, NTP-8055, NTP-8059, NTP-8067, and NTP-8135 as compared vehicle (negative control). The Y-axis shows the percent reduction of seizures, with a lower score as indicative of anti-seizure activity. NTP-16004, NTP-8010, NTP-8012, NTP-8014, NTP-8020, NTP-8023, NTP-8025, NTP-8034, NTP-8055, NTP-8059, NTP-8067, and NTP-8135 exhibit anti-seizure effects in a MTLE model of epilepsy and may be expected to show anti-seizure effects in patients.

FIGURE 3 depicts the results of a formalin paw mode! (both early phase and late phase) using several compounds described herein: NTP-8051, NTP-8055, NTP-8059, NTP-8135, and NTP-8137 as compared to gabapentin (positive control) and vehicle (negative control). These compounds exhibit antinociceptive effects in persistent pain in both the early phase, which reflects direct activation of nociceptors, and in the late phase, which is indicative of inflammatory pain. Antinociceptive effects are represented as a decrease in hind paw licking time (e.g., reduction in response to painful stimuli in the hind paw from the formalin injection). Thus, NTP-8051, NTP-8055, NTP-8059, NTP-8135, and NTP-8137 show antinociceptive effects in persistent pain involving both acute and inflammatory/neuropathic pain.

FIGURE 4A-D depicts the results of a formalin paw model using several compounds described herein show antinociceptive effects: (4A) NTP-16031, NTP-16033 as compared to gabapentin (positive control) and vehicle (negative control); (4B) NTP-8001, NTP-8002, NTP-8012, NTP-8020, and NTP-12001 as compared to gabapentin (positive control) and vehicle (negative control); (4C) NTP-16024, NTP-8067, NTP-8177, and NTP-8087 as compared to gabapentin (positive control) and vehicle (negative control); and (4D) NTP-8023, NTP-8025, NTP-8030, NTP-8034, and NTP-16004 as compared to gabapentin (positive control) and vehicle (negative control). Antinociceptive effects are represented as an increase shown in the Y-axis (e.g., a higher value is indicative of an antinociceptive effect). Thus, several of the compounds described herein exhibit antinociceptive effects in persistent pain.

FIGURE 5A-H depicts the results of a tail flick model of nociception where several compounds described herein exhibit antinociceptive effects: (5A) NTP-8001 at 52.44 mg/kg; (5B) NTP-8002 at 45.31 mg/kg; (5C) NTP-8009 at 54.20 mg/kg; (5D) NTP-8010 at 56.75 mg/kg; (5E) NTP-8012 at 54.20 mg/kg; (5F) NTP-8013 at 47.12 mg/kg; (5G) NTP-8014 at 55.95 mg/kg; and (5H) NTP-8015 at 48.94 mg/kg. Antinociceptive effects are represented as an increase the mean % antinoceception (reduced sensitivity to painful stimuli) shown in the Y-axis. This data demonstrates that NTP-8001, NTP-8002, NTP-8009, NTP-8010, NTP-8012, NTP-8013, NTP-8014, and NTP-8015 exhibit antinociceptive effects
in acute pain.

[0056] FIGURE 6 depicts the results of an amphetamine hyperactivity model of schizophrenia using several compounds described herein: NTP-8020, NTP-8025, NTP-16004 as compared vehicle (negative control) and amphetamine (negative control—known to increase the number of crossings), and haloperidol (positive control—antipsychotic). A decrease in the number of crossings is indicative of a reduction in hyperactivity. This data shows that NTP-8020, NTP-8025, NTP-16004 reduce hyperactivity and may have similar effects in schizophrenia and other neuropsychiatric disorders.

Detailed Description of the Invention

[0057] The foregoing and other aspects of the present invention will now be described in more detail with respect to embodiments described herein. It should be appreciated that the invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

Definitions

[0058] The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the embodiments of the invention and the appended claims, the singular forms "a," "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Also, as used herein, "and/or" refers to and encompasses any and all possible combinations of one or more of the associated listed items. Furthermore, "about," as used herein when referring to a measurable value such as an amount of a compound, dose, time, temperature is meant to encompass variations of 20%, 10%, 5%, 1%, 0.5%, or even 0.1% of the specified amount. Unless otherwise defined, all terms, including technical and scientific terms used in the description, have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0059] "Administration" as used herein, refers broadly to any means by which a composition is given to a patient. A preferred route of administration is oral, and unless otherwise indicated, any reference herein to "administration" includes "oral administration."

[0060] When describing the compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms have the following meanings unless otherwise indicated. It should also be understood that 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. It should be further understood that the terms "groups" and "radicals" can be considered interchangeable when used herein.

[0061] "Acyl" refers to a radical -C(0)R, where R is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylialkyl as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl,
benzylcarbonyl and the like.

[0062] "Acylamino" refers to a radical -NR\(^2\)C(0)R\(^{22}\), where R\(^2\) is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroaryalkyl and R\(^{22}\) is hydrogen, alkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroaryalkyl, as defined herein. Representative examples include, but are not limited to, formyamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino, benzylcarbonylamino and the like.

[0063] "Acyloxy" refers to the group -O-C(0)R\(^2\) where R\(^2\) is hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, alkoxy, heteroalkyl, heteroaryl, or heteroaryalkyl.

[0064] "Substituted alkenyl" includes 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, alkoxy, substituted alkoxy, alkoxy carbonylamino, substituted alkoxy carbonylamino, amino, substituted amino, amino carbonylamino, amino carbonyloxy, aryl, acyloxy, aminocarbonylamino, aminocarbonyloxy, aryl, acyloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryl, thiol, thiol, alkyl-S(0)-, alkyl-S(0)-, alkyl-S(0)-, and alkyl-S(0)-.

[0065] "Alkoxy" refers to the group -OR\(^2\) where R\(^2\) is alkyl. Particular alkoxy groups include, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

[0066] "Substituted alkoxy" includes those groups recited in the definition of "substituted" herein, and particularly refers to an alkoxy 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, alkoxy, substituted alkoxy, alkoxy carbonylamino, substituted alkoxy carbonylamino, amino, substituted amino, amino carbonylamino, amino carbonyloxy, aryl, acyloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, heteroaryl, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryl, thiol, thiol, alkyl-S(0)-, alkyl-S(0)-, alkyl-S(0)-, and alkyl-S(0)-.

[0067] "Alkoxy carbonylamino" refers to the group -NR\(^2\)-C(0)R\(^{22}\), where R\(^2\) is hydrogen, alkyl, aryl or cycloalkyl, and R\(^{22}\) is alkyl or cycloalkyl.

[0068] "Alkyl" refers to monovalent saturated alkane radical groups particularly having up to about 11 carbon atoms, more particularly as a lower alkyl, from 1 to 8 carbon atoms and still more particularly, from 1 to 6 carbon atoms. The hydrocarbon chain may be either straight-chained or branched. This term is exemplified by groups such as methyl, ethyl, \(^{\wedge}\)-propyl, isopropyl, n-butyl, \(\text{iso-}\)-butyl, iert-butyl, \(\text{i-}\)-hexyl, \(\text{i-}\)-octyl, fert-octyl and the like. The term "lower alkyl" refers to alkyl groups having 1 to 6 carbon atoms. The term "alkyl" also includes "cycloalkyls" as defined below.

[0069] "Substituted alkyl" includes 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, selected from the group consisting of acyl, acylammo, acyloxy, alkoxo, substituted alkoxo, alkoxyacarbonyl, alkoxyacylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, ary1, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, heteroaryl, keto, nitro, thioalkoxy, substituted thiaoalkoxy, thiaoxyloxy, thioketo, thiol, alkyl-S(O)-, ary1-S(O)-, alkyl-S(O)2, and ary1-S(O)2.

[0070] "Alkylene" refers to divalent saturated alkenie 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.

[0071] "Substituted alkylene" includes 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, alkoxo, substituted alkoxo, alkoxyacarbonyl, alkoxyacylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, ary1, aryloxy, azido, carboxyl, cyano, halogen, hydroxyl), keto, nitro, thioalkoxy, substituted thiaoalkoxy, thiaoxyloxy, thioketo, thiol, alkyl-S(O)-, ary1-S(O)-, alkyl-S(O)2, and ary1-S(O)2.

[0072] "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((¼)= (¼)), vinyl and substituted vinyl, and the like.

[0073] "Alkenylene" refers to divalent olefinically unsaturated hydrocarbyl groups particularly having up to about 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 ethylene (-CH=CH2), the propylene isomers (e.g., -CH=CHCH2- and -C(CH3)=CH- and -CH=C(CH3)2) and the like.

[0074] "Alkynyl" refers to acetylenically or alkynically unsaturated hydrocarbyl groups particularly 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 acetylenic, ethynyl (-C≡CH), propargyl (-CH2C≡CH), and the like.

[0075] "Substituted alkynyl" includes 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, alkoxo, substituted alkoxo, alkoxyacarbonyl, alkoxyacylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, ary1, aryloxy, azido, carboxyl, cyano,
cycloalkyl, substituted cycloalkyl, halogen, hydroxy], keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioaryl, alkyl-S(O)-, ary1-S(O)-, alkyl-S(0) 2- and ary1-S(0) 2-.

[0076] "Alkanoyl" or "acyl" as used herein refers to the group R 25-C(0)-, where R 27 is hydrogen or alkyl as defined above.

[0077] "Aryl" refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthenes, fluorene, hexacene, hexaphie, hexalene, 1,6-indacene, 9-indene, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. Particularly, an aryl group comprises from 6 to 14 carbon atoms.

[0078] "Substituted Aryl" includes 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, selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkoxy carbonyl, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminocarbonyl, aminocarboxyleno, aminocarbonyloxy, ary1, ary1oxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxy], nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioaryl, alkyl-S(O)-, ary1-S(O)-, alkyl-S(0) 2- and ary1-S(0) 2-.

[0079] "Fused Aryl" refers to an aryl having two of its ring carbon in common with a second aryl ring or with an aliphatic ring.

[0080] "Alkaryl" refers to an aryl group, as defined above, substituted with one or more alkyl groups, as defined above.

[0081] "Aralkyl" or "ary1alkyl" refers to an alkyl group, as defined above, substituted with one or more aryl groups, as defined above.

[0082] "Aryl amine" refers to -O-aryl groups wherein "aryl" is as defined above.

[0083] "Alkylamino" refers to the group alkyl-NR 28R 29, wherein each of R 28 and R 29 are independently selected from hydrogen and alkyl.

[0084] "Arylamino" refers to the group ary1-NR 30R 31, wherein each of R 20 and R 31 are independently selected from hydrogen, aryl and heteroaryl.

[0085] "Alkoxyamino" refers to a radical -N(II)OR 32 where R 32 represents an alkyl or cycloalkyl group as defined herein.

[0086] "Alkoxy carbonyl" refers to a radical -C(0)alkoxy where alkoxy is as defined herein.

[0087] "Alkylarylamino" refers to a radical -NR 33R 34 where R 33 represents an alkyl or cycloalkyl group and R 34 is an aryl as defined herein.
"Alkylsulfonyl" refers to a radical -S(0) R where R is an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl and the like.

"Alkylsulfinyl" refers to a radical -S(0) R where R is an alkyl or cycloalkyl group as defined herein. Representative examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl and the like.

"Alkylthio" refers to a radical -SR where R is an alkyl or cycloalkyl group as defined herein that may be optionally substituted as defined herein. Representative examples include, but are not limited to, methylthio, ethylthio, propylthio, butylthio, and the like.

"Aminocarbonyl" refers to the group -C(0)NR R where each R is independently hydrogen, alkyl, aryl, cycloalkyl, or where the R groups are joined to form an alkylene group. When both R groups are hydrogen, -N(R=H) 2 is a mono group.

"Aminocarbonylamino" refers to the group -NR C(0)NR R where each R is independently hydrogen, alkyl, aryl or cycloalkyl, or where two R groups are joined to form an alkylene group.

"Aminocarbonyloxy" refers to the group -OC(0)NR where each R is independently hydrogen, alkyl, aryl or cycloalkyl, or where the R groups are joined to form an alkylene group.

"Arylamino" means a radical -NH R where R represents an aryl group as defined herein.

"Aryloxycarbonyl" refers to a radical -C(0)-O-aryl where aryl is as defined herein.

"Arylsulfonyl" refers to a radical -S(0)- R where R is an aryl or heteroaryl group as defined herein.

"Azido" refers to the radical -N 3.

"Bicycloaryl" refers to a monocyclic aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent bicycloaromatic ring system. Typical bicycloaryl groups include, but are not limited to, groups derived from indane, indene, naphthalene, tetrahydroquinolene, and the like. Particularly, an aryl group comprises from 8 to 11 carbon atoms.

"Bicycloheteroaryl" refers to a monocyclic bicycloheteroaromatic group derived by the removal of one hydrogen atom from a single carbon atom of a parent bicycloheteroaromatic ring system. Typical bicycloheteroaryl groups include, but are not limited to, groups derived from benzofuran, benzimidazole, benzindazole, benzodioxane, chromene, chromane, cinnoline, phthalazine, indole, indoline, indolizine,
isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, benzothiazole, benzoxazole, naphthyridine, benzoxadiazole, pteridine, purine, benzopyran, benzopyrazine, pyridopyrimidine, quinazoline, quinoline, quinolizine, quinoxaline, benzomorphan, tetrahydroisoquinoline, tetrahydroquinoline, and the like. Preferably, the bicyclobenzoaryl group is between 9-11 membered bicycloheteroaryl, with 5-10 membered heteroaryl being particularly preferred. Particular bicycloheteroaryl groups are those derived from benzothiophene, benzofuran, benzothiazole, indole, quinoline, isoquinoline, benzimidazole, benzoxazole and benzodiazone.

[0103] “Biocompatible polymer” as used herein refers broadly to a polymer moiety that is substantially non-toxic and does not tend to produce substantial immune responses, clotting or other undesirable effects. Accordingly to some embodiments of the present invention, polyalkylene glycol is a biocompatible polymer where, as used herein, polyalkylene glycol refers to straight or branched polyalkylene glycol polymers such as polyethylene glycol, polypropylene glycol, and polybutylene glycol, and further includes the monoalkylenher of the polyalkylene glycol. In some embodiments of the present invention, the polyalkylene glycol polymer is a lower alkyl polyalkylene glycol moiety such as a polyethylene glycol moiety (PEG), a polypropylene glycol moiety, or a polybutylene glycol moiety. PEG has the formula \( \text{H}_2 \left( \text{C}_\text{n} \text{H}_\text{4}\right) \text{O}_\text{n} \text{H} \), where \( n \) can range from about 1 to about 4000 or more. In some embodiments, \( n \) is 1 to 100, and in other embodiments, \( n \) is 5 to 30. The PEG moiety can be linear or branched. In further embodiments, PEG can be attached to groups such as hydroxyl, alkyl, aryl, acyl, or ester. In some embodiments, PEG can be an alkoxy PEG, such as methoxy-PEG (or mPEG), where one terminus is a relatively inert alkoxy group, while the other terminus are a hydroxyl group.

[0104] “Carbamoyl” refers to the radical \(-\text{C}(\text{O})\text{N}(\text{R}^42)_2\) where each \( \text{R}^42 \) group is independently hydrogen, alkyl, cycloalkyl or aryl, as defined herein, which may be optionally substituted as defined herein.

[0105] “Carboxy” refers to the radical \(-\text{C}(\text{O})\text{OH}\).

[0106] “Carboxyamino” refers to the radical \(-\text{N}(\text{H})\text{C}(\text{O})\text{OH}\).

[0107] “Cycloalkyl” refers to cyclic hydrocarbyl groups having from 3 to about 10 carbon atoms and having a single cyclic ring or multiple condensed rings, including fused and bridged ring systems, which optionally can be substituted with from 1 to 3 alkyl groups. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, and multiple ring structures such as adamantanyl, and the like.

[0108] “Substituted cycloalkyl” includes 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, selected from the group consisting of acy, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxyacarbonyl, alkoxy carbamoylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano,
cycloalkyl, substituted cycloalkyl, halogen, hydroxy!, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alky!-S(0)_2 and aryl-S(0)_2.

[0109] "Cycloalkoxy" refers to the group -OR where R^3 is cycloalkyl. Such cycloalkoxy groups include, by way of example, cyclopentoxy, cyclohexoxy and the like.

[0110] "Cycloalkenyl" 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 cycloalkenyl groups include, by way of example, single ring structures such as cyclohexenyl, cyclopentenyl, cyclopropenyl, and the like.

[0111] "Substituted cycloalkenyl" includes those groups recited in the definition of "substituted" herein, and particularly refers to a cycloalkenyl 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, aerylino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, aikoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, aminocarbonyloxy, aryl, aryloxy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioketo, thiol, alkyl-S(O)-, aryl-S(O)-, alky!-S(0)_2 and aryl-S(0)_2.

[0112] "Fused Cycloalkenyl" refers to a cycloalkenyl having two of its ring carbon atoms in common with a second aliphatic or aromatic ring and having its olefinic unsaturation located to impart aromaticity to the cycloalkenyl ring.

[0113] "Cyanato" refers to the radical -OCN.

[0114] "Cyano" refers to the radical -CN.

[0115] "Dialkylamino" means a radical -NR^4R^5 where R^4 and R^5 independently represent an alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, or substituted heteroaryl group as defined herein.

[0116] "Effective amount" or "effective," as used herein, refers broadly to a dose that causes a relief of symptoms of a disease or disorder as noted through clinical testing and evaluation, patient observation, and/or the like. "Effective amount" or "effective" further can further designate a dose that causes a detectable change in biological or chemical activity. The detectable changes may be detected and/or further quantified by one skilled in the art for the relevant mechanism or process. Moreover, "effective amount" or "effective" can designate an amount that maintains a desired physiological state, i.e., reduces or prevents significant decline and/or promotes improvement in the condition of interest. As are generally understood in the art, the dosage will vary depending on the administration routes, symptoms, and body weight of the patient but also depending upon the compound being administered.

[0117] "Ethynyl" refers to substituted or unsubstituted -(C≡C)-.

[0118] "Ethylene" refers to substituted or unsubstituted -(C=C)-.

[0119] "Ethynyl" refers to -(C≡C)-.
"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo. Preferred halo groups are either fluoro or chloro.

"Hydroxy" refers to the radical -OH.

"Nitro" refers to the radical -NO₂.

"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 include, but are not limited to, -X, -R⁴, -O⁻, =0, -OR⁴, -SR⁴, -S⁻, =S, -NR⁴R⁵⁺, =NR⁴, -CX₃, -CF₃, -CN, -OCN, -SCN, -NO, -NO₂, =N₂, -N₃, -S(O)₂⁻, =S(O)₂OH, -S(O)₂R⁴, -OS(O)₂R⁴⁺, -P(O)(0)R⁴⁻, -P(O)(OR₄)₂⁻, -OP(0)(OR₄)(OR⁴⁺), -C(O)R⁴⁺, -C(S)R⁴⁺, -C(O)OR⁴⁺, -C(O)NR⁴⁺, -C(O)O⁻, -C(S)OR⁴⁺, -NR⁴(S)NR⁴⁺, -S(O)₂C(S)NR⁴⁺, -NR⁴C(S)NR⁴⁺, -NR⁴C(NR⁴⁺)NR⁴⁺, and -C(NR⁴⁺)NR⁴⁺, where each X is independently a halogen; each R⁴⁺, R⁴⁺, R⁴⁺ and R⁴⁺ are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heterocyloalkyi, substituted heterocyloalkyi, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroaryalkyl, substituted heteroaryalkyl, heteroarylalkyl, substituted heteroarylalkyl, heterocycloalkyi, substituted heterocycloalkyi, heteroalkyl, substituted heteroalkyl, cycloalkyl, substituted alkyl, heterocyloalkyi, substituted heterocycloalkyi, heteroaryalkyl, substituted heteroaryalkyl, heteroaryl, substituted heteroaryl, heteroaryalkyl or substituted heteroaryalkyl.

Examples of representative substituted aryls include the following:

[0120]

In these formulae one of R⁵² and R⁵³ may be hydrogen and at least one of R⁵² and R⁵³ is each independently selected from alkyl, alkynyl, heterocyloalkyi, alkanoyl, alkoxy, aryloxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, NR⁵⁴COR⁵⁵, NR⁵⁴SOR⁵⁵, NR⁵⁴S₀₂R⁵⁷, COOalkyl, COOaryl, CONR⁵⁵, CONR⁵⁴OR⁵⁵, NR⁵⁴R⁵⁵, S₀₂NR⁵⁴R⁵⁵, S-alkyl, S-aryl, SOalkyl, S₀₉S₀₂aryl; or R⁵² and R⁵³, may be joined to form 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. R⁵⁴, R⁵⁵, and R⁵⁶ are independently hydrogen, alkyl, alkenyi, alkylnyi, perfluoroalkyl, cycloalkyl, heterocyloalkyi, aryl, substituted aryl, heteroaryl, substituted or hetero alkyl or the like.

"Hetero" when used to describe a compound or a group present on a compound 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. heteroalkyl, cycloalkyl, e.g. heterocyloalkyi, aryl, e.g. heteroaryl, cycloalkenyi, cycloheteroalkenyi, and
the like having from 1 to 5, and especially from 1 to 3 heteroatoms.

[0127] "Heteroaryl" refers to a monovalent heteroaromatic group derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, arsindole, carbazole, β-carboline, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, pthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. Preferably, the heteroaryl group is between 5-15 membered heteroaryl, with 5-10 membered heteroaryl being particularly preferred. Particular heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzo furan, indole, pyridine, quinoline, imidazole, oxazole and pyrazine.

[0128] Examples of representative heteroaryls include the following:

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[diagram of heteroaryls]
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wherein each Y is selected from carbonyl, N, NR, O, and S; and R is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroalkyl or the like.

[0129] "Heterocycloalkyl," as used herein, refers broadly to a stable heterocyclic non-aromatic ring and fused rings containing one or more heteroatoms independently selected from N, O and S. 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, piperazinyl, homopiperazinyl, piperidinyl and morpholiny], and are shown in the following illustrative examples:
wherein each $X_i$ is selected from $\text{C}_R^\text{NR}, \text{O}$ and $\text{S}$; and each $Y_i$ is selected from $\text{NR}^\text{S}$, $\text{O}$ and $\text{S}$; and $R^5$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroalkyl or the like. These heterocycloalkyl rings may be optionally substituted with one or more groups selected from the group consisting of acyl, acylamino, acyloxy, alkoxy, substituted alkoxy, alkoxycarbonyl, alkoxycarbonylamino, amino, substituted amino, aminocarbonyl, aminocarbonylamino, ammocarbonyloxy, aryl, arylxoy, azido, carboxyl, cyano, cycloalkyl, substituted cycloalkyl, halogen, hydroxyl, keto, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thiokeeto, thiol, alkyl-S(O)-, aryl-S(O)-, aikyl-S(O)2 and aryl-S(O)2. Substituting groups include carbonyl or thiocarbonyl which provide, for example, lactam and urea derivatives.

[0130] Examples of representative cycloheteroalkenyls include the following:

wherein each $X$ is selected from $\text{C}_R^\text{NR}, \text{O}$ and $\text{S}$; and each $Y$ is selected from $\text{NR}_5^\text{S}$, $\text{O}$ and $\text{S}$; and $R^5_i$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroalkyl or the like.

[0131] Examples of representative aryl having hetero atoms containing substitution include the following:

wherein each $X$ is selected from $\text{C}_R^\text{NR}, \text{O}$ and $\text{S}$; and each $Y$ is selected from $\text{NR}_5^\text{S}$, $\text{O}$ and $\text{S}$; and $R^5_i$ is independently hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, heteroalkyl or the like.
"Hetero substituent" refers to a halo, O, S or N atom-containing functionality that may be present as an R^4 in a R^1C group present as substituents directly on A, B, W, Y or Z of the compounds of this invention or may be present as a substituent in the "substituted" aryl and aliphatic groups present in the compounds.

Examples of hetero substituents include:
- halo,
- NO_2, -NH_2, -NHR, -NR(R^8)_2,
- NRCOR, -NR^3S^9OR, -NR^3SO_3R^9, OH, CN,
- C=O, H,
- R^9, -OH, -0-R, -COOR,
- CON(R^8)_2, -CONROR,
- S0_3H, -R^9S, -SO_3N(R^9)_2,
- S(0)R^5, -S(0)R^9

wherein each R^9 is independently an aryl or aliphatic, optionally with substitution. Among hetero substituents containing R^9 groups, preference is given to those materials having aryl and alky! R^9 groups as defined herein. Preferred hetero substituents are those listed above.

"Hydrogen bond donor" group refers to a group containing O-H, or N-H functionality. Examples of "hydrogen bond donor" groups include -OH, -NH_2, and -NH-R^9 and wherein R^9 is alkyl, cycloalkyl, aryl, or heteroaryl.

"Isotopic variant," as used herein, refers broadly 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 (2D 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 ^2H/2H, 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 purpose 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 ^11C, ^18F, ^15O and ^13N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

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

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".

[0138] "Mammal" as used herein, refers broadly to any and all warm-blooded vertebrate animals of the class Mammalia, including humans, characterized by a covering of hair on the skin and, in the female, milk-producing mammary glands for nourishing the young. Examples of mammals include but are not limited to alpacas, armadillos, badger, capybaras, cats, chimpanzees, chinchillas, cattle, dogs, goats, gorillas, hamsters, horses, humans, lemurs, llamas, mice, non-human primates, pigs, rats, sheep, shrews, and tapirs. Mammals include but are not limited to bovine, canine, equine, feline, murine, ovine, porcine, primate, and rodent species. Mammal also includes any and all those listed on the Mammal Species of the World maintained by the National Museum of Natural History, Smithsonian Institution in Washington DC, hereby incorporated by reference in its entirety.

[0139] "Dihydroxyphosphoryl" refers to the radical -PO(OH) 2.

[0140] "Substituted dihydroxyphosphoryl" includes those groups recited in the definition of "substituted" herein, and particularly refers to a dihydroxyphosphoryl radical wherein one or both of the hydroxyl groups are substituted. Suitable substituents are described in detail below.

[0141] "Aminohydroxyphosphoryl" refers to the radical -PO(OH)NH 2.

[0142] "Substituted aminohydroxyphosphoryl" includes 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.

[0143] "Thioalkoxy" refers to the group -SR 6 where R 60 is alkyl.

[0144] "Substituted thioalkoxy" includes those groups recited in the definition of "substituted" herein, and particularly refers to a thioalkoxy 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, alkoxy, substituted alkoxy, alkoxy carbonyl, alkoxy carbonylamino, amino, substituted amino,aminocarbonyl,aminocarbonylamino,aminocarbonyloxy,aryl,aryloxy,azido,carboxyl,cyano,cycloalkyl,substituted cycloalkyl,halogen,hydroxyl,keto,nitro,thioalkoxy,substituted thioalkoxy,thioaryl,thioketo,thiol,a'kyl-S(O) -,aryl-S(O) -,alkyl-S(0) 2 and aryl-S(0) 2.

[0145] "Sulfanyl" refers to the radical HS-. "Substituted sulfanyl" refers to a radical such as RS-wherein R is any substituent described herein.

[0146] "Sulfonyl" refers to the divalent radical -S(0) 2-. "Substituted sulfonyl" refers to a radical such as R 61 -S(0) 2 wherein R 61 is any substituent described herein. "Aminosulfonyl" or "Sulfonamide" refers to the radical H 2 N(0) 2S- and "substituted aminosulfonyl" "substituted sulfonamide" refers to a radical such as R 62 N(0) 2S- wherein each R 62 is independently any substituent described herein.

[0147] "Sulfonyl" refers to the group -SO 2R 63. In particular embodiments, R 63 is selected from H, lower alkyl, alkyl, aryl and heteroaryl.

[0148] "Thioaryl" refers to the group -SR 64 where R 64 is aryl.
"Thioketo" refers to the group =S. "Thiol" refers to the group -SH.

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.

"Parasympathic" as used herein, refers broadly to receptors (e.g., GABA_A receptors) located outside or in the perimeter of the synapse (e.g., synaptic cleft). Also, "parasympathic" refers broadly to any receptors located perisynaptically, extrasynaptically, and presynaptically.

"Pharmacologically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

"Pharmacologically acceptable salt" refers to a salt of a compound of the invention that is pharmacologically acceptable and that possesses the desired pharmacological activity of the parent compound. 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-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluensulfonic 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, hydroxynaphthoic 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 "pharmacologically acceptable cation" refers to a non toxic, acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

"Pharmacologically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.
A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" is a carrier, usually a liquid, in which an active therapeutic agent is formulated. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington. The Science And Practice of Pharmacy. 20th Edition, (Gennaro, A. R., Chief Editor), Philadelphia College of Pharmacy and Science, 2000, which is incorporated by reference in its entirety.

"Pharmaceutically acceptable carrier" or "excipient," as used herein, refers broadly to solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, sublingual, or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances are well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

"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.

"Solvate" refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. 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.

"Subject" includes humans. The terms "human," "patient" and "subject" are used interchangeably herein. A subject may be a mammal.

"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. The term "effective amount" is interchangeable with "therapeutically effective amount."

"Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or 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.

[0163] "Preventing" or "prevention" refers to a reduction in risk of acquiring a disease or disorder.

[0164] 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 preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxy carbonyl)oxy)alkylesters. Preferred are the C₁ to C₈ alky], C₂-C₈ alkenyl, aryl, C₇-C₁₂ substituted aryl, and C₇-C₁₂ arylalkyl esters of the compounds of the invention.

[0165] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable 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 levo rotatory (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".

[0166] "Substituted" as used herein refers broadly to replacement of one or more of the hydrogen atoms of the group replaced by substituents known to those skilled in the art and resulting in a stable compound as described below. Examples of suitable replacement groups include, but are not limited to, alkyl, acyl, alkenyl, alkynyl cycloalkyl, aryl, alkaryl, hydroxy, thio, alkoxy, aryloxy, acyl, amino, amido, carboxy, carboxyalkyl, thio carboxyalkyl, carboxyaryl, thio carboxyaryl, halo, o xo, mercapto, sulfanyl, sulfonyl, sulfonamido, amidino, carbamoyl, cycloalkyl, heterocycloalkyl, dialkylamin oalkyl, carboxylic acid, carboxamido, haloalkyl, di haloalkyl, tri haloalkyl, tri haloalkoxy, alkylthio, aralkyl, alkyl sulfonyl, a rylthio, amino, alkylamino, dialkylamino, guanidino, ureido, nitro and the like. Substitutions are permissible when such combinations result in compounds stable for the intended purpose. For example, substitutions are permissible when the resultant compound is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic or diagnostic agent or reagent.

[0167] "Therapy" or "therapeutic" as used herein refers broadly to treating a disease, arresting or reducing the development of the disease or its clinical symptoms, and/or relieving the disease, causing
regression of the disease or its clinical symptoms. Therapy encompasses prophylaxis, prevention, treatment, cure, regimen, remedy, minimization, reduction, alleviation, and/or providing relief from a disease, signs, and/or symptoms of a disease. Therapy encompasses an alleviation of signs and/or symptoms in patients with ongoing disease signs and/or symptoms (e.g., pain, inflammation.) Therapy also encompasses "prophylaxis" and "prevention." Prophylaxis includes preventing disease occurring subsequent to treatment of a disease in a patient or reducing the incidence or severity of the disease in a patient. The term "reduced," for purpose of therapy, refers broadly to the clinical significant reduction in signs and/or symptoms. Therapy includes treating relapses or recurrent signs and/or symptoms (e.g., of pain.) Therapy encompasses but is not limited to precluding the appearance of signs and/or symptoms anytime as well as reducing existing signs and/or symptoms and eliminating existing signs and/or symptoms. Therapy includes treating chronic disease ("maintenance") and acute disease,

[0168] Therapy can be for patients with risk factors, at risk patients in a susceptible population, patients with a history of disease, patients with symptoms, patients with signs, patients with signs but no symptoms, and patients with symptoms but no signs. Therapy can also be for patients without risk factors, not at risk, patients not in a susceptible population, patients with no history of disease, patients with no symptoms, patients without signs. Therapy can alleviate, allay, abate, assuage, curtail, decrease, ease, lessen, lighten, make better, make healthy, mitigate, mollify, pacify, relieve, rehabilitate, remedy, repair, and/or soothe a disease, disease signs, and/or disease symptoms.

[0169] "Treating" or "treatment," as used herein, refers broadly to a course of therapy where signs and/or symptoms are present in the patient. The term "reduced," for purpose of therapy, refers broadly to clinically significant reduction in signs and/or symptoms. Treatment includes treating chronic disease ("maintenance") and acute disease. Treatment can be for patients with risk factors, at risk patients in a susceptible population, patients with a history of disease, and/or patients with symptoms, patients with signs. Treatment can alleviate, allay, abate, assuage, curtail, decrease, ease, lessen, lighten, make better, make healthy, mitigate, mollify, pacify, relieve, rehabilitate, remedy, repair, and/or soothe a disease, disease signs, and/or disease symptoms. By the terms "treating" or "treatment" of a disorder involving the Na+K+Cl- co-transporters, it is intended that the severity of the disorder or the symptoms of the disorder are reduced, or the disorder is partially or entirely eliminated, as compared to that which would occur in the absence of treatment. Treatment does not require the achievement of a complete cure of the disorder. By the terms "preventing" or "prevention" of the disorder involving the Na+K+Cl- co-transporters, it is intended that the inventive methods eliminate or reduce the incidence or onset of the disorder, as compared to that which would occur in the absence of treatment. Alternatively stated, the present methods slow, delay, control, or decrease the likelihood or probability of the disorder in the subject, as compared to that which would occur in the absence of treatment. Further, the terms "treating" or "treatment" of a disorder involving the GABA_A receptor, are intended that the severity of the disorder or the symptoms of the disorder are reduced, or the disorder is partially or entirely eliminated, as compared
to that which would occur in the absence of treatment. Treatment does not require the achievement of a complete cure of the disorder.

"Tautomers" refer to compounds that are interchangeable 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 phenylnitromethane, that are likewise formed by treatment with acid or base.

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

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.

"Signs" of disease, as used herein, refers broadly to any abnormality indicative of disease, discoverable on examination of the patient; an objective indication of disease, in contrast to a symptom, which is a subjective indication of disease.

"Symptoms" of disease as used herein, refers broadly to any morbid phenomenon or departure from the normal in structure, function, or sensation, experienced by the patient and indicative of disease.

THE COMPOUNDS

The present invention relates to novel compounds that are GABAₐ inhibitors with or without presynaptic-selective activity and/or NKCC co-transporters useful for the treatment of anxiety disorders, ascites, bipolar disorder, cancer, endothelial corneal dystrophy, edema, depression, epilepsy, glaucoma, ischemia, migraine, neuropathic pain, nociceptive neuralgia, ocular diseases, pain, postherpetic neuralgia, and schizophrenia.

Additionally, the compounds are useful for the treatment of Alzheimer's Disease, addictive disorders, anxiety disorders, autism, bipolar disorder, depression, epilepsy, Huntington's Disease, inflammatory pain, insomnia, migraine, neuropathic pain, nociceptive pain, pain, itch, excessive itch, pruritis, neuropathic pruritis, Parkinson's disease, personality disorders, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.

Accordingly, in a first aspect of the invention, a compound of the invention is disclosed having a formula I:
wherein:
Cy is aryl or heteroaryl;
L¹ is substituted or unsubstituted alkylene, or -C(=0)-;
L² is a single bond, or -0-;
R¹ is selected from hydroxy, amino, substituted or unsubstituted amino, substituted or unsubstituted N containing heterocycloalkyi, and substituted or unsubstituted alkoxy;
or L¹ is a single bond or substituted or unsubstituted alkylene, and R¹ is selected from H, halo, CN, substituted or unsubstituted 5-12 membered heteroaryl, and substituted or unsubstituted 4-8 membered heterocycloalkyi;
R²a is H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, or substituted or unsubstituted heteroarylalkyl;
R²b is substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, or substituted or unsubstituted heteroarylalkyl;
or R²a and R²b may join together to form a 4-7 membered heterocycloalkyi ring;
R³ is selected from halo, alky!, substituted or unsubstituted haloalkyl, CN, and S(0)±R³b;
the subscript x is 0, 1, or 2;
R³b is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, aryl or heteroaryl;
or
R³b is substituted or unsubstituted amino, or substituted or unsubstituted N-containing heterocycloalkyi, and wherein the N of the heterocycle is bonded to S via a single bond; provided that L¹ is other than ~C(=0)-;
or
R³b is substituted or unsubstituted amino, or substituted or unsubstituted N-containing heterocycloalkyi, and wherein the N of the heterocycle is bonded to S via a single bond; provided that R²a is other than H; and the subscript n is other than 0;
each R^4 is independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkynylthio, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylarylamino, substituted or unsubstituted amino, substituted or unsubstituted aroyl, hydroxy, substituted or unsubstituted alkoxy, substituted sulfonyl, substituted sulfanyl, substituted sulfanylamino, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted arylsulfinyl, azido, substituted or unsubstituted carbamoyl, carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, substituted or unsubstituted dialkylamino, halo, nitro, and thiol; or two adjacent R^3's may join together to form cycloalkyl or heterocycloalkyl; and the subscript n is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

i) when R^3 is S(0)_x(R^3)_x, x is 2, L^1 is -C(=0)-, R^1 is OH, R^3_2 is unsubstituted alkyl, L^2 is -0-, R^2_2 is H, and R^2_2 is unsubstituted benzyl; then n is other than 0; and

ii) when the R^3 is S(0)_x(R^3)_x, x is 2, L^1 is -C(=0)-, R^1 is OH, R^3_2 is unsubstituted alkyl, L^2 is -0-, one of R^2_2 and R^2_2 is n-Bu, and the other is H, unsubstituted alkyl, unsubstituted aralkyl, or unsubstituted heteroarylalkyl; then n is other than 0; and

iii) when L^1 is -C(=0)-, R^1 is OH, R^3 is Br, L^2 is a single bond, and R^2_2 is Me; then R^2_2 is other than Me;

iv) when the R^3 is S(0)_x(R^3)_x, x is 2, L^1 is -C(=0)-, R^1 is OH, R^3_2 is methoxymethyl, L^2 is -0-, one of R^2_2 and R^2_2 is n-Bu, and the other is H; then n is other than 0;

v) when the R^3 is S(0)_x(R^3)_x, x is 2, L^1 is -C(=0)-, R^1 is OH, R^3_2 is Me, L^2 is -0-, the NR^2_2R^2_2 group is unsubstituted pyrrolidin-1-yl; then n is other than 0;

vi) when R^3 is S(0)_x(R^3)_x, x is 2, L^1 is a single bond, R^1 is tetrazolyl, and L^2 is -0-; then n is other than 0;

vii) when L^1 is a single bond or alkylene, R^1 is Cl, R^2_2 is H or Me, and R^2_2 is Me; then R^3 is other than Cl; and

viii) when L^1 is a single bond or alkylene, R^1 is H, and R^3 is Cl; then R^2_2 is other than H;

ix) when R^1 is substituted or unsubstituted acyl, L^1 is -C(=0)-, and R^1 is OH; then R^3 is selected from halo, alkyl, substituted or unsubstituted haloalkyl, CN, and S(0)_x(R^3)_x, the subscript x is 0, 1, or 2; and R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, aryl or heteroaryl; and

x) the compound is other than
In another aspect, the present invention provides compounds according to formula 1a:

\[
\text{Cy} \quad \begin{array}{c}
\text{L}^1 \\
\text{R}^1
\end{array}
\begin{array}{c}
\text{R}^3 \\
\text{L}^2
\end{array}
\begin{array}{c}
\text{R}^{2a} \\
\text{R}^{2b}
\end{array}
\begin{array}{c}
\text{Cy} \\
(R^4)_n
\end{array}
\]

wherein:
- Cy is aryl or heteroaryl;
- L^1 is substituted or unsubstituted alkylene;
- L^2 is a single bond, or -O-;
- R^1 is selected from hydroxy, amino, substituted or unsubstituted amino, substituted or unsubstituted N containing heterocycloalkyl, and substituted or unsubstituted alkoxy;
- or L^1 is a single bond or substituted or unsubstituted alkylene, and R' is selected from H, halo, CN, substituted or unsubstituted 5-12 membered heteroaryl, and substituted or unsubstituted 4-8 membered heterocycloalkyl;
- R^{2a} is H, substituted or unsubstituted alkyi, substituted or unsubstituted arylalkyl, or substituted or unsubstituted heteroarylalkyl;
- R^{2b} is substituted or unsubstituted alkyi, substituted or unsubstituted arylalkyl, or substituted or unsubstituted heteroarylalkyl;
- or R^{2a} and R^{2b} may join together to form a 4-7 membered heterocycloalkyl ring;
- R^3 is selected from S(0)^x-R^{3x};
- the subscript x is 0, 1, or 2;
- R^{3x} is substituted or unsubstituted amino, or substituted or unsubstituted N-containing heterocycloalkyl, and wherein the N of the heterocycle is bonded to S via a single bond;
- each R^4 is independently selected from substituted or unsubstituted alkyi, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkythio, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted
alkyiarylamino, substituted or unsubstituted amino, substituted or unsubstituted arylalkyl, hydroxy, substituted or unsubstituted alkoxy, substituted sulfonyl, substituted sulfinyl, substituted sulfanyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, azido, substituted or unsubstituted carbamoyl, carboxyli, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, substituted or unsubstituted dialkylamino, halo, nitro, and thiol; or two adjacent R's may join together to form cycloalkyl or heterocycloalkyl; and the subscript n is 0, 1, 2, or 3; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

d) when R² is S(0)ₓ-R²ₓ, x is 2, L¹ is a single bond, R₁ is tetrazolyl, and L² is -O--; then n is other than 0.

[0179] In one embodiment, with respect to the compound of formula I, Cy is aryl.

[0180] In one embodiment, with respect to the compound of formula I, Cy is heteroaryl.

[0181] In one particular embodiment, with respect to the compound of formula I, Cy is phenyl.

[0182] In one particular embodiment, with respect to the compound of formula I, Cy is pyridyl.

[0183] In one embodiment, with respect to the compound of formula I, L¹ is C₁-C₄ alkylene, unsubstituted or substituted with halo.

[0184] In one embodiment, with respect to the compound of formula I, L¹ is -CH₂-, -C(Me)H-, or -CH₂-C₃=.

[0185] In another embodiment, L' is -C₃=.

[0186] In one particular embodiment, with respect to the compound of formula I, L¹ is -C(=0)-.

[0187] In one embodiment, with respect to the compound of formula I, R¹ is amino, or substituted amino.

[0188] In another embodiment, with respect to the compound of formula I, L¹ is a single bond or C₁-C₄ alkylene; and R¹ is CN. In a particular embodiment, L¹ is a single bond; and R¹ is CN.

[0189] In another embodiment, with respect to the compound of formula I, L¹ is a single bond or C₁-C₄ alkylene; and R¹ is substituted or unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyld, or quinolinyld. In one embodiment, R¹ is unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyld, or quinolinyld. In another embodiment R¹ is pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyld, or quinolinyld, substituted with alkyl, haloalkyl, or oxo. One particular embodiment, R¹ is substituted with oxo.
In another embodiment, with respect to the compound of formula I, L is a single bond or C<sub>1</sub>-C<sub>4</sub> alkylen; and R<sub>1</sub> is substituted or unsubstituted 4-8 membered heterocycloalkyl.

In another embodiment, with respect to the compound of formula I, L is a single bond or C<sub>1</sub>-C<sub>4</sub> alkylen; and R<sub>1</sub> is substituted or unsubstituted piperidinyl, piperazinyl, or morpholinyl.

In one embodiment, with respect to the compound of formula I, the compound is according to formula IIa, IIb, IIc, or IID:

and wherein R<sub>2a</sub>, R<sub>3b</sub>, R<sub>4</sub>, n, and L<sub>2</sub> are as described for formula I; and R<sub>2a</sub> is independently H, or substituted or unsubstituted alkyl; R<sub>3b</sub> is substituted or unsubstituted acyl, or substituted or unsubstituted alkyl or R<sub>2a</sub> and R<sub>3b</sub> may join together to form a 4-7 membered heterocycloalkyl ring; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

In one embodiment, with respect to the compound of formula I, the compound is according to formula IIIa, IIIb, IIId, or IID:

and wherein R<sub>2a</sub>, R<sub>3b</sub>, R<sub>4</sub>, n, and L<sub>2</sub> are as described for formula I; and R<sub>3b</sub> is independently H, or substituted or unsubstituted alkyl; R<sub>2b</sub> is substituted or unsubstituted acyl, or substituted or unsubstituted alkyl; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

In one embodiment, with respect to the compound of formulae IIa-IId and IIa-IID, R<sub>1</sub> is Me,
Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu. In another embodiment, R is H.

[0195] In one embodiment, with respect to the compound of formula I, R is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.

[0196] In one embodiment, with respect to the compound of formula II, R and R' are joined together to form a 4-7 membered heterocyclic ring.

[0197] In one embodiment, with respect to the compound of formula I, R and R are joined to form piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, or azetidinyl.

[0198] In one embodiment, with respect to the compound of formula Ulc-IIId, R is SO₂NH₂.

[0199] In one embodiment, with respect to the compound of formula I, the compound is according to formula IVa, IVb, IVc, or IVd:

![Chemical structures](image)

and wherein R², R²b, R³, n, and L² are as in claim 1; and R³ is as in claim 1 or claim 2; and X is F, Cl, Br, or I;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;
provided that
i) when the compound is according to formula IVc, X is Cl, R² is H or Me, and R²b is Me; then R³ is other than Cl; and
ii) when the compound is according to formula IVd, and R³ is Cl; then R²b is other than H

[0200] In one embodiment, with respect to the compound of formula IVc, X is F. In another embodiment, X is Cl. In yet another embodiment, X is Br or I.

[0201] In one embodiment, with respect to the compound of formula I, the compound is according to formula IVe, or IVf:
and wherein R\textsuperscript{2a}, R\textsuperscript{2b}, R\textsuperscript{3}, R\textsuperscript{4}, n, and L\textsuperscript{2} are as described for formula I; and R\textsuperscript{1} is substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

[0202] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is H, F, Cl, Br, or I.

[0203] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.

[0204] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is CF\textsubscript{3}.

[0205] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is CN.

[0206] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is S(0)\textsubscript{x}-R\textsuperscript{3a}; x is 0, 1 or 2; and R\textsuperscript{3a} is as described for formula 1. In one embodiment, x is 1 or 2; and R\textsuperscript{3a} is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu. In a particular embodiment, x is 2, and R\textsuperscript{3a} is Me.

[0207] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is SOMe, SOEt, SO-i-Pr, or SO-n-Bu.

[0208] In one embodiment, with respect to the compound of formulae I-IVf, s O\textsubscript{2}Me, S0 \textsubscript{2}Et, S0 \textsubscript{2}-i-Pr, or S0 \textsubscript{2}-n-Bu. In a particular embodiment, R\textsuperscript{3} is S0 \textsubscript{2}Me.

[0209] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is S(0)\textsubscript{x}-R\textsuperscript{3a}; x is 1 or 2; and R\textsuperscript{3a} is cycloalkyl. In another embodiment, R\textsuperscript{3a} is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0210] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is SO-cyclopropyl, SO-cyclobutyl, SO-cyclopentyl, or SO-cyclohexyl.

[0211] In one embodiment, with respect to the compound of formulae I-IVf, R\textsuperscript{3} is SO\textsubscript{2}-cyclopropyl, SO\textsubscript{2}-cyclobutyl, SO\textsubscript{2}-cyclopentyl, or SO\textsubscript{2}-cyclohexyl.

[0212] In one embodiment, with respect to the compound of formulae Ia-IVf, R\textsuperscript{3} is S(0)\textsubscript{x}-R\textsuperscript{3a}; x is 1 or 2; and R\textsuperscript{3a} is substituted or unsubstituted amino.

[0213] In one embodiment, with respect to the compound of formulae Ia-IVf, R\textsuperscript{3a} is NH\textsubscript{2}, NMe\textsubscript{2}, or NET\textsubscript{2}.

[0214] In one embodiment, with respect to the compound of formulae Ia-IVf, R\textsuperscript{3a} is N-containing
heterocycle. In another embodiment $R^{3a}$ is selected from piperidinyl, morpholinyl, pyrroldinyl, or piperazinyl.

[0215] In one embodiment, with respect to the compound of formulae Ia-IVf, $R^3$ is $S\_2NH_2$, $S\_2NMe_2$, or $S\_2NEt_2$.

[0216] In one embodiment, with respect to the compound of formulae Ia-IVf, $R^3$ is $SO_2Me$, or $SO_2Et$.

[0217] In one embodiment, with respect to the compound of formulae Ila-IIId, $R^3$ is $SMe$, or $S\_2Et$.

[0218] In one embodiment, with respect to the compound of formulae Ila-IIId, $n$ is other than 0.

[0219] In one embodiment, with respect to the compound of formulae Ila-IIId, $n$ is 1; and $R^4$ is 4-Me or 4-Cl.

[0220] In one embodiment, with respect to the compound of formula lid, $NR^{3a}R^{1b}$ is piperidinyl, morpholinyl, or piperazinyl.

[0221] In one embodiment, with respect to the compound of formula lid, $NR^{3a}R^{1b}$ is $NCH_2CH_2OH$.

[0222] In one embodiment, with respect to the compound of formula I, the compound is according to formula Va, Vb, Vc, Vd, Ve, Vf, or Vg:

and wherein $R^{3a}$, $R^{2b}$, $R^4$, $n$, and $L^2$ are as in claim 1; and $R^{3b}$ is substituted or unsubstituted amino, or substituted or unsubstituted $N$-containing heterocycloalkyl, and wherein the $N$ of the heterocycle is bonded to $S$ via a single bond;

or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and
tautomers thereof;

provided that

i) when the compound is according to formula Vd or Ve, \( L^2 \) is -0-. \( R^{2a} \) is H, and \( R^{2b} \) is unsubstituted benzyl, then \( n \) is other than 0; and

ii) when the compound is according to formula Vd or Ve, \( L^2 \) is -0-. one of \( R^{2a} \) and \( R^{2b} \) is n-Bu, and the other is H, unsubstituted alkyl, unsubstituted aralkyi, or unsubstituted heteroarylalkyi; then \( n \) is other than 0; and

iii) when the compound is according to formula Vg, then \( n \) is other than 0; and

iv) when the compound is according to formula Vg, then \( R^{2b} \) is other than substituted or unsubstituted acyl.

[0223] In one embodiment, with respect to the compound of formula Vg, \( R^3 \) is \( S(0)_{x}\cdot R^{3a}; x \) is 1 or 2; and \( R^{3b} \) is substituted or unsubstituted amino.

[0224] In one embodiment, with respect to the compound of formula Vg, \( R^{3a} \) is NH\(_2\), NMe\(_2\), or NE\(_4\).

[0225] In one embodiment, with respect to the compound of formula Vg, \( R^{3a} \) is N-containing heterocycle. In another embodiment \( R^{3a} \) is selected from piperidinyl, morpholinyl, pyrrolidinyl, or piperazinyl.

[0226] In one embodiment, with respect to the compound of formula Vg, \( n \) is other than 0.

[0227] In one embodiment, with respect to the compound of formula Vg, \( n \) is 1; and \( R^4 \) is 4-Me or 4-Cl.

[0228] In one embodiment, with respect to the compound of formula I, the compound is according to formula Via, VIIb, Vic, VId, Vie, Vlf, or VIg:
and wherein $R^2$, $R^4$, $n$, and $L^2$ are as described for formula I; and $R^1$ is CN, substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

i) when the compound is according to formula Vlg, $L^2$ is -0-; $R^1$ is tetrazolyl, then $n$ is other than 0.

[0229] In one embodiment, with respect to the compound of formulae I-Vlg, $L^2$ is a single bond.

[0230] In one particular embodiment, with respect to the compound of formulae I-Vlg, $L^2$ is -0-.

[0231] In one embodiment, with respect to the compound of Formula I, the compound is according to formula Vila, VHb, VIIc, Vlld, VIIe, or VIIf:
and wherein \( R^{2a}, R^{2b}, R^4, n, \) and \( L^2 \) are as described for formula I; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof; provided that when the compound is according to formula Vila, \( R^{3u} \) is other than \( H \).

[0232] In one embodiment, with respect to the compound of formula I, the compound is according to formula Villa, VIlb, VIIIc, VIlld, VIne, or VIlIf:
and wherein $R_{2a}$, $R_{2b}$, $R_4$, and $n$ are as described for formula I; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof; provided that

i) when the compound is according to formula Villa, $R_{2a}$ is other than H; and

ii) when the compound is according to formula Villd or VIlle, one of $R_{2a}$ and $R_{2b}$ is unsubstituted benzyl or n-Bu, and the other is H, unsubstituted alkyl, unsubstituted aralkyl, or unsubstituted heteroaryalkyl; then $n$ is other than 0.

[0233] In one embodiment, with respect to the compound of formula I, the compound is according to formula IXa, IXb, IXc, IXd, IXe, IXf, or IXg:
and wherein $R^{2b}$, $R^{2b}$, $R^{4}$, $n$, and $L^{2}$ are as described in formula I; and $R^{1}$ is CN, substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl; or a pharmaceutically acceptable salt, or a solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

[0234] In one embodiment, with respect to the compound of formula I, the compound is according to formula Xa, Xb, Xc, Xd, Xe, Xf, or Xg:
and wherein R²a, R²b, R₄, n, and L² are as described for formula I; and R¹ is F, Cl, Br, I, CN, substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

when the compound is according to formula Xg, R' is tetrazolyl; then n is other than 0; and
when the compound is according to formula Xb, R²b is H or Me, and R²b is Me; then R¹ is other than Cl.

[0235] In one embodiment, with respect to the compound of formulae Vla-Vlg and Xa-Xg, R¹ is CN.
[0236] In one embodiment, with respect to the compound of formulae Xa-Xg, R¹ is F.
[0237] In one embodiment, with respect to the compound of formulae Xa-Xg, R¹ is Cl.
[0238] In one embodiment, with respect to the compound of formulae Xa-Xg, R¹ is Br.
[0239] In one embodiment, with respect to the compound of formulae Xa-Xg, R¹ is I.
[0240] In one embodiment, with respect to the compound of formulae Vla-Vlg and Xa-Xg, R¹ is pyrazolyl, imidazolyl, triazolyl, oxazolyl, oxadiazolyl, pyridyl, and tetrozolyl; provided that when the compound is according to formula VIII or Xg, and R¹ is tetrazolyl; then n is other than 0. In one embodiment, R' is substituted or unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxothiadiazolyl, tetrozolyl, pyridyl, pyrimidyl, or quinolinyl. In one embodiment, R¹ is unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxothiadiazolyl, tetrozolyl, pyridyl, pyrimidyl, or quinolinyl. In another embodiment R' is pyrrolyl, pyrazolyl, imidazolyl, oxazolyl,
isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxthiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, or quinolinyl, substituted with alkyl, haloalkyl, or oxo. One particular embodiment, R^1 is substituted with oxo.

[0241] In one embodiment, with respect to the compound of formulae Vla-VIg and Xa-Xg, R^1 is piperidinyl or morpholinyl.

[0242] In one embodiment, with respect to the compound of formulae I-Xg, R^{2a} is H, alkyl, or aralkyl.

[0243] In one particular embodiment, with respect to the compound of formulae I-Xg, R^{2a} is H.

[0244] In one embodiment, with respect to the compound of formulae I-Xg, R^{2a} is unsubstituted alkyl. In another embodiment, R^{2a} is alkyl substituted with hydroxyl, substituted or unsubstituted amino, cyano, substituted or unsubstituted alkoxy, or halo.

[0245] In one particular embodiment, with respect to the compound of formulae I-Xg, R^{2a} is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, benzyl, or phenethyl.

[0246] In another particular embodiment, with respect to the compound of formulae I-Xg, R^{2a} is -CH\_2\_CF\_3, -CH\_2\_CH\_2\_NMe\_2, -CH\_2\_CH\_2\_OH, or -CH\_2\_CH\_2\_CN.

[0247] In yet another particular embodiment, with respect to the compound of formulae I-Xg, R^{2a} is H.

[0248] In yet another particular embodiment, with respect to the compound of formulae I-Xg, R^{2a} is

and wherein m is 0, 1, 2, or 3; and R^{2e} is independently selected from halo, alkyl, haloalkyl, alkoxy, and haloalkoxy.

[0249] In one embodiment, m is 0. In another embodiment, m is 1 or 2.

[0250] In one embodiment, each R^{2e} is independently selected from Cl, F, Br, OMe, Me, i-Pr, CF\_3, or OCF\_3.

[0251] In one embodiment, with respect to the compound of formulae I-Xg, R^{2b} is alkyl, or aralkyl.

[0252] In one embodiment, with respect to the compound of formulae I-Xg, R^{2b} is unsubstituted alkyl. In another embodiment, R^{2b} is alkyl substituted with hydroxyl, substituted or unsubstituted amino, cyano, substituted or unsubstituted alkoxy, or halo.

[0253] In one particular embodiment, with respect to the compound of formulae I-Xg, R^{2b} is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, benzyl, or phenethyl.

[0254] In another particular embodiment, with respect to the compound of formulae I-Xg, R^{2b} is -CH\_2\_CF\_3, -CH\_2\_CH\_2\_NMe\_2, -CH\_2\_CH\_2\_OH, -CH\_2\_CH\_2\_OMe, or -CH\_2\_CH\_2\_CN.

[0255] In yet another particular embodiment, with respect to the compound of formulae I-Xg, R^{2b} is
and wherein \( m \) is 0, 1, 2, or 3; and \( R^2 \) is independently selected from halo, CN, alkyl, haloalkyl, alkoxy, and haloalkoxy.

[0256] In one embodiment, \( m \) is 0. In another embodiment, \( m \) is 1 or 2.

[0257] In one embodiment, each \( R^2 \) is independently selected from Cl, F, Br, OMe, CN, Me, i-Pr, CF\(_3\), or OCF\(_3\).

[0258] In one embodiment, with respect to the compound of formulae \( I-Vie \), and \( \text{VIIa-Xf} \), \( R^2b \) is unsubstituted acyl. In another embodiment, \( R^2b \) is substituted acyl. In one embodiment, \( R^2b \) is as described in this paragraph, and \( R^2a \) is H.

[0259] In one embodiment, with respect to the compound of formulae \( I-Vie \), and \( \text{VIIa-Xf} \), \( R^2b \) is \(-C(=0)-alkyl. In another embodiment, \( R^2b \) is \(-C(=0)-cycloalkyl. In another embodiment, \( R^2b \) is \(-C(=0)\)-heterocycloalkyl. In another embodiment, \( R^2b \) is \(-C(=0)-aryl. In another embodiment, \( R^2b \) is \(-C(=0)-heteroaryl. In one embodiment, the alkyl, cycloalkyl, aryl or heteroaryl are substituted or unsubstituted. In one embodiment, the alkyl, cycloalkyl, aryl or heteroaryl are substituted with halo, CN, alkoxy, alkyl, phenyl, or haloalkyl. In one embodiment, \( R^2b \) is as described in this paragraph, and \( R^2a \) is H.

[0260] In one embodiment, with respect to the compound of formulae \( I-Vie \), and \( \text{VIIa-Xf} \), \( R^2b \) is \(-C(=0)-benzyl. In another embodiment, \( R^2b \) is \(-C(=0)-furanyl. In another embodiment, \( R^2b \) is \(-C(=0)-cyclopropyl. In another embodiment, \( R^2b \) is \(-C(=0)-(substituted or unsubstituted)phenyl. In another embodiment, \( R^2b \) is \(-C(=0)-naphthyl. In one embodiment, \( R^2b \) is as described in this paragraph, and \( R^2a \) is H.

[0261] In one embodiment, with respect to the compound of formulae \( I-Xg \), \( R^2a \) and \( R^2b \) are joined together to form a 4-7 membered heterocyclic ring. In another embodiment, \( R^2a \) and \( R^2b \) are joined together to form azetidinyl, pyrrolidinyl, piperidinyl, or piperazinyl ring.

[0262] In one embodiment, with respect to the compound of formulae \( I-Xg \), the group \(-NR^2a R^2b \) is

\[
\text{\begin{align*}
\text{N} & , \\
\text{N} & , \\
\text{N} & , \\
\text{N} & \text{N} \text{R}^2d \\
\end{align*}}
\]

and wherein \( R^2d \) is H or alkyl.

[0263] In one embodiment, the group \(-NR^2a R^2b \) is as described above, and \( R^2d \) is Me, Et, or i-Pr.

[0264] In one embodiment, the group \(-NR^2a R^2b \) is pyrrolidin-1-yl. In another embodiment, the group \(-NR^2a R^2b \) is piperidin-1-yl.
In one particular embodiment, with respect to the compound of formulae I-Xg, each of $R^{2a}$ and $R^{2b}$ is n-Bu.

In one embodiment, with respect to the compound of formula I, the compound is according to formula X1a, X1b, X1c, X1d, X1e, X1f:

![Chemical structures](image)

and wherein $R^4$, and $n$ are as described for formula I;

or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

when the compound is according to formula X1d or X1e, $n$ is other than 0.

In one embodiment, with respect to the compound of formula I, the compound is according to formula X1n, X1l, X1c, X1d, X1e, X1f, or X1l:

![Chemical structures](image)
and wherein $R^4$, and $n$ are as described for formula I; and $R^1$ is substituted or unsubstituted 5-12 membered heteroary! or substituted or unsubstituted 4-8 membered heterocycloalky!

or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

i) when the compound is according to formula XIIg, and $R^1$ is tetrazolyl; then $n$ is other than 0.

[0268] In one embodiment, with respect to the compound of formula XIIa-XIIg, $R'$ is pyrazolyl, imidazolyl, triazolyl, oxazolyl, oxadiazolyl, pyridyl, tetrazolyl, piperidinyl or morpholinyl, unsubstituted or substituted with alkyl, hydroxy, or oxo; In another embodiment, with respect to the compound of formula XIIg, and $R^1$ is tetrazolyl; and $n$ is other than 0. In one embodiment, $R^1$ is substituted or unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, or quinolinyll. In one embodiment, $R^1$ is unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, or quinolinyll. In another embodiment $R^1$ is pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, or quinolinyll, substituted with alkyl, haloalkyly, or oxo. One particular embodiment, $R'$ is substituted with oxo.

[0269] In one embodiment, with respect to the compound of formula I, the compound is according to formula XIIIa, XIIIb, XIIIc, XIIIc, XIHe, XIIIe, or XIIIf; or XIIIf:
In one embodiment, with respect to the compound of formulae I-XIIIg, n is 0.

In one embodiment, with respect to the compound of formulae I-XIIIg, n is 1, 2, or 3.

In one particular embodiment, with respect to the compound of formulae I-XIIIg, n is 1 or 2. In a more particular embodiment, n is 1.

In one embodiment, with respect to the compound of formulae I-XIIIg, n is 1 or 2; and R^4 is independently alkyl, alkoxy, haloalkyl, halo, CN, hydroxy, alkylsulfonyl, arylsulfonyl, S=O, amido, substituted amido, carboxy, carbalkoxy, amino, or substituted amino.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently selected from Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, F, Cl, Br, I, CN, CF_3, OMe, OEt, OCF_3, O-i-Pr, S=OMe, and S=OEt.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently F, Cl, Br, I, CN, or CF_3.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently OMe, OEt, OCF_3, or O-i-Pr.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently S=OMe or S=OEt.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently F, Cl, Br, I, CN, or CF_3.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently OMe, OEt, OCF_3, or O-i-Pr.

In one embodiment, with respect to the compound of formulae I-XIIIg, each R^4 is independently S=OMe or S=OEt.
independently is Cl, Me, or OMe.

[0280] In one particular embodiment, with respect to the compound of formula I, the compound is according to formula XIVa, XIVb, XIVc, XIVd, or XIVe:

![Chemical structures](image)

or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

[0281] In one particular embodiment, with respect to the compound of formula I, the compound is according to formula XVa, XVb, XVc, XVd, XVe, or XVI:
and $R^1$ is substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

i) when the compound is according to formula XVf, and $R^1$ is tetrazolyl; then $n$ is other than 0.

[0282] In one embodiment, with respect to the compound of formulae XVa-XVf, $R'$ is pyrazolyl, imidazolyl, triazolyl, oxazolyl, oxadiazolyl, oxathiadiazolyl, pyridyl, tetrazolyl, piperidinyl or morpholinyl, unsubstituted or substituted with alkyl, hydroxy, or oxo: provided that when the compound is according to formula XVf, and $R^1$ is tetrazolyl; then $n$ is other than 0. In one embodiment, $R^1$ is substituted or unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, or quinolinyl. In one embodiment, $R^1$ is unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, or quinolinyl. In another embodiment $R^1$ is pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl,
thienyl, furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxthiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, or quinoliny], substituted with alkyl, haloalkyl, or oxo. One particular embodiment, R is substituted with oxo.

[0283] In one particular embodiment, with respect to the compound of formula I, the compound is according to formula XVIa, XVIb, XVIc, XVIId, XVIe, or XVIf:

![Chemical structures](image)

or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

[0284] In one embodiment, with respect to the compound of formulae Vd, VId, VIIId, IXId, IXd, Xd, Xlld, Xnid, XIVd, XVd, or XVId, the Me of S0 2Me group is replaced with Et, n-Pr, i-Pr, n-Bu, i-Bu or sec-Bu. In a particular embodiment, the Me of S0 2Me is replaced with Et. In another particular embodiment, the Me of S0 2Me is replaced with i-Pr. In yet another particular embodiment, the Me of S0 4Me is replaced with i-Bu.

[0285] In one embodiment, with respect to the compound of formulae Vd, VId, VIIId, VIIIId, IXd, Xd, Xlld, or Xlild the Me of S0 4Me group is replaced with Et, n-Pr, i-Pr, n-Bu, i-Bu or sec-Bu; and n is 0.

[0286] In one embodiment, with respect to the compound of formulae Vd, VId, VIIId, IXd, Xd, Xlld, or Xlild, the Me of S0 2Me group is replaced with Et, n-Pr, i-Pr, n-Bu, i-Bu or sec-Bu; and n is
In one particular embodiment, with respect to the compound of formula I, the compound is according to formula XVIIa, XVIIb, XVIIc, XVIIId, XVIIe, XVIIIf, XVIIg, XVIIh, or XVIII: 

and wherein R³, R⁴, and n are as in claim 1 or 2;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and
tautomers thereof;
provided that
i) when the compound is according to formula XVIIa; then n is other than 0.

[0288] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is F, Cl, Br, or I.
[0289] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.
[0290] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is CF₃.

[0291] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is CN.

[0292] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is S(0)ₓR₂; x is 1 or 2; and R₂ is as in claim 1.

[0293] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.

[0294] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is SOMe, SOEt, SO-i-Pr, SO-n-Bu, SO₂Me, SO₂Et, SO₂-i-Pr, or SO₂-n-Bu.

[0295] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0296] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is SO-cyclopropyl, SO-cyclobutyl, SO-cyclopentyl, SO-cyclohexyl, SO₂-cyclopropyl, SO₂-cyclobutyl, SO₂-cyclopentyl, or SO₂-cyclohexyl.

[0297] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is substituted or unsubstituted amino.

[0298] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, R³ is N₄, or N₄.

[0299] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, n is 0.

[0300] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, n is 1, or 2.

[0301] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, n is 1, or 2; and R₄ is as in claim 1.

[0302] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, n is 1, or 2; and R₄ is independently alkyl, alkoxy, haloalkyl, halo, CN, hydroxyl, alkylsulfonyl, arylsulfonyl, SO₂OH, amido, substituted amido, carboxy, carbalkoxy, amino, or substituted amino.

[0303] In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, each R₄ is independently Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu.
In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, each R\textsuperscript{4} is independently F, Cl, Br, I, CN, or CF\textsubscript{3}.

In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, each R\textsuperscript{4} is independently OMe, OEt, OCF\textsubscript{3}, or O-i-Pr.

In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, each R\textsuperscript{4} is independently SO\textsubscript{2}Me, or SOOEt.

In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, each R\textsuperscript{4} is independently CI, Me, or OMe.

In one particular embodiment, with respect to the compound of formula XVIIa-XVIIi, each R\textsuperscript{4} is independently 4-Cl, 4-Me, 4-F, 4-CN, 4-CF\textsubscript{3}, or 4-OMe.

In a further aspect of the invention, a compound of the invention is disclosed having a formula XVIII:

![Chemical structure](image)

wherein:
- each R\textsuperscript{3a} and R\textsuperscript{2b} is independently unsubstituted C\textsubscript{1}-C\textsubscript{4} alkyl or unsubstituted benzyl;
- or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;
- provided that when R\textsuperscript{3a} is Me, and R\textsuperscript{2b} is n-Bu at the same time; then the compound is in a form of a sodium, potassium, calcium, ammonium or magnesium salt.

In one embodiment, with respect to the compound of formula XVIII, R\textsuperscript{3a} is Me, Et, n-Pr, i-Pr, n-
Bu, i-Bu, or t-Bu. In another embodiment, R₁ is n-Pr or i-Pr. In another embodiment, R³ is i-Bu.

[0312] In one particular embodiment, with respect to the compound of formula XVIII, R³ is Me.

[0313] In one embodiment, with respect to the compound of formula XVin, the compound is according to formula XIX:

![Image of compound XIX]

XIX

and wherein R² is as described for formula XVIII;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that when R² is n-Bu at the same time; then the compound is in a form of a sodium, potassium, calcium, ammonium or magnesium salt.

[0314] In one embodiment, with respect to the compound of formulae XVIH-XIX, R² is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.

[0315] In one embodiment, with respect to the compound of formula XVin, the compound is according to formula XXa, XXb, XXc, or XXd:
or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants thereof; provided that when and the compound is according to formula IIId; then the compound is in a form of a sodium, potassium, calcium, ammonium or magnesium salt.

[0316] In one embodiment, with respect to the compound of formula XVIII, the compound is according to formula XXa. In another embodiment, the compound is according to formula XXb. In a yet another embodiment, the compound is according to formula XXc. In a particular embodiment, the compound is according to formula XXd; and the compound is in a form of a sodium, potassium, calcium, ammonium or magnesium salt.

[0317] In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-8034.

[0318] In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8034.

[0319] In a particular embodiment, the compound is the sodium salt of NTP-8034.

[0320] In a particular embodiment, the compound is the potassium salt of NTP-8034.

[0321] In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-8055.

[0322] In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium
salt of NTP-8055.

[0323] In a particular embodiment, the compound is the sodium salt of NTP-8055.

[0324] In a particular embodiment, the compound is the potassium salt of NTP-8055.

[0325] In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-8067.

[0326] In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8067.

[0327] In a particular embodiment, the compound is the sodium salt of NTP-8067.

[0328] In a particular embodiment, the compound is the potassium salt of NTP-8067.

[0329] In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-8069.

[0330] In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8069.

[0331] In a particular embodiment, the compound is the sodium salt of NTP-8069.

[0332] In a particular embodiment, the compound is the potassium salt of NTP-8069.

[0333] In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-8081.

[0334] In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8081.

[0335] In a particular embodiment, the compound is the sodium salt of NTP-8081.

[0336] In a particular embodiment, the compound is the potassium salt of NTP-8081.

[0337] In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-8097.

[0338] In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8097.

[0339] In a particular embodiment, the compound is the sodium salt of NTP-8097.

[0340] In a particular embodiment, the compound is the potassium salt of NTP-8097.

[0341] In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-8147.

[0342] In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8 147.

[0343] In a particular embodiment, the compound is the sodium salt of NTP-8 147.

[0344] In a particular embodiment, the compound is the potassium salt of NTP-8 147.

[0345] In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-8 153.
In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8153.

In a particular embodiment, the compound is the sodium salt of NTP-8153.

In a particular embodiment, the compound is the potassium salt of NTP-8153.

In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-16031.

In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-16031.

In a particular embodiment, the compound is the sodium salt of NTP-16031.

In a particular embodiment, the compound is the potassium salt of NTP-16031.

In one particular embodiment, the compound is a pharmaceutically acceptable salt of the compound NTP-16033.

In a particular embodiment, the compound is the sodium, potassium, calcium, or magnesium salt of NTP-16035.

In a particular embodiment, the compound is the sodium salt of NTP-16035.

In a particular embodiment, the compound is the potassium salt of NTP-16035.

In one embodiment, with respect to the compound of formula XVIII, the compound is an alkaline metal salt of compound of formula I.

In one particular embodiment, with respect to the compound of formula XVIII, the compound is 3-(N,N-dibutylamino)-4-phenoxy-5-methylsulfonyl-benzoic acid.

In one particular embodiment, with respect to the compound of formula XVIII, the compound is a pharmaceutically acceptable salt of S-CN-benzyl-W-butyOamino-^phenoxy-S-methylsulfonyl-benzoic acid.

In one embodiment, with respect to the compound of formula XVIII, the compound is 3-(N,N-dibutylamino)-4-phenoxy-5-methylsulfonyl-benzoic acid, sodium salt.

In one embodiment, with respect to the compound of formula XVIII, the compound is 3-(N,N-dibutylamino)-4-phenoxy-5-methylsulfonyl-benzoic acid, potassium salt.

In one embodiment, with respect to the compound of formula XVIII, the compound is 3-(N,N-dibutylamino)-4-phenoxy-5-methylsulfonyl-benzoic acid, calcium salt.
In one embodiment, with respect to the compound of formula XVIIT, the compound is 3-(N,N-dibutylamino)-4-phenoxy-5-methylsulfonyl-benzoic acid, magnesium salt.

In one embodiment a compound of the invention is not an isotopic variant.

In one aspect a compound of the invention is a solvate.

In one aspect a compound of the invention is a solvate of a pharmaceutically acceptable salt of the compound.

In certain aspects, the present invention provides prodrugs and derivatives of a compound of the invention according to the formula above. Prodrugs are derivatives of a compound of the invention, which have metabolically 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.

While specified groups for each embodiment have generally been listed above separately, a compound of the invention includes one in which several or each embodiment in the above Formula, as well as other formulae presented herein, is selected from one or more of particular members or groups designated respectively, for each variable. Therefore, this invention is intended to include all combinations of such embodiments within its scope.

In further aspects, the present invention provides pharmaceutical compositions comprising a compound of formulae I-XXd or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound selected from the group consisting of the sodium, potassium, calcium, or magnesium salt(s) of NTP-8034, NTP-8055, NTP-8067, NTP-8069, NTP-808 L, NTP-8097, NTP-8147, NTP-8 153, NTP-16031 , NTP-16033, NTP-1 6035, or mixtures thereof.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-8034.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-8034.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-8034.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8034.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-8055.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-8055.

In further aspects, the present invention provides a pharmaceutical composition comprising a
pharmaceutically acceptable carrier and the calcium salt of NTP-8055.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8055.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-8067.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-8067.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8067.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-8067.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8067.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-8069.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-8069.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-8069.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8069.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-8081.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-8081.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-8081.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8081.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-8097.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-8097.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-8097.

In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8097.
[0399] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-8147.

[0400] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-8147.

[0401] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-8147.

[0402] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8147.

[0403] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-8153.

[0404] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-8153.

[0405] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-8153.

[0406] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-16031.

[0407] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-16031.

[0408] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-16031.

[0409] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-16031.

[0410] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-16033.

[0411] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the potassium salt of NTP-16033.

[0412] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-16033.

[0413] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-16033.

[0414] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-16033.

[0415] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the sodium salt of NTP-16035.

[0416] In further aspects, the present invention provides a pharmaceutical composition comprising a
pharmaceutically acceptable carrier and the potassium salt of NTP-16035,

[0417] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the calcium salt of NTP-1 6035.

[0418] In further aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the magnesium salt of NTP-1 6035.

[0419] In one particular embodiment, the compound is any one of compounds listed in Table 1.

[0420] In one particular embodiment, with respect to the compound of formula 1, the compound is according to formula XXIa, XXIb, or XXIc:

![Chemical Structures](image)

and wherein each $R^{3b}$ is independently NH$_2$, NMe$_2$, NEt$_2$, Me, Et, n-Pr, i-Pr, or n-Bu; and each $R^4$ is independently alkyl, haloalkyl, halo, alkoxy, or haloalkoxy;

or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

[0421] In one particular embodiment, with respect to the compound of formula XXIa-XXIc, $R^{3b}$ is Me. In another particular embodiment, $R^{3b}$ is Et.

[0422] In one particular embodiment, with respect to the compound of formula XXIa-XXIc, $R^{3b}$ is NH$_2$. In another particular embodiment, $R^{3b}$ is NMe$_2$. In yet another particular embodiment, $R^{3b}$ is NEt$_2$.

[0423] In one particular embodiment, with respect to the compound of formula XXIa, each $R^4$ is independently Me, CI, F, CF$_3$, or OCF$_3$.

[0424] In one particular embodiment, with respect to the compound of formula XXIb-XXIc, each $R^4$ is independently CI, F, CF$_3$, or OCF$_3$. In another particular embodiment, each $R^4$ is F.

[0425] In one particular embodiment, the compound is any one of the compounds NTP-8001-8 138 or NTP-81 41-8 182.

[0426] In one particular embodiment, the compound is any one of the compounds NTP-8034, NTP-8055, NTP-8067, NTP-8069, NTP-8081, NTP-8097, NTP-8147 or NTP-8 153.

[0427] In one particular embodiment, the compound is any one of the compounds NTP-8034, NTP-8055, or NTP-8067.

[0428] In a specific embodiment, the compound is according to formula:
or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

[0429] In a specific embodiment, the compound is according to formula:

or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

[0430] In a specific embodiment, the compound is according to formula:

or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

[0431] In a specific embodiment, the compound is according to formula:

or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

[0432] In one particular embodiment, the compound is any one of the compounds NTP-1 1001, NTP-1 1002 or NTP-1 1003.

[0433] In one particular embodiment, the compound is any one of the compounds NTP-12001-1 2100 or NTP-12001.

[0434] In one particular embodiment, the compound is according to formula I, R$^{2b}$ is acyl; and the compound is any one of the compounds NTP-1 2045-1 2040, NTP-12045-1 2048, NTP-12057-12062, NTP-12070-12072, NTP-12077-1 2081, NTP-12084-12088, NTP-12090, NTP-12092 or NTP-12094.

[0435] In one particular embodiment, the compound is any one of the compounds NTP-1 5001-15021 or NTP-1 5022.
In one particular embodiment, with respect to the compound of formula I, the compound is according to formula XXIIa, or XXIIb:

and wherein each R· is independently NH₂, NMe₂, NEt₂, Me, Et, n-Pr, i-Pr, or n-Bu; and each R² is independently H, alkyl, haloalkyl, halo, alkoxy, or haloalkoxy;

or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

In one particular embodiment, with respect to the compound of formula XXIIa-XXIIb, R³a is Me. In another particular embodiment, R³a is Et.

In one particular embodiment, with respect to the compound of formula XXIIa-XXIIb, R³a is NH₂, NMe₂, or NEt₂.

In one particular embodiment, with respect to the compound of formula XXIIa-XXIIb, R⁴ is H Cl, F, CF₃, or OCF₃. In another particular embodiment, R⁴ is H.

In one particular embodiment, with respect to the compound of formula XXIIb-XXIIc, each R⁴ is independently Cl, F, CF₃, or OCF₃. In another particular embodiment, each R⁴ is F.

In one particular embodiment, the compound is any one of the compounds selected from compounds with compound NTP-16001-16036.

In one particular embodiment, the compound is any one of the compounds NTP-16024, NTP-16031, NTP-16032 or NTP-16033.

In certain aspects, the present invention provides compounds according to formula:
or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

[0446] In one particular embodiment, the compound is NTP-13001 or NTP-13002.

[0447] In one particular embodiment, the compound is NTP-3046.

[0448] In one embodiment a compound of the invention is not an isotopic variant.

[0449] In one aspect a compound of the invention is a solvate.

[0450] In certain aspects, the present invention provides prodrugs and derivatives of a compound of the invention according to the formula above. Prodrugs are derivatives of a compound of the invention, which have metabolically 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.

[0452] While specified groups for each embodiment have generally been listed above separately, a compound of the invention includes one in which several or each embodiment in the above Formula, as well as other formulae presented herein, is selected from one or more of particular members or groups designated respectively, for each variable. Therefore, this invention is intended to include all combinations of such embodiments within its scope.

[0453] In certain aspects, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an epilepsy-treating amount of a compound according to formula XXnia, or XXHlb:
In one embodiment, with respect to the pharmaceutical composition, the epilepsy-treating amount is about 0.5 mg/kg body weight/day to about 100 mg/kg body weight/day.

In one embodiment, with respect to the pharmaceutical composition, the epilepsy-treating amount is about 1 mg/kg body weight/day to about 50 mg/kg body weight/day.

In one embodiment, with respect to the pharmaceutical composition, the epilepsy-treating amount is about 1 mg/kg body weight/day to about 10 mg/kg body weight/day.

In certain aspects, the present invention provides a unit dosage form of the pharmaceutical composition of a compound of formula XXIIIa or XXIIIb comprising about 1 to 2000 mg of the compound.

In one embodiment, with respect to the unit dose, the dose comprises about 1 to 1700 mg of the compound according to formula XXIIIa or XXIIIb.

In one embodiment, with respect to the unit dose, the dose comprises about 1 to 1000 mg of the compound according to formula XXIIIa or XXIIIb.

In one embodiment, with respect to the unit dose, the dose comprises about 1 to 750 mg of the compound according to formula XXIIIa or XXIIIb.

In one embodiment, with respect to the unit dose, the dose comprises about 250 to 750 mg of the compound according to formula XXIIIa or XXIIIb.

In one embodiment, with respect to the unit dose, the dose comprises about 500 to 750 mg of the compound according to formula XXIIIa or XXIIIb.

In further aspects, the present invention provides pharmaceutical compositions comprising a compound of formulae I-XXIIIb or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In one embodiment, with respect to the pharmaceutical composition, the carrier is a parenteral carrier.

In one embodiment, with respect to the pharmaceutical composition, the carrier is an oral carrier.

In one embodiment, with respect to the pharmaceutical composition, the carrier is a topical
carrier.

[0467] In further aspects, the present invention provides methods for treating NKCC mediated disease or condition in a mammal comprising the step of administering to said mammal a compound of formulae I-I\text{Xe} or a pharmaceutical composition thereof.

[0468] In one embodiment, with respect to the method, the condition is selected from the group consisting of addictive disorders, Alzheimer's Disease, anxiety disorders, ascites, autism, bipolar disorder, cancer, depression, endothelial corneal dystrophy, edema, epilepsy, glaucoma, Huntington's Disease, inflammatory pain, insomnia, ischemia, migraine, migraine with aura, migraine without aura, neuropathic pain, nociceptive neuralgia, nociceptive pain, ocular diseases, pain, itch, excessive itch, pruritis, neuropathic pruritis, Parkinson's disease, personality disorders, postherpetic neuralgia, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.

[0469] In further aspects, the present invention provides methods for treating GABA\textsubscript{A} receptor mediated disease or condition in a mammal comprising the step of administering to said mammal a compound of invention or a pharmaceutical composition thereof.

[0470] In one embodiment, with respect to the method, the condition is selected from the group consisting of addictive disorders, Alzheimer's Disease, anxiety disorders, ascites, autism, bipolar disorder, cancer, depression, endothelial corneal dystrophy, edema, epilepsy, glaucoma, Huntington's Disease, inflammatory pain, insomnia, ischemia, migraine, migraine with aura, migraine without aura, neuropathic pain, nociceptive neuralgia, nociceptive pain, ocular diseases, pain, itch, excessive itch, pruritis, neuropathic pruritis, Parkinson's disease, personality disorders, postherpetic neuralgia, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.

[0471] In one particular embodiment, with respect to the method, the disease is epilepsy.

[0472] In further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound of formulae I-XXIII\textsubscript{b} or a pharmaceutical composition thereof.

[0473] In a particular aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition of a compound according to formula I:
wherein Cy, L', R', R, R, R, n, and L are as described herein.

In a particular aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound selected from the group consisting of the sodium, potassium, calcium, or magnesium salt(s) of NTP-8034, NTP-8055, NTP-8067, NTP-8069, NTP-808 1, NTP-8097, NTP-8147, NTP-8153, NTP-1 603 1, NTP 16033, NTP-1 6035, or mixtures thereof or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and said compound.

In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-8034.

In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-8034.

In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-8034.

In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-8034.

In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-8055.

In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-8055.
[0482] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-8055.

[0483] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-8067.

[0484] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-8067.

[0485] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-8067.

[0486] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-8069.

[0487] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-8069.

[0488] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-8069.

[0489] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-8069.

[0490] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-8069.

[0491] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-8081.

[0492] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-8081.

[0493] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-8081.
[0494] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-8081.

[0495] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-8097.

[0496] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-8097.

[0497] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-8097.

[0498] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-8097.

[0499] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-8147.

[0500] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-8147.

[0501] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-8147.

[0502] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-8147.

[0503] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-8153.

[0504] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-8153.

[0505] In a further aspect, the present invention provides a method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-8153.
In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-8153.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-16031.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-16031.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-16031.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-16033.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-16033.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-16033.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-16033.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the sodium salt of NTP-16035.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the potassium salt of NTP-16035.

In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the calcium salt of NTP-16035.
[0518] In a further aspect, the present invention provides a method to treat epilepsy in a mammel comprising the step of administering to said mammal a compound or a pharmaceutical composition comprising said compound, wherein the compound is the magnesium salt of NTP-1 6035.

Synthetic Methods

[0519] Embodiments of the present invention provide methods of modifying compounds of the present invention to increase their lipophilicity. The lipophilicity can be measured by determining the hydrophilic-lipophile balance (HLB) or the partition coefficient (e.g., the distribution of a compound between water and octanoic). In some embodiments, the compound is a diuretic or diuretic-like compound, and in particular embodiments, the compound is termed a "loop diuretic." For a discussion of pharmacological properties of diuretics. See generally, Hardman, Limbird, and Gilman, (Eds.) (2001) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill Medical Publishing Division (10th ed.). Further included are compounds that affect cation-chloride cotransporters. Furosemide and bumetanide are classic examples of NKCC antagonists.


[0521] Compounds of the present invention can include isomers, tautomers, zwitterions, enantiomers, diastereomers, racemates, or stereochemical mixtures thereof. Compounds of the present invention can also comprise isosteres.

[0522] The term "isosteres" as used herein broadly refers to elements, functional groups, substituents, molecules, or ions having different molecular formulae but exhibiting similar or identical physical properties. For example, tetratole is an isostere of carboxylic acid because it mimics the properties of carboxylic acid even though they both have different molecular formulae. Typically, two isosteric molecules have similar or identical volumes and shapes. Other physical properties that isosteric compounds usually share include boiling point, density, viscosity, and thermal conductivity. However, certain properties are usually different: dipolar moments, polarity, polarization, size, and shape since the external orbitals may be hybridized differently.

[0523] The term "isomers" as used herein refers broadly to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing with respect to the arrangement or configuration of the atoms in space. Additionally, the term "isomers" includes stereoisomers and geometric isomers. The terms "stereoisomer" or "optical isomer" as used herein refer to a stable isomer that has at least one chiral atom or restricted rotation giving rise to perpendicular dissymmetric planes (e.g., certain biphenyls, allenes, and spiro compounds) and can rotate plane-polarized light. Because asymmetric centers and other chemical structure can exist in some of the compounds of the present
invention, which may give rise to stereoisomerism, the invention contemplates stereoisomers and mixtures thereof. The compounds of the present invention and their salts can include asymmetric carbon atoms and may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. Typically, such compounds will be prepared as a racemic mixture. If desired, however, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. Tautomers are readily interconvertible constitutional isomers and there is a change in connectivity of a ligand, as in the keto and enol forms of ethyl acetoacetate (including tautomers of any said compounds.) Zwitterions are inner salts or dipolar compounds possessing acidic and basic groups in the same molecule. At neutral pH, the cation and anion of most zwitterions are equally ionized.

Pharmaceutical Compositions

[0524] The compounds (e.g., analogs, derivatives, and prodrugs) of the present invention or pharmacologically acceptable salts thereof may be formulated into pharmaceutical compositions of various dosage forms. To prepare the pharmaceutical compositions of the invention, at least one compound, or pharmaceutically acceptable salts thereof, as the active ingredient is intimately mixed with appropriate carriers and additives according to techniques well known to those skilled in the art of pharmaceutical formulations. Remington, The Science And Practice of Pharmacy, 20th Edition, (Gennaro, A. R., Chief Editor), Philadelphia College of Pharmacy and Science, 2000, which is incorporated by reference in its entirety.

[0525] Pharmaceutically acceptable salts of the compounds described herein include the salt form of the compound permitting its use or formulation as a pharmaceutical and which retains the biological effectiveness of the free acid and base of the specified compound and that is not biologically or otherwise undesirable. Examples of such salts are described in Wermuth and Stahi, (Eds.) (2002) Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Wiley-Verlag Helvetica Acta, Zurich, herein incorporated by references in its entirety. Examples of such salts include alkali metal salts and addition salts of free acids and bases. Examples of pharmaceutically acceptable salts, without limitation, include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogen phosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyrate-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates, methanesulfonates, ethane sulfonates, propanesulfonates, toluenesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates. In some embodiments, pharmaceutically acceptable salt includes sodium, potassium, calcium, ammonium, trialkylaryl ammonium, and tetraalkylammonium salts.
Similarly, compositions for liquid preparations include solutions, emulsions, dispersions, suspensions, syrups, and elixirs, with suitable carriers and additives including but not limited to water, alcohols, oils, glycols, preservatives, flavoring agents, coloring agents, and suspending agents. Typical preparations for parenteral administration comprise the active ingredient with a carrier such as sterile water or parenterally acceptable oil including but not limited to polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil, with other additives for aiding solubility or preservation may also be included. In the case of a solution, it can be lyophilized to a powder and then reconstituted immediately prior to use. For dispersions and suspensions, appropriate carriers and additives include aqueous gums, celluloses, silicates, or oils.

The pharmaceutical compositions according to embodiments of the present invention include those suitable for oral, rectal, topical, nasal, inhalation (e.g., via an aerosol) buccal (e.g., sub-lingual), vaginal, topical (e.g., both skin and mucosal surfaces, including airway surfaces), transdermal administration and parenteral (e.g., subcutaneous, intramuscular, intradermal, intraarticular, intrapleural, intraperitoneal, intrathecal, intracerebral, intracranially, intraarterial, or intravenous), although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active agent which is being used. Pharmaceutical compositions of the present invention are particularly suitable for oral, sublingual, parenteral, implantation, nasal, and inhalational administration. The carriers and additives used for such pharmaceutical compositions can take a variety of forms depending on the anticipated mode of administration.

Compositions for oral administration may be solid preparations including but not limited to tablets, sugar-coated tablets, hard capsules, soft capsules, granules, lozenges, and powders, with suitable carriers and additives being starches, sugars, binders, diluents, granulating agents, lubricants, and disintegrating agents. Tablets and capsules represent advantageous oral dosage forms for many medical conditions because of their ease of use and higher patient compliance.

Compositions for injection will include the active ingredient together with suitable carriers including organic solvents, propylene glycol-alcohol-water, isotonic water, sterile water for injection (USP), emulPhor®-alcohol-water, cremophor-EL® or other suitable carriers known to those skilled in the art. These carriers may be used alone or in combination with other conventional solubilizing agents such as ethanol, a glycol, or other agents known to those skilled in the art.

Where the compounds of the present invention are to be applied in the form of solutions or injections, the compounds may be used by dissolving or suspending in any conventional diluent. The diluents include but are not limited to physiological saline, Ringer's solution, an aqueous glucose solution, an aqueous dextrose solution, an alcohol, a fatty acid ester, glycerol, a glycol, an oil derived from plant or animal sources, and a paraffin. These preparations may be prepared according to any conventional method known to those skilled in the art.

Compositions for nasal administration may be formulated as aerosols, drops, powders, and gels.
Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a physiologically acceptable aqueous or non-aqueous solvent. Such formulations are typically presented in single or multidose quantities in a sterile form in a sealed container. The sealed container can be a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device such as a single use nasal inhaler, pump atomizer or an aerosol dispenser fitted with a metering valve set to deliver an effective amount, which is intended for disposal once the contents have been completely used. When the dosage form comprises an aerosol dispenser, it will contain a propellant such as a compressed gas, air as an example, or an organic propellant including a fluorochlorohydrocarbon or fluorohydrocarbon.

Compositions suitable for buccal or sublingual administration include but are not limited to tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth or gelatin and glycerin.

Compositions for rectal administration include but are not limited to suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include but are not limited to ointments, gels, and patches.

The preferred forms of administration in the present invention are oral forms known in the art of pharmaceutics. The pharmaceutical compositions of the present invention may be orally administered as a capsule (hard or soft), tablet (film coated, enteric coated or uncoated), powder or granules (coated or uncoated) or liquid (solution or suspension). The formulations may be conveniently prepared by any of the methods well-known in the art. The pharmaceutical compositions of the present invention may include one or more suitable production aids or excipients including fillers, binders, disintegrants, lubricants, diluents, flow agents, buffering agents, moistening agents, preservatives, colorants, sweeteners, flavors, and pharmaceutically compatible carriers.

For each of the recited embodiments, the compounds can be administered by a variety of dosage forms as known in the art. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, chewable tablets, quick dissolve tablets, effervescent tablets, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, tablets, multi-layer tablets, bi-layer tablets, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, beads, powders, gum, granules, particles, microparticles, dispersible granules, cachets, douches, suppositories, creams, topicals, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, ingestibles, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

Other compositions known to those skilled in the art can also be applied for percutaneous or subcutaneous administration, such as plasters.
Further, in preparing such pharmaceutical compositions comprising the active ingredient or ingredients in admixture with components necessary for the formulation of the compositions, other conventional pharmacologically acceptable additives may be incorporated, including but are not limited to excipients, stabilizers, antiseptics, wetting agents, emulsifying agents, lubricants, sweetening agents, coloring agents, flavoring agents, isotonicity agents, buffering agents, and antioxidants. Additives include but are not limited to starch, sucrose, fructose, dextrose, lactose, glucose, mannitol, sorbitol, precipitated calcium carbonate, crystalline cellulose, carboxymethyl cellulose, dextrin, gelatin, acacia, EDTA, magnesium stearate, talc, hydroxypropylmethylcellulose, and sodium metabisulfite.

Compounds of the present invention may be used in conjunction with delivery systems that facilitate delivery of the agents to the central nervous system. For example, various blood brain barrier permeability enhancers may be used, if desired, to transiently and reversibly increase the permeability of the blood brain barrier to a treatment agent. Such BBB permeability enhancers include but are not limited to leukotrienes, bradykinin agonists, histamine, tight junction disruptors (e.g., zonulin, zot), hyperosmotic solutions (e.g., mannitol), cytoskeletal contracting agents, and short chain alkylglycerols (e.g., 1,0-pentylglycerol). Oral, sublingual, parenteral, implantation, nasal and inhalational routes can provide delivery of the active agent to the CNS. In some embodiments, the compounds of the present invention may be administered to the CNS with minimal effects on the peripheral nervous system.

Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the compounds described herein can be formulated in a time release formulation, for example in a composition that includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers may be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

Other compounds which can be included by admixture are, for example, medically inert ingredients (e.g., solid and liquid diluent), such as lactose, dextrosesaccharose, cellulose, starch or calcium
phosphate for tablets or capsules, olive oil or ethyl oleate for soft capsules and water or vegetable oil for suspensions or emulsions; lubricating agents such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; gelling agents such as colloidal clays; thickening agents such as gum tragacanth or sodium alginate, binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinylpyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuff; sweeteners; wetting agents such as lecithin, polysorbates or laurysulphates; and other therapeutically acceptable accessory ingredients, such as humectants, preservatives, buffers and antioxidants, which are known additives for such formulations.

[0543] In further embodiments, the present invention provides kits including one or more containers comprising pharmaceutical dosage units comprising an effective amount of one or more compounds of the present invention. Kits may include instructions, directions, labels, marketing information, warnings, or information pamphlets.

Prodrugs

[0544] The blood-brain barrier (BBB) is a physical barrier and system of cellular transport mechanisms between the blood vessels in the central nervous system (CNS) and most areas of the CNS itself. The BBB maintains homeostasis by restricting the entry of potentially harmful chemicals from the blood, and by allowing the entry of essential nutrients. However, the BBB can pose a formidable barrier to delivery of pharmacological agents to the CNS for treatment of disorders or maintaining or enhancing normal and desirable brain functions, such as cognition, learning, and memory. Prodrugs of the present invention are capable of passage across the blood-brain barrier and may undergo hydrolysis by CNS esterases to provide the active compound. Further, the prodrugs provided herein may also exhibit improved bioavailability, improved aqueous solubility, improved passive intestinal absorption, improved transporter-mediated intestinal absorption, protection against accelerated metabolism, tissue-selective delivery, less (or fewer) side effects, lessened or no deleterious drug interaction with other medications, and/or passive enrichment in the target tissue.

[0545] The term “prodrug” is intended to refer to a compound that is converted under physiological conditions, by solvolysis or metabolically to a specified compound that is pharmaceutically/pharmacologically active. The “prodrug” can be a compound of the present invention that has been chemically derivatized such that it retains some, all or none of the bioactivity of its parent drug compound and is metabolized in a subject to yield the parent drug compound. The prodrug of the present invention may also be a “partial prodrug” in that the compound has been chemically derivatized such that it retains some, all or none of the bioactivity of its parent drug compound and is metabolized in a subject to yield a biologically active derivative of the compound.

[0546] Moreover, as shown in the previously presented schemes, prodrugs can be formed by attachment of biocompatible polymers, such as those previously described including polyethylene glycol (PEG), to compounds of the present invention using linkages degradable under physiological conditions.
See also Schacht, et al. (1997) Poly(ethylene glycol) Chemistry and Biological Applications, American Chemical Society, San Francisco, CA 297-315. Attachment of PEG to proteins can be employed to reduce immunogenicity and/or extend the half-life of the compounds provided herein. Any conventional PEGylation method can be employed, provided that the PEGylated agent retains at least some pharmaceutical activity.


Dosages

The amount of active compound in a therapeutic composition according to this invention may vary according to factors such as the disease state, age, gender, weight, patient history, risk factors, predisposition to disease, administration route, pre-existing treatment regime (e.g., possible interactions with other medications), and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of therapeutic situation.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. In therapeutic use for treatment of conditions in mammals (e.g., humans) for which the compounds of the present invention or an appropriate pharmaceutical composition thereof are effective, the compounds of the present invention may be administered in an effective amount. The dosages as suitable for this invention may be a composition, a pharmaceutical composition or any other compositions described herein.

For each of the recited embodiments, the dose for a patient can be about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, or 0.10 μg, as well as about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0 μg, as well as about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 μg, as well as about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 μg, as well as about 10, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 μg, as well as about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1,000 μg and all increments therein. Preferably, the dose for a patient can be about 0.05-5 μg and all increments therein. Alternatively, the dose for a
patient can be about 1-10 µg and all increments therein. The dose for a patient can also be about 10-
40 µg and all increments therein, about 6-24 µg and all increments therein, about 20-80 µg and all
increments therein, about 40-80 µg and all increments therein, about 100-250 µg and all increments
therein, or about 100-500 µg and all increments therein. More preferably, the dosage can be about 0.5, 1,
2, 5, 6, 10, 12, 18, 20, 24, 30, 40, 50, 80, or 90 µg. Preferably, the dosage can be about 0.5, 2, 6, 8, 10, 12, 18,
20, 30, 40, or 80 µg.

Alternatively, for each of the recited embodiments, the dose for a patient may be about 0.01,
0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, or 0.10 mg, as well as about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8,
0.9, or 1.0 mg, as well as about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg, as well as about 10, 11, 12, 13, 14,
15, 16, 17, 18, 19, or 20 mg, as well as about 10, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90,
95 or 100 mg, as well as about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1,000 mg and all
increments therein. Preferably, the dose for a patient may be about 0.05-5 mg and all increments therein.
Alternatively, the dose for a patient may be about 1-10 mg and all increments therein. The dosage for a
patient may also be about 10-40 mg and all increments therein, about 6-24 mg and all increments therein,
about 20-80 mg and all increments therein, about 40-80 mg and all increments therein, about 100-
250 mg and all increments therein, or about 100-500 mg and all increments therein. More preferably, the
dosage may be about 0.5, 1, 2, 5, 6, 10, 12, 18, 20, 24, 30, 40, 50, 80, or 90 mg. Preferably, the dosage
may be 0.5, 2, 6, 8, 10, 12, 18, 20, 30, 40, or 80 mg.

Alternatively, for each of the recited embodiments, the dose for a patient may be about 0.01,
0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, or 0.10 g, as well as about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8,
0.9, or 1.0 g, as well as about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 g, as well as about 10, 11, 12, 13, 14,
15, 16, 17, 18, 19, or 20 g, as well as about 10, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90,
95 or 100 g, as well as about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1,000 g and all
increments therein. Preferably, the dose for a patient may be about 0.05-5 g and all increments therein.
Alternatively, the dose for a patient may be about 1-10 g and all increments therein. The dose for a patient may also be
about 10-40 g and all increments therein, about 6-24 g and all increments therein, about 20-80 g and all
increments therein, about 40-80 g and all increments therein, about 100-250 g and all increments therein,
or about 100-500 g and all increments therein. More preferably, the dosage may be about 0.5, 1, 2, 5, 6,
10, 12, 18, 20, 24, 30, 40, 50, 80, or 90 g. Preferably, the dosage may be 0.5, 2, 6, 8, 10, 12, 18, 20, 30, 40,
or 80 g.

For each of the recited embodiments, the dose for a patient can be about 0.01, 0.02, 0.03, 0.04,
0.05, 0.06, 0.07, 0.08, 0.09, or 0.10 µg/kg, as well as about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or
1.0 µg/kg, as well as about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 µg/kg, as well as about 10, 11, 12, 13, 14,
15, 16, 17, 18, 19, or 20 µg/kg, as well as about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 µg/kg, as well as about 10, 11,
12, 13, 14, 15, 16, 17, 18, 19, or 20 µg/kg, as well as about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 µg/kg, as well as about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1,000 µg/kg and all
increments therein. Preferably, the dose for a patient can be about 0.05-5 µg/kg and all increments
therein. Alternatively, the dose for a patient can be about 1-10 μg/kg and all increments therein. The dose for a patient can also be about 10-40 μg/kg and all increments therein, about 6-24 μg/kg and all increments therein, about 20-80 μg/kg and all increments therein, about 40-80 μg/kg and all increments therein, about 100-250 μg/kg and all increments therein, or about 100-500 μg/kg and all increments therein. More preferably, the dosage can be about 0.5, 1, 2, 5, 6, 10, 12, 18, 20, 24, 30, 40, 50, 80, or 90 μg/kg.

Preferably, the dosage can be 0.5, 2, 6, 8, 10, 12, 18, 20, 30, 40, or 80 μg/kg.

Alternatively, for each of the recited embodiments, the dosage may be about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, or 0.10 mg/kg, as well as about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0 mg/kg, as well as about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg/kg, as well as about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg, as well as about 10, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 mg/kg, as well as about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1,000 mg/kg and all increments therein. Preferably, the dosage for a patient may be about 0.05-5 mg/kg and all increments therein. Alternatively, the dose for a patient may be about 1-10 mg/kg and all increments therein. The dose for a patient may also be about 10-40 mg/kg and all increments therein, about 6-24 mg/kg and all increments therein, about 20-80 mg/kg and all increments therein, about 40-80 mg/kg and all increments therein, about 100-250 mg/kg and all increments therein, or about 100-500 mg/kg and all increments therein. More preferably, the dosage may be about 0.5, 1, 2, 5, 6, 10, 12, 18, 20, 24, 30, 40, 50, 80, 90, or 100 mg/kg. Preferably, the dosage may be 0.5, 2, 6, 8, 10, 12, 18, 20, 30, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 80, 85, 90, or 100 mg/kg.

Alternatively, for each of the recited embodiments, the dose for a patient can be about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, or 0.10 g/kg, as well as about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0 g/kg, as well as about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 g/kg, as well as about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 g/kg, as well as about 10, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 g/kg, as well as about 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1,000 g/kg and all increments therein. Preferably, the dose for a patient can be about 0.05-5 g/kg and all increments therein. Alternatively, the dose for a patient can be about 1-10 g/kg and all increments therein. The dose for a patient can also be about 10-40 g/kg and all increments therein, about 6-24 g/kg and all increments therein, about 20-80 g/kg and all increments therein, about 40-80 g/kg and all increments therein, about 100-250 g/kg and all increments therein, or about 100-500 g/kg and all increments therein. More preferably, the dosage can be about 0.5, 1, 2, 5, 6, 10, 12, 18, 20, 24, 30, 40, 50, 80, or 90 g/kg. Preferably, the dosage can be 0.5, 2, 6, 8, 10, 12, 18, 20, 30, 40, or 80 g/kg.

For each of the recited embodiments, the dosage is typically administered once, twice, or thrice a day, although more frequent dosing intervals are possible. The dosage may be administered every day, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, and/or every 7 days (once a week). In one embodiment, the dosage may be administered daily for up to and including 30 days, preferably
between 7-10 days. In another embodiment, the dosage may be administered twice a day for 10 days. If the patient requires treatment for a chronic disease or condition, the dosage may be administered for as long as signs and/or symptoms persist. The patient may require “maintenance treatment” where the patient is receiving dosages every day for months, years, or the remainder of their lives. In addition, the composition of this invention may be to effect prophylaxis of recurring symptoms. For example, the dosage may be administered once or twice a day to prevent the onset of symptoms in patients at risk, especially for asymptomatic patients.

For each of the recited embodiments, the patient can receive “pretreatment” with the compounds described herein wherein the compounds described herein are administered every day, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, and/or every 7 days (once a week). In one embodiment, the dosage can be administered daily for up to and including 30 days, preferably between 7-10 days. In another embodiment, the dosage can be administered twice a day for 10 days. If the patient requires treatment for a chronic disease or condition requiring prolonged treatment, the dosage of alkaline may be administered for as long as symptoms persist.

In one embodiment, the compounds described herein are administered in an initial dose of 20-80 mg on the first day of treatment and then at least two dosages of about 40 mg on the second day. In another embodiment the compounds described herein are administered in an initial dose of 0.5-2 mg on the first day of treatment and then at least two dosages of about 2 mg on the second day. In another embodiment, the compounds described herein are administered in an initial dose of 10-20 mg on the first day of treatment and then at least two dosages of about 20 mg on the second day. In yet another embodiment, the compounds described herein are administered in an initial dose of 5-10 mg on the first day of treatment and then at least two dosages of about 10 mg on the second day.

For administration via injection, in one embodiment the treatment begins as a course of 4 injections at 0, 12, 24, and 36 hours. The injections then may continue once, twice, or thrice a day for as long as signs and/or symptoms persists. Alternatively, the injections may be maintained to prevent the recurrence of disease. Also, the injections may be administered as a prophylaxis for patients at risk, especially asymptomatic patients.

The dosage may be administered as a single dose, a double dose, a triple dose, a quadruple dose, and/or a quintuple dose. The dosages may be administered singularly, simultaneously, and sequentially.

For each of the recited embodiments, the dosage of the compounds described herein may be an effective amount of the compounds described herein, an amount effective for prophylaxis, and for acute treatment, or an amount effective for prevention. The dosage of the compounds described herein may be an amount of the compounds described herein effective to reduce signs or symptoms of a disease, an amount effective to prevent signs and/or symptoms of a disease, to reduce the severity of signs and/or symptoms of a disease, to eliminate signs and/or symptoms of a disease, to slow the development of signs or symptoms of a disease, to prevent the development of signs and/or symptoms of a disease, or effect
prophylaxis of signs or symptoms of a disease.

[0563] The dosage form may be any form of release known to persons of ordinary skill in the art. The compositions of the present invention may be formulated to provide immediate release of the active ingredient or sustained or controlled release of the active ingredient. In a sustained release or controlled release preparation, release of the active ingredient may occur at a rate such that blood levels are maintained within a therapeutic range but below toxic levels over an extended period of time (e.g., 4 to 24 hours). The preferred dosage forms include immediate release, extended release, pulse release, variable release, controlled release, timed release, sustained release, delayed release, long acting, and combinations thereof. The ability to obtain immediate release, extended release, pulse release, variable release, controlled release, timed release, sustained release, delayed release, long acting characteristics, and combinations thereof is known in the art.

[0564] It will be appreciated that the pharmacological activity of the compositions may be monitored using standard pharmacological models that are known in the art. Furthermore, it will be appreciated that the inventive compositions may be incorporated or encapsulated in a suitable polymer matrix or membrane for site-specific delivery, or may be functionalized with specific targeting agents capable of effecting site specific delivery. For instance, the dosage form may be made such that it preferably releases in the central nervous system or peripheral nervous system. These techniques, as well as other drug delivery techniques are well known in the art. Determination of optimal dosages for a particular situation is within the capabilities of those skilled in the art. See e.g., Gennaro (2000) Remington, The Science And Practice of Pharmacy, 20th Edition, Philadelphia College of Pharmacy and Science.

[0565] In further embodiments, compounds according to the present invention may be administered 1.5 to 6 mg daily, for example, 1 tablet or capsule three times a day. In some embodiments, compounds according to the present invention may be administered 60 to 240 mg/day, for example, 1 tablet or capsule three times a day. In other embodiments, compounds according to the present invention may be administered 10 to 20 mg daily, for example, 1 tablet or capsule once a day. In some embodiments, compounds according to the present invention may be administered 60 mg per day. In other embodiments, compounds according to the present invention may be administered 10 to 20 mg daily, for example, 1 tablet or capsule once a day. It should be noted that lower doses may be administered, particularly for intravenous administration. Moreover, administration of a lower dose than administered for the parent compound may prevent undesirable peripheral effects such as diuresis.

[0566] In additional further embodiments, compounds are administered at about 0.5, 1.0, or 2.0 mg; compounds are administered at about 20-80 mg or two 40 mg doses daily; compounds are administered 0, 200, 500, or 1,250 mg/kg, preferably at about 10-30 mg/kg or 200-500 mg/kg; compounds are administered at 5, 10, 20, 40, or 200 mg. More preferably, the compounds are administered orally and daily at about 1, 10, or 20 mg.
Routes of Administration

The compositions described herein may be administered in any of the following routes: buccal, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardiac intracerebroventricular, intradermal, intramuscular, intranasal, intracocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. The preferred routes of administration are buccal and oral. The administration can be local, where the composition is administered directly, close to, in the locality, near, at, about, or in the vicinity of, the site(s) of disease, e.g., inflammation, or systemic, wherein the composition is given to the patient and passes through the body widely, thereby reaching the site(s) of disease. Local administration can be administration to the cell, tissue, organ, and/or organ system, which encompasses and/or is affected by the disease, and/or where the disease signs and/or symptoms are active or are likely to occur. Administration can be topical with a local effect, composition is applied directly where its action is desired. Administration can be enteral wherein the desired effect is systemic (non-local), composition is given via the digestive tract. Administration can be parenteral, where the desired effect is systemic, composition is given by other routes than the digestive tract.

Second Agents

Second agents for treatment in combination with compositions of the present invention include, but are not limited to, phenytoin, carbamazepine, barbiturates, phenobarbitai, mephobarbital, trimethadione, mephenytoin, paramethadione, phenethyldate, phenacemide, metharbital, benzchlorpropamide, phensuximide, primidone, methsuximide, ethosuximide, amidoglutethimide, diazepam, clonazepam, clorazepate, fosphenytoin, ethosuximide, valproate, felbamate, gabapentin, lamotrigine, retigabine, rufinamide, topiramate, vigabatrin, pregabalin, tiagabine, zonisamide, clobazam, thiopental, midazolam, propofol, levetiracetam, oxcarbazepine, CCPene, GYK152466, serotonin receptor agonists, ergotamine, dihydroergotamine, sumatriptan, propranolol, metoprolol, atenolol, timolol, nadolol, nifedipine, nimodipine, verapamil, aspirin, ketoprofen, tofenamic acid, mfenamic acid, naproxen, methysergide, paracetamol, clonidine, isuride, iprazochromine, butalbital, benzodiazepines, divalproex sodium and other similar classes of compounds. See U.S. Patent No. 6,495,601 and U.S. Patent Application Publication No. 2002/0082252.

For example, in addition to the composition described herein patients may also be treated with antidepressants (e.g., tricyclic antidepressants [e.g., amitriptyline (Elavil®), desipramine (Norpramin®), imipramine (Tofranil®), nortriptyline (Aventyl®, Pamelon®)] ; Serotonin and norepinephrine reuptake inhibitors (SNRIs) [e.g., venlafaxine (Effexor®), duloxetine (Cymbalta®)]; norepinephrine and dopamine reuptake inhibitors (NDRIs) [e.g., bupropion (Wellbutrin®)]; combined reuptake inhibitors and receptor blockers [e.g., trazodone (Desyrel®), nefazodone (Serzone®), maprotiline, mirtazpine (Remeron®)]; monamine oxidase inhibitors (MAOIs) [e.g., isocarboxazid (Marplan®), phenelzine (Nardil®), tranylcypromine (Parnate®)] and selective serotonin reuptake inhibitors (SSRIs) [e.g., citalopram
(Celexa®), escitalopram (Lexapro®), fluoxetine (Prozac®), paroxetine (Paxil®, Pexeva®), sertraline (Zoloft®)] fluvoxamine (Luvox®), and amitriptyline; anticonvulsants to stabilize abnormal electrical activity in the nervous system caused by injured nerves (e.g., gabapentin (NEURONTIN®), pregabalin (LYRICA®), carbamazepine (Tegretol®), lamotrigine (Lamictal®), topiramate (Topamax®), felbamate (Felbatol®), tiagabine (Gabitril®), diazepam rectal (Diastat®), pheno barbital, phenytoin (Dilantin®) primidone (Mysoline®), valproate (Depakote®), vigabatrin, oxcarbazepine (Trileptal®), zonisamide (Zonegran®), and levetiracetam (Keppra®)); steroids (e.g., corticosteroid); analgesics (e.g., acetaminophen (Tylenol®), codeine (Tylenol #2,3,4®), propoyl APA (Darvocet®), propoeylphene (Darvon®), fentanyl patch (duragesic®), hydromo rphone (Palladone®), morphine (MS Contin®), oxycodone (Percocet®, OxyContin®, Percodan®), pentazocine (Talwin NX®), tramadol APAP (Ultracet®), tamadol (Ultram®), hydrocode APAP (Vicodin®)); lithium, and non-steroidal anti-inflammatory drugs (NSAID) (e.g., Tylenol®, Motrin®, salicylates (e.g., acetylsalicylic acid (Aspirin), aminopyrinn, benorylate/benorilate, choline magnesium salicylate, Difunisal®, ethenzamide, fainlamine, methyl salicylate, magnesium salicylate, salicyl salicylate, and salicylamide), aryalkanoic acids (e.g., Diclofenac®, Aceclofenac®, Acemethacin®, Aliclofenac®, Bromfenac®, Etodolac®, Indomethacin®, Nabumetone®, Oxametacin®, Proglumetacin®, Sulindac®, and Tolmetin®) 2-Arylpropionic acids (profens) (e.g., Ibuprofen®, Alminoprofen®, Carprofen®, Dexibuprofen®, Dexketoprofen®, Fenbufen®, Fenoprofen®, Flunoxaprofen®, Flurbiprofen®, Ibuprofen®), Indoprofen®, Ketorolac®, Loxoprofen®, Naproxen®, Oxaprozin®, Pirprofen®, Suprofen®, Tiaprofenic acid); N-Arylanthranilic acids (fenamic acids) (e.g., mefenamic acid, fluynamic acid, meclofenamic acid, tolenamic acid, pyrazolidine derivatives, Phenylbutazone®, Ampyrone®, Azapropazone®, Clofenez®, Kebuzone®, Metamizole®, Mofebutazone®, Oxyphenbutazone®, Phenazone®, and Sulfipyrazone®); and oxicams (e.g., Piroxicam®, Droxicam®, Lornoxicam®, Meoxicam®, and Tenoxicam®).

[0570] Such second agents can be administered in the same formulation (e.g., the same pill) or in a separate formulation as the compounds of the present invention. It is preferred that the second agents described above be co-administered with the compounds of the present invention.

[0571] The second agents described herein can be administered with the compounds of the present invention simultaneously, sequentially, prior to, or after administering of the compounds of the present invention. Where the administration of the second agents described herein is simultaneous, the second agent and the compounds of the present invention are administered together or within a very short time interval (e.g., 5 minutes). Where the administration of the second agent is administered as pre-treatment, the second agent is administered prior to administration of the compounds of the present invention for any length of time contemplated herein.

Nutritional Compositions

[0572] The compositions of the compounds described herein may be used in (or consumed in) nutritional supplements; dietary supplements; medical foods; nutriceuticals; food-stuffs such as
pharmaceutical-benefit foods (e.g., "foods"); beverages including fortified (e.g., orange juice with calcium); traditional (e.g., regular oatmeal, whole-grain breads), and "designer" products (e.g., protein bars, smart spreads, smart bars, energy bars). The compounds described herein may be formulated in health bars, confections, animal feeds, cereals, dietary supplements, yogurts, cereal coatings, foods, nutritive foods, functional foods, and combinations thereof.

Psychotherapy

[0573] The compounds, pharmaceutical compositions, and treatment regimes described herein may be used in combination with psychotherapy. In one embodiment, methods for the treatment of addictive disorder, anxiety disorders, bipolar disorders, and/or depression may further comprise psychotherapy.

[0574] Several types of psychotherapy or "talk therapy"-can help people with depression. In some embodiments, the regimens are short-term (e.g., 10 to 20 weeks) and other regimens are longer-term (e.g., 1-10 years), depending on the needs of the individual. Two main types of psychotherapies: cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT)-have been shown to be effective in treating neuropsychiatric disorders (e.g., addictive disorders, anxiety disorders, bipolar disorders, and depression).

GABA<sub>A</sub> Receptors in Disease

[0575] GABA<sub>A</sub> receptors have a pentameric structure generally comprising two α subunits and two β subunits with a fifth regulatory subunit. Specific GABA<sub>A</sub> subunits are expressed throughout the brain in distinct spatial and developmental patterns and display different responses to known pharmacological modulators. The specific GABA<sub>A</sub> variant receptors are described in the PCT publication WO2010/085352, which is incorporated herein by reference herein.

[0576] In particular, compounds of invention described herein may be used for the regulation, including prevention, prophylaxis, diagnosis, prognosis, management, and treatment, of a range of conditions that involve the GABA<sub>A</sub> receptor including but not limited to the disorders described herein.

[0577] In another embodiment, compounds described herein show selective effect on GABA<sub>A</sub> receptors in the CNS and less side-effects usually associated with agents that act on GABA<sub>A</sub> receptors. For example, compounds described herein exhibit less sedation, decreased respiration, decreased cognition, or decreased motor function.

[0578] For example, compounds described herein are effective in humans and animals to decrease seizures, decrease pain responses, and decrease migraine. Several of the compounds described herein preferentially bind to GABA<sub>A</sub> receptor subtypes and have a modulatory effect on GABA<sub>A</sub> receptors that is different from classic benzodiazepine and barbiturate mechanisms. Such compounds may also show specific effects on presynaptic release of GABA or other transmitters that alters or normalizes neuronal excitability. Unlike some compounds described herein, several compounds described herein do not act on the Na"K"2Cl" cotransporter (NKCC1 or NKCC2). Some compounds described herein that are similarly ineffective at NKCC1 or NKCC2 are contemplated. Compounds described herein described herein may
not elicit diuresis. For example, many of compounds described herein may not increase urine output, sodium excretion, or potassium excretion.

[0579] Overall, compounds described herein may be well-tolerated toxicologically and demonstrate no CNS side effects after oral administration. The inventors surprisingly discovered that selected compounds described herein may act to specifically increase neuronal inhibition via a novel mechanism of action (not NKCC dependent). The inventors surprisingly discovered that selected compounds described herein may act at GABAergic interneurons or interneuron terminals, that regulate neuronal Firing, and therefore, these compounds may inhibit abnormal firing. More specifically, selected compounds described herein may increase pre-synaptic inhibition without depressing post-synaptic GABA receptors. This highly selective mechanism of action is novel and contrasts with the broad, non-specific activity of benzodiazepines and barbiturates.

[0580] Benzodiazepines and barbiturates are known to be effective but are poorly tolerated because these compounds activate most GABA_A subtype receptors (e.g., "fire-hose effect"). In contrast, selected compounds described herein may enhance inhibition via action at specific GABA_A receptor subtypes, preferentially those that modulate synaptic release of GABA. Due to this selectivity selected compounds described herein may avoid the typical CNS side effects (e.g., sedation) usually associated with known GABAergic compounds.

[0581] All publications (e.g., Non-Patent Literature), patents, patent application publications, and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All such publications (e.g., Non-Patent Literature), patents, patent application publications, and patent applications are herein incorporated by reference to the same extent as if each individual publication, patent, patent application publication, or patent application was specifically and individually indicated to be incorporated by reference.

[0582] Further embodiments of the present invention will now be described with reference to the following examples. The examples contained herein are offered by way of illustration and not by any way of limitation. Exemplary syntheses for compounds according to the present invention are provided in, e.g., Published U.S. Application No. US 2007/0 149526A1 and International Patent Application No. PCT/US201 0/001 70, the entire disclosures of which are incorporated by reference as if fully set forth herein.

**GENERAL SYNTHETIC PROCEDURES**

[0583] The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. 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.

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.

The compounds provided herein, for example, may be prepared by the reaction of a carboxylic acid 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 substituted biarylamides that have been listed herein. The compounds provided herein may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.


The compounds of the invention can be prepared using general procedures or synthetic schemes described below.

**GENERAL SYNTHETIC SCHEMES**

The following general schemes are or can be used to prepare the compounds of the invention.

**Synthesis of Sulfones** 
(R$^3 = SO_2R_3^{3b}$)

The sulfones compounds of the invention are or can be prepared using the synthetic schemes described below.

Generic Synthetic Scheme G1
[0590]  a. ClSO₂H, 150°C; b. i) Na₂SO₃, NaOH, H₂O; ii) R₃I, MeOH, NaOH; c. H₂SO₄, HNO₃; d. NaHCO₃; e. SOCl₂, ROH; f. Zn, NH₄Cl; g. R²CHO (R² = R₃); NaBH(OAc)₃, CCl₃; h. LiOH; i. R²CHO, Et₃SiH, TFA, CH₃CN

Generic Synthetic Scheme G2
[0591] a. CISO$_3$H, 150°C; b. i) Na$_2$S0$_3$, NaOH, H$_2$O; ii) R$^{3}$I, MeOH, NaOH; c. H$_2$SO$_4$, HNO$_3$; d. NaHC$_3$O$_3$; e. SO$_2$Cl, ROH; f. Zn, NH$_4$Cl; g. R$^{2a}$CHO (R$^{2a}$ = R$^{2b}$), NaBH(OAc)$_3$, C$_2$H$_5$CH$_2$Cl; h. LiOH; i. R$^{2b}$CHO, Et$_3$SiH, TFA, CH$_3$CN

Generic Synthetic Scheme G3 (Tetrazoles and Oxadiazoles)*
[0592] a. N₃, HBTU, DEA, DMF; b. TFAA, DIEA, Pyridine; or POCl₃, 1,4-dioxane; c. NaN₃, NH₄Cl, DMF; d. i) NH₂OH.HCl, NaHCO₃, MeOH; ii) CDI, THF;

[0593] *see Schemes G1 and G2 for the synthesis of the starting carboxylic acid

Alternate Synthetic Scheme G4 (Oxadiazoles)***
[0594] a. CuCN, NMP, µW, 200 °C; b. the carboxamide side product can be converted back to the nitrile by reacting with POCl₃; c. i) NH₂OH·HCl, NaHCO₃, MeOH; ii) CDI, THF; d. KOH, MeOH;

[0595] Starting bromo compound can be prepared by following synthetic methods known to the skilled in the art.

[0596] In the above Schemes G1-G4 L², n, R², R³b, R³a, R⁴ are as described herein.

EXAMPLES

Synthesis of Representative Compounds of the Invention

Compound 1

3-(N,N'-DibutylaminoM-phenoxy-S-methylsulfonylbenzamide

General Method A

Scheme 1

a) 4-Chloro-3-methanesulfonyl-benzoic acid

[0597] A round bottom flask was charged with sodium sulfite (14.82 g, 0.118 mol), water (50 mL) and
the reaction cooled to 0°C and 4-chloro-3-(chlorosulfonyl)benzoic acid (10 g, 0.039 mol) was added in portions. The reaction mixture turned turbid (white). The reaction mixture was stirred at room temperature for 3 h. and acidified with 6N HCl. The sulfinsc acid precipitated out which was filtered and dried. The solid was dissolved in methanol (15 mL) and water (7 mL) and 6N NaOH was added to make the pH 9 and iodomethane (13.33 mL, 0.214 mol) was added and the reaction was stirred at room temperature for 3 days. Methanol was removed under reduced pressure and the resultant solution was acidified with 3N HCl. The product precipitated out which was filtered and dried to give a pale brown solid (7.26 g). 1H NMR (300 MHz, DMSO-d6) δ 8.49 (d, J=2.1 Hz, 1H), 8.19 (dd, J= 8.1 & 2.4 Hz, 1H), 7.86 (d, J= 8.4 Hz, 1H), 3.41 (s, 3H).

b) 4-chloro-3-(methylsulfonyl)-5-nitrobenzoic acid

[0598] A round bottom flask was charged with 4-chloro-3-(methylsulfonyl)benzoic acid (5.30 g, 22.59 mmol), sulfuric acid (12 mL, 0.226 mol) and the reaction mixture was cooled to 0 °C and nitric acid (1.44 mL, 33.88 mmol) was added slowly and the reaction was stirred at 110 °C for 1 hour. HPLC indicated the formation of the product. The reaction mixture was cooled to room temperature and poured into ice cold water. The product precipitated out which was filtered and dried to give the product as white solid (4.95 g). 1H NMR (300 MHz, DMSO-d6) δ 8.77 (d, J=2.1 Hz, 1H), 8.65 (d, J= 2.1 Hz, 1H), 3.49 (s, 3H).

c) 3-(Methylsulfonyl)-S-nitro-4-phenoxybenzoic acid

[0599] A round bottom flask was charged with 4-chloro-3-(methylsulfonyl)-5-nitrobenzoic acid (2.12 g, 7.58 mmol), phenol (2.0 mL, 22.74 mmol), sodium bicarbonate (4.46 g, 53.07 mmol) and water (20 mL) and the reaction was heated to 85 °C over night. LC/MS indicated completion of the reaction so the reaction was cooled to room temperature. 3N HCl was added and the product precipitate out which was filtered and dried in the oven to give the product as off white solid (1.44 g). MS m/z: 335.9 [M-1].

[0600] 1H NMR (300 MHz, DMSO-d6) δ 8.70 (d, J=1.8 Hz, 1H), 8.61 (d, J= 2.1 Hz, 1H), 7.30 (t, J=7.5 Hz, 2H), 7.08 (t, J=7.2 Hz, 1H), 6.89 (d, J= 7.5 Hz, 2H), 3.35 (s, 3H).

d) Methyl 3-(methylsulfonyl)-5-nitro-4-phenoxybenzoate

[0601] A round bottom flask was charged with 3-(methylsulfonyl)-5-nitro-4-phenoxybenzoic acid (2.45 g, 7.26 mmol), methanol (40 mL) and thionyl chloride (1.85 mL, 25.42 mmol) was added slowly at room temperature. The reaction mixture was then heated to 60 °C over night. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The resultant solid was dissolved in ethyl acetate and washed with saturated sodium bicarbonate. The solvents were removed under reduced pressure to give the product as yellow solid (2.2 g).

[0602] 1H NMR (300 MHz, CDCl3) S 8.99 (d, J=2.1 Hz, 1H), 8.78(d, J= 2.4 Hz, 1H), 7.32 (t, J=9.0 Hz, 2H), 7.14 (t, J=7.2 Hz, 1H), 6.90 (d, J= 7.5 Hz, 2H), 4.03 (s, 3H), 3.35 (s, 3H).
e) 3-Amino-5-(methylsulfonyl)-4-phenoxybenzoate

A round bottom flask was charged with methyl 3-(methylsulfonyl)-5-nitro-4-phenoxy benzoate (2.5 g, 7.12 mmol) and ethanol (50 mL) and the reaction mixture was heated to 85°C and ammonium chloride (3.81 g, 71.16 mmol) in water (25 mL) was added and the reaction was continued at 85°C. Iron powder (1.59 g, 28.46 mmol) was then added in 3 portions over 15 minutes and heating was continued for another 2 hours. The reaction mixture was cooled to 60°C and poured into CH2Cl2 (150 mL). The two layers formed were separated and the organic layer washed with brine and dried over Na2SO4. The solvents were removed to give the product as pale yellow solid (1.75 g).

f) Methyl 3-(butylamino)-5-(methylsulfonyl)-4-phenoxybenzoate

A reaction vial was charged with methyl 3-amino-5-(methylsulfonyl)-4-phenoxybenzoate (600 mg, 1.87 mmol), butyraldehyde (0.893 mL, 9.97 mmol) and 1,2-dichloroethane (5 mL) and the reaction was stirred for 15 minutes. Triacetoxyborohydride (0.985 g, 4.65 mmol) was added and the reaction was stirred at room temperature over night. There was still some amine left and so one more batch of triacetoxyborohydride (0.985 g, 4.65 mol) and butyraldehyde (0.893 mL, 9.97 mmol) were added and the reaction was stirred for another day. LC/MS indicated both mono and di-alkylated products. The reaction was quenched with water and extracted with ethyl acetate. The solvents were removed and the residue purified by flash chromatography to give the product as white solid (540 mg).

g) 3-(Butylamino)-5-(methylsulfonyl)-4-phenoxybenzoic acid

A round bottom flask was charged with methyl 3-(butylamino)-5-(methylsulfonyl)-4-phenoxybenzoate (540 mg, 1.43 mmol), methanol (3 mL), THF (3 mL) and IN lithium hydroxide (1.44 mL, 1.44 mmol) and the reaction was stirred for 2 hours. The organic solvents were removed under reduced pressure and the aqueous residue was acidified with 3N HCl. White solid precipitated out which was filtered and dried under vacuum to give the product as white solid.

h) 3-(Dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzoic acid
A round bottom flask was charged with 3-(butylamino)-5-(methylsulfonyl)-4-phenoxybenzoic acid (500 mg, 1.38 mmol), butyraldehyde (0.129 mL, 1.44 mmol), and acetonitrile (7 mL) and the reaction was cooled to 0 °C and trifluoroacetic acid (0.756 mL, 10.18 mmol) was added slowly. The reaction was stirred at 0 °C for 30 minutes and triethylsilane (1.67 mL, 10.46 mmol) was added slowly and the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water at 0 °C and basified with ammonium hydroxide to pH 9. The reaction mixture was stirred for 30 minutes and acidified to pH 5 by adding saturated citric acid. The reaction mixture was extracted with ethyl acetate, washed with brine, dried over Na₂SO₄. The organic solvents were removed under reduced pressure and the residue was purified by flash chromatography to afford the product as pale yellow solid (540 mg).

**Compound 7**

[0610] MS m/z: 418.3 [M-1]^+; ¹H NMR (300 MHz, DMSO-d₆) δ 8.00 (d, J=1.8 Hz, IH), 7.82 (d, J=2.1 Hz, IH), 7.25 (t, J=8.1 Hz, 2H), 7.02 (t, J=7.2 Hz, IH), 6.77 (d, J=7.8 Hz, 2H), 3.28 (s, 3H), 3.01 (t, J=7.2 Hz, 4H), 1.19-1.10 (m, 4H), 1.00-0.93 (m, 4H), 0.72 (t, J=7.2 Hz, 6H).

i) 3-(Dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzamide

[0611] A reaction vial was charged with 3-(dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzoic acid (50 mg, 0.12 mmol), HATU (54 mg, 0.14 mmol), N,N-diisopropylethyl amine (0.026 mL, 0.14 mmol), 0.5 M ammonia in dioxane (3 mL) and DMF (4 mL). The reaction was stirred at room temperature overnight, and then quenched with water and extracted with ethyl acetate. The solvents were removed and the residue was purified by flash chromatography to give the product as white solid (33.1 mg).

[0612] MS m/z: 419.2 [M+1]^+; ¹H NMR (300 MHz, DMSO-d₆) δ 8.23 (bs, IH), 7.98 (d, J=2.4 Hz, IH), 7.82 (d, J=2.1 Hz, IH), 7.51 (bs, IH), 7.24 (t, J=8.7 Hz, 2H), 7.01 (t, J=7.2 Hz, IH), 6.75 (d, J=8.4 Hz, 2H), 3.28 (s, 3H), 3.01 (t, J=7.2 Hz, 4H), 1.17-1.06 (m, 4H), 1.01-0.91 (m, 4H), 0.72 (t, J=7.5 Hz, 6H).

**Compound 4**

(3-(Dibutylamino)-5-(methylsulfonyl)-4-phenoxyphenyl)(4-morpholinyl)methanone

[0613] The title compound was prepared following General Method A using morpholine in step i. MS m/z: 489.3 [M+1]^+.

**Compound 7**
3-(Methylsulfonyl)-4-phenoxy-5-(piperidin-1-yl)benzoic acid

Scheme 2

a) Methyl 3-(methylsulfonyl)-4-phenoxy-5-(piperidin-1-yl)benzoate

[0614] A microwave vial was charged with methyl 3-amino-5-(methylsulfonyl)-4-phenoxybenzoate (200 mg, 0.62 mmol), potassium carbonate (0.5161 g, 3.73 mmol), diiodopentane (0.1389 ml, 0.93 mmol), acetonitrile (5.0 ml) and the reaction was heated in a microwave reactor for 5 h at 160° C. The reaction was only 50% complete by LC/MS. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to give the product as colorless oil (72 mg). MS m/z: 390.2 [M+1]. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.34 (d, $J$ = 2.1 Hz, 1H), 7.91 (d, $J$=2.1 Hz, 1H), 7.25 (t, $J$=7.2 Hz, 2H), 7.06 (t, $J$=6.0 Hz, 1H), 6.82 (d, $J$ = 6.3 Hz, 2H), 3.94 (s, 3H), 2.94 (t, $J$=5.1 Hz, 4H), 1.35-1.22 (m, 6H).

b) 3-(Methylsulfonyl)-4-phenoxy-5-(piperidin-1-yl)benzoic acid

[0615] A round bottom flask was charged with methyl 3-(methylsulfonyl)-4-phenoxy-5-(piperidin-1-yl)benzoate (72 mg, 0.18 mmol), methanol (3ml), THF (3 mL) and 1N lithium hydroxide (3.0 ml) was added and the reaction was stirred at room temperature over night. The organic solvents were removed under reduced pressure and the aqueous layer was acidified with 3N HCl. The product precipitated out was filtered and dried to give a pale yellow solid (39 mg). MS m/z: 376.3 [M+1]. $^1$H NMR (300 MHz, DMSO-d6) $\delta$ 8.06 (d, $J$=1.8 Hz, 1H), 7.82 (d, $J$=2.1 Hz, 1H), 7.28 (t, $J$=7.5 Hz, 2H), 7.05 (t, $J$=7.2 Hz, 1H), 6.83 (d, $J$=8.1 Hz, 2H), 2.89 (t, $J$=5.1 Hz, 4H), 1.26-1.13 (m, 6H).
Compound 12

3-{N,N-Dibutylamino)-4-phenoxy-5-ethylsulfonyl}benzoic acid

[0616] The title compound was prepared following General Method A and beginning with ethyl iodide in step 1 to give the product as a white solid. MS m/z: 434.2 [M+H]^+.

[0617] ^1H NMR (300 MHz, DMSO- d_6) δ 7.98 (d, J=1.5 Hz, 1H), 7.84 (d, J= 1.8 Hz, 1H), 7.25 (t, J=8.1 Hz, 2H), 7.02 (t, J=7.2 Hz, 1H), 6.75 (d, J= 8.1 Hz, 2H), 3.39 (q, J=7.5 Hz, 2H), 3.02 (t, J=6.9 Hz, 4 H), 1.22-1.07 (m, 7H), 1.03-0.91 (m, 4H), 0.72 (t, J=7.2 Hz, 6H).

Compound 16

3-(Methylsulfonyl)-4-phenoxy-5-(2,2,2-trifluoroethylamino)benzoic acid

Scheme 3

a) Methyl 3-(methylsulfonyl)-4-phenoxy-5-(2,2,2-trifluoroethylamino)benzoate

[0618] A round bottom flask was charged with methyl 3-amino-5-(methylsulfonyl)-4-phenoxybenzoate (150 mg, 0.47 mmol), trifluoroacetic acid (10.4 ml, 0.140 mol) and sodium borohydride (53 mg, 1.40
mmol) was added in portions and the reaction was stirred at 70° C over night. The reaction mixture was cooled and water was added and extracted with ethyl acetate. The solvents were removed under reduced pressure and the residue was purified by flash chromatography to give the product as pale brown solid (135 mg).

**[0619]** 1H NMR (300 MHz, CDC13) δ 8.14 (d, J= 1.8 Hz, IH), 7.77 (d, J= 1.8 Hz, IH), 7.32 (t, J=6.9 Hz, 2H), 7.11(t, J=8.4 Hz, IH), 6.87 (d, J= 8.7 Hz, 2H), 23.85-3.76 (m, 2H).

b) 3-(Methylsulfonyl)-4-phenoxy-5-(2,2,2-trifluoroethylamino)benzoic acid

**[0620]** A round bottom flask was charged with methyl 3-(methylsulfonyl)-4-phenoxy-5-(2,2,2-trifluoroethylamino)benzoate (135 mg, 0.33 mmol), methanol (3 ml), THF (3 mL) and 1N lithium hydroxide (0.33 ml, 0.33 mmol) and the reaction stirred for 2 hours. The organic solvents were removed under reduced pressure and the aqueous residue was acidified with 3N HCl. The mixture was extracted with ethyl acetate and the solvents were removed under reduced pressure. The residue was purified by flash chromatography to give the product as pale yellow solid.

**[0621]** MS m/z: 388.0 [M-1]. 1H NMR (300 MHz, DMSO- d6) δ 7.79-7.76 (m, 2H), 7.28 (d, J= 2.1 Hz, IH), 7.28 (t, J=8.4 Hz, 2H), 7.03 (t, J=7.5 Hz, IH), 6.78 (d, J= 7.8 Hz, 2H), 5.12 (t, J=6.6 Hz, IH), 4.07-4.01 (m, 2H).

**Compound 20**

3-(A,iV-Dibutylamino)-4-phenoxy-5-iso-butyIsulfonylbenzoic acid

[0622] The title compound was prepared following General Method A and beginning with iso-butyl bromide in step 1 to give the product as a white solid. MS m/z: 460.3 [M-1].

**[0623]** 1H NMR (300 MHz, DMSO- d6) δ 7.99 (d, J=2.1 Hz, IH), 7.83 (d, J= 2.1 Hz, IH), 7.25 (t, J=7.8 Hz, 2H), 7.03 (t, J=7.2 Hz, IH), 6.76 (d, J= 7.8 Hz, 2H), 3.32 (d, J=6.6 Hz, 2H), 3.03 (t, J=6.9 Hz, 4 H), 1.98-1.89 (m, IH), 1.20-1.10 (m, 4H), 1.03-0.95 (m, 4H), 0.91 (s, 3H), 0.89 (s, 3H), 0.73 (t, J=7.2 Hz, 6H).

**Compound 21**

2-(Dibutylamino)-6-(methylsulfonyl)-[1,1'-biphenyl]-4-carboxylic acid
a) Ethyl 4-chloro-3-(methylsulfonyl)-5-nitrobenzoate

[0624] To a stirred mixture of crude 4-chloro-3-(methylsulfonyl)-5-nitrobenzoic acid (3.80 g, 13.59 mmol) and potassium carbonate (2.254 g, 16.31 mol) in DMF (30 mL) was added iodoethane (1.30 mL, 16.31 mmol) and the reaction mixture was stirred at rt overnight. The mixture was partitioned between water and EtOAc and the aqueous phase was extracted with EtOAc. The combined EtOAc phases were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by silica gel column (0-50% EtOAc/hexane) to afford the product as light yellow solid (2.8 g, 67%).

[0625] $^1$H NMR (300 MHz, CDC$_1$_3): 8 8.98 (d, 1H, $J$ = 2.1 Hz), 8.61 (d, 1H, $J$ = 2.1 Hz), 4.49 (q, 2H, $J$ = 7.2 Hz), 3.37 (s, 3H), 1.46 (t, 3H, $J$ = 7.2 Hz).

b) Ethyl 2-(methylsulfonyl)-6-nitro-[1,1'-biphenyl]-4-carboxylate

[0626] To a solution of ethyl 4-chloro-3-(methylsulfonyl)-5-nitrobenzoate (300 mg, 0.97 mmol),
phenylboronic acid (178 mg, 1.46 mmol), toluene (10 mL), and 2.0 M aq. potassium carbonate (1.46 mL, 2.92 mmol) under nitrogen was added tetrakis(triphenylphosphine)palladium(0) (56 mg, 0.05 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with EtOAc (20 mL) and filtered with Celite. The filter cake was washed with ethyl acetate (10 mL). The filtrate was concentrated and the residue was purified by silica gel column (0-50% EtOAc/hexane) to afford an off-white solid (230 mg, 68%).

[0627] 1H NMR (300 MHz, CDCl3): δ 9.08 (d, 1H, J = 1.8 Hz), 8.62 (d, 1H, J = 1.5 Hz), 7.60-7.38 (m, 5H), 4.51 (q, 2H, J = 7.2 Hz), 2.65 (s, 3H), 1.48 (t, 3H, J = 7.2 Hz).

c) Ethyl 2-amino-6-(methylsulfonyl)-[1,l'-biphenyl]-4-carboxylate

[0628] A round bottom flask was charged with ethyl 2-(methylsulfonyl)-6-nitro-[1,l'-biphenyl]-4-carboxylate (230 mg, 0.66 mmol), ammonium chloride (352 mg, 6.58 mmol), and THF-MeOH (1:1, 20 mL). Zinc (430 mg, 6.58 mmol) was added under nitrogen and the reaction mixture was stirred at rt for 20 min and then heated at 65 °C for 1 h. TLC and LC-MS indicated completion of the reaction. The reaction mixture was concentrated to dryness and the residue was treated with EtOAc and filtered through Celite and the filter cake was washed with EtOAc. The filtrate was concentrated in vacuo to afford the title compound as a white foam (210 mg, 100%).

[0629] MS m/z: 320.1 [M+1] +; 1H NMR (300 MHz, CDCl3): δ 8.24 (d, 1H, J = 1.5 Hz), 7.68 (d, 1H, J = 1.5 Hz), 7.60-7.45 (m, 3H), 7.37 (d, 2H, J = 7.8 Hz), 4.43 (q, 2H, J = 7.2 Hz), 3.79 (s, 2H), 2.70 (s, 3H), 1.44 (t, 3H, J = 7.2 Hz).

d) Ethyl 2-(butylamino)-6-(methylsulfonyl)-[l,l'-biphenyl]-4-carboxylate

[0630] A reaction vial was charged with ethyl 2-amino-6-(methylsulfonyl)-[1,l'-biphenyl]-4-carboxylate (210 mg, 0.66 mmol), butyaldehyde (0.295 ml, 3.29 mmol) and 1,2-dichloroethane (10 mL), and the reaction was stirred for 15 minutes. Sodium triacetoxyborohydride (697 mg, 3.29 mmol) was added and the reaction was stirred at rt overnight. The reaction was quenched with aq. Na2CO₃ and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-40% EtOAc/hexane) to afford the products as a white solid (190 mg, 77%).

[0631] MS m/z: 376.2 [M+1] +; 1H NMR (300 MHz, CDCl3): δ 8.16 (s, 1H), 7.60-7.48 (m, 4H), 7.32 (d, 2H, J = 6.3 Hz), 4.44 (q, 2H, J = 7.2 Hz), 3.51 (t, 1H, J = 4.8 Hz), 3.13 (q, 2H, J = 6.6 Hz), 2.69 (s, 3H), 1.55-1.40 (m, 5H), 1.35-1.20 (m, 2H), 0.90 (t, 3H, J = 7.2 Hz).

e) 2-(Butylamino)-6-(methylsulfonyl)-[l,l'-biphenyl]-4-carboxylic acid

[0632] To a stirred solution of ethyl 2-(butylamino)-6-(methylsulfonyl)-[1,l'-biphenyl]-4-carboxylate (190 mg, 0.51 mmol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide monohydrate (170
mg, 4.05 mmol). The reaction mixture was stirred at 45 °C overnight, and then the mixture was concentrated in vacuo. The residue was treated with water and adjusted to pH=3 with 2N aq. HCl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-70% EtOAc/hexane) to afford the product as an off-white foam (160 mg, 91%).

**[0633]** MS m/z: 348.2 [M+1]+; 'H NMR (300 MHz, CDCl₃): δ 8.25 (d, 1H, J = 1.2 Hz), 7.64-7.30 (m, 4H), 7.34 (d, 2H, J = 6.9 Hz), 3.15 (t, 2H, J = 6.9 Hz), 2.71 (s, 3H), 1.60-1.40 (m, 2H), 1.36-1.22 (m, 2H), 0.91 (t, 3H, J = 7.2 Hz).

f) 2-(Dibutylamino)-6-(methylsulfonyl)-[1,1′-biphenyl]-4-carboxylic acid

**[0634]** A round bottom flask was charged with 2-(butylamino)-6-(methylsulfonyl)-[1,1′-biphenyl]-4-carboxylic acid (160 mg, 0.46 mmol), butyraldehyde (0.165 mL, 1.84 mmol) and acetonitrile (5 mL). The reaction was cooled to 0 °C and trifluoroacetic acid (0.34 mL, 4.61 mmol) was added slowly. The reaction was stirred at 0 °C for 30 minutes and triethylsilane (0.74 mL, 4.61 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred over night. The reaction mixture was diluted with water at 0 °C and basified with ammonium hydroxide to pH 9. The mixture was stirred for 30 minutes and then acidified to pH 3 by adding saturated citric acid. The reaction mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column (0-60% EtOAc/hexane) to afford the product as pale yellow foam (178 mg, 96%).

**[0635]** MS m/z: 404.5 [M+1]+; 'H NMR (300 MHz, CDCl₃): δ 8.65 (s, 1H), 8.10 (s, 1H), 7.60-7.38 (m, 5H), 2.86 (t, 4H, J = 6.9 Hz), 2.48 (s, 3H), 1.30-1.00 (m, 8H), 0.84 (t, 6H, J = 6.9 Hz).

Compound 163

3-(Dibutylamino)-5-(ethylsulfonyl)-4-(pyridin-3-yl)benzoic acid

![Scheme 5](image-url)
a) 4-Bromo-3-(ethylsulfonyl)benzoic acid

A round bottom flask was charged with sodium sulfite (12.62 g, 0.10 mol) and water (50 mL) and cooled to 0 °C. 4-Bromo-3-(chlorosulfonyl)benzoic acid (10.0 g, 33.39 mmol) was added in portions. The reaction mixture was stirred at room temperature for 3 h, and then acidified with 6N HCl. The solids precipitated out were collected by filtration and dried to give the crude sulfinic acid intermediate. 7 g of the sulfinic acid was dissolved in methanol (15 mL) and water (7 mL) and 6N NaOH was added to adjust pH 9. Iodoethane (14.6 mL, 0.182 mol) was added and the reaction mixture was stirred at room temperature for 3 days. Methanol was removed under reduced pressure and the resultant solution was acidified with 3N HCl. The solids precipitated out were collected by filtration and dried to give the product as a pale brown solid.

b) 4-Bromo-3-(ethylsulfonyl)-5-nitrobenzoic acid

A round bottom flask was charged with 80.0% 4-bromo-3-(ethylsulfonyl)benzoic acid (7.35 g, 20.06 mmol), sulfuric acid (10.7 mL, 0.20 mol) and the reaction mixture was cooled to 0 °C and nitric acid (1.28 mL, 30.09 mmol) was added slowly and the reaction was stirred at 60 °C for 2 days. HPLC indicated the formation of the product. The reaction mixture was cooled to room temperature and then poured into ice cold water. The solids precipitated out were collected by filtration and dried to give the product as white solid (6.1 g, 90%).

c) Ethyl 4-bromo-3-(ethylsulfonyl)-5-nitrobenzoate

To a stirred mixture of 4-bromo-3-(ethylsulfonyl)-5-nitrobenzoic acid (4.1 g, 12 mmol) and potassium carbonate (6.7 g, 48 mmol) in DMF (50 mL) was added iodoethane (4 mL, 48 mmol) and the
reaction mixture was stirred at rt overnight. The mixture was partitioned between water and EtOAc and the aqueous phase was extracted with EtOAc. The combined EtOAc phases were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo to afford the product as light yellow solid (4.06 g).

**[0639]** $^1$H NMR (300 MHz, CDC$_1$3): δ 8.93 (d, 1H, J = 2.1 Hz), 8.47 (d, 1H, J = 2.1 Hz), 4.49 (q, 2H, J = 7.2 Hz), 3.55 (q, 2H, J = 7.2 Hz), 1.46 (t, 3H, J = 7.2 Hz), 1.37 (t, 3H, J = 7.2 Hz).

d) Ethyl 3-amino-4-bromo-5-(ethylsulfonyl)benzoate

**[0640]** A mixture of ethyl 4-bromo-3-(ethylsulfonyl)-5-nitrobenzoate (2.0 g, 5.5 mmol), SnCl$_2$ (5.2 g, 27 mmol), and EtOAc (60 mL) was stirred under nitrogen at 65 °C overnight. TLC indicated the reaction was complete. After cooling, the reaction mixture was treated with water and adjusted to pH 9-10 with solid K$_2$CO$_3$. The organic phase was separated and aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined EtOAc layers were washed with brine and dried over Na$_2$SO$_4$, and concentrated to afford the product as yellow solid (1.5 g).

**[0641]** $^1$H NMR (300 MHz, DMSO-d$_6$): δ 7.69 (s, 2H), 6.24 (s, 2H), 4.32 (q, 2H, J = 7.2 Hz), 3.51 (q, 2H, J = 7.2 Hz), 1.32 (t, 3H, J = 7.2 Hz), 1.12 (t, 3H, J = 7.2 Hz).

e) Ethyl 4-bromo-3-(butylamino)-5-(ethylsulfonyl)benzoate

**[0642]** To a stirred solution of ethyl ethyl 3-amino-4-bromo-5-(ethylsulfonyl)benzoate (1.5 g, 4.5 mmol) and butyraldehyde (1.8 mL, 20 mmol) in 1,2-dichloroethane (40 mL) was added sodium triacetoxyborohydride (4.3 g, 20 mmol) and the reaction mixture was stirred at rt overnight. TLC and LC-MS indicated the reaction was complete with some di-alkylated product. The reaction was quenched with aq. Na$_2$CO$_3$ and extracted with CH$_2$C$_2$ (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by silica gel column (0-20% EtOAc/hexane) to afford the product as white solid (900 mg).

**[0643]** $^1$H NMR (300 MHz, CDC$_1$3): δ 8.07 (d, 1H, J = 1.8 Hz), 7.51 (d, 1H, J = 1.5 Hz), 4.85 (m, 1H), 4.42 (q, 2H, J = 7.2 Hz), 3.47 (q, 2H, J = 7.5 Hz), 3.29 (q, 2H, J = 6.6 Hz), 1.80-1.67 (m, 2H), 1.58-1.44 (m, 2H), 1.43 (t, 3H, J = 7.2 Hz), 1.32 (t, 3H, J = 7.5 Hz), 1.02 (t, 3H, J = 7.2 Hz).

f) Ethyl 3-(butylamino)-5-(ethylsulfonyl)-4-(pyridin-3-yl)benzoate

**[0644]** To a solution of ethyl 4-bromo-3-(butylamino)-5-(ethylsulfonyl)benzoate (130 mg, 0.33 mmol), 3-pyridineboronic acid MIDA ester (155 mg, 0.66 mmol), DMF (4 mL), and 2.0 M aq. potassium carbonate (0.5 mL, 1.0 mmol) under nitrogen was added tetrakis(triphenylphosphine)palladium(0) (38 mg, 0.033 mmol). The mixture was stirred at 100 °C overnight. After cooling, the mixture was diluted with EtOAc (20 mL), washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by silica gel column to afford the product (103 mg).

**[0645]** $^1$H NMR (300 MHz, CDC$_1$3): δ 8.74 (dd, 1H, J = 4.8, 1.5 Hz), 8.48 (d, 1H, J = 1.8 Hz), 8.11 (d,
1H, J = 1.2 Hz), 7.73 (dt, 1H, J = 7.8, 1.8 Hz), 7.60 (s, 1H), 7.50 (dd, 1H, J = 7.8, 4.8 Hz), 4.45 (q, 2H, J = 7.2 Hz), 3.35 (t, 1H, J = 4.8 Hz), 3.14 (q, 2H, J = 6.6 Hz), 2.90-2.60 (m, 2H), 1.55-1.40 (m, 5H), 1.38-1.21 (m, 2H), 1.18 (t, 3H, J = 7.2 Hz), 0.91 (t, 3H, J = 7.2 Hz).

**g) 3-(Butylamino)-5-(ethylsulfonyl)-4-(pyridin-3-yl)benzoic acid**

[0646] To a stirred solution of ethyl 3-(butylamino)-5-(ethylsulfonyl)-4-(pyridin-3-yl)benzoate (103 mg, 0.26 mmol) in water (10 mL) and MeOH (10 mL) was added lithium hydroxide monohydrate (55 mg, 1.3 mmol). The reaction mixture was stirred at rt for 3 h, and then concentrated in vacuo. The residue was treated with water and adjusted to pH=6 with 2N aq. HC1 solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo to afford the product.

[0647] MS m/z: 363.2 [M+1]$^+$; $^1$H NMR (300 MHz, CDC$_3$): δ 8.78 (d, 1H, J = 3.6 Hz), 8.54 (s, 1H), 8.20 (s, 1H), 7.77 (d, 1H, J = 7.8 Hz), 7.65 (s, 1H), 7.54 (dd, 1H, J = 7.5, 5.1 Hz), 3.37 (br s, 1H), 3.16 (t, 2H, J = 6.9 Hz), 2.90-2.65 (m, 2H), 1.58-1.42 (m, 2H), 1.38-1.22 (m, 2H), 1.20 (t, 3H, J = 7.2 Hz), 0.91 (t, 3H, J = 7.2 Hz).

**h) 3-(Dibutylamino)-5-(ethylsulfonyl)-4-(pyridin-3-yl)benzoic acid**

[0648] A round bottom flask was charged with 3-(butylamino)-5-(ethylsulfonyl)-4-(pyridin-3-yl)benzoic acid (73 mg, 0.20 mmol), butyraidehyde (0.18 mL, 2.0 mmol) and acetonitrile (6 mL). The reaction was cooled to 0 °C and trifluoroacetic acid (0.3 mL, 4 mmol) was added slowly. The reaction was stirred at 0 °C for 30 minutes and triethylsilane (0.64 mL, 4 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred over weekend. The reaction mixture was diluted with water at 0 °C and basified with ammonium hydroxide to pH 9. The mixture was stirred for 30 minutes and then acidified to pH 5 by adding saturated citric acid. The reaction mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by silica gel column to afford the title product.

[0649] MS m/z: 419.2 [M+1]+$^+$; $^1$H NMR (300 MHz, DMSO-d$_6$): δ 8.57 (d, 1H, J = 4.2 Hz), 8.41 (s, 1H), 8.25 (s, 1H), 8.00 (s, 1H), 7.75 (d, 1H, J = 7.8 Hz), 7.47 (dd, 1H, J = 7.8, 4.8 Hz), 2.85-2.60 (m, 6H), 1.15-0.85 (m, 11H), 0.76 (t, 6H, J = 6.3 Hz).

**Compound 301**

3-(Dibutylamino)-5-((methylamino)methyl)-2-phenoxybenzenesulfoxonamide
a) 3-(Dibutylamino)-N-methyl-4-phenoxy-5-sulfamoylbenzamide:

[0650] A reaction vial was charged with 3-dibutylamino-4-phenoxy-5-sulfamoyl-benzoic acid (500 mg, 1.193 mmol), methylvamine hydrochloride (95 mg, 1.43 mmol), 0-(7-azabenzotriazol-1-yl)-MMN,M-tetramethyl uranium hexafluorophosphate (544 mg, 1.43 mmol), N,N-diisopropyl ethyl amine (480µL, 2.98 mmol), DMF (5mL) and the mixture was stirred at room temperature over night. The reaction was diluted with ethyl acetate and washed with water, brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue purified by flash chromatography to give the product as white solid (432 mg). MS m/z: 434.2 [M+]⁺.

b) 3-(Dibutylamino)-5-((methylamino)methyl-2-phenoxybenzenesulfonamide:

[0651] A round bottom flask was charged with 3-(dibutylamino)-N-methyl-4-pfienoxy-5-sulfamoylbenzamide (70 mg, 0.161 mmol), THF (3 mL) and B¾.THF (1.0 M in THF) (0.32 mL, 0.323 mmol) was added slowly. The reaction was stirred at room temperature for 1 hour. The reaction was quenched by the dropwise addition of water and extracted with ethyl acetate. The solvent was removed under reduced pressure and the residue purified by flash chromatography to give the product as white solid (11 mg). MS m/z: 420.1 [M+1]⁺. IH NMR (DMSO-d6, 300 MHz): 7.42 (d, J=1.8 Hz, IH), 7.34(d, J=2.1 Hz, 1H), 7.21-7.15 (m, 4H), 6.93 (t, J=7.2 Hz, IH), 6.71 (d, J=7.8 Hz, 2H), 6.43 (bs, IH), 3.93-3.85 (m, IH), 3.56-3.44 (m, IH), 2.97 (t, J=7.2 Hz, 4H), 2.19 (d, J=5.4 Hz, 3H), 1.18-1.09 (m, 4H), 1.03-0.91 (m, 4H), 0.71 (t, J=7.5 Hz, 6H).

Compound 401
3-(N,N-Dibutylamino)-4-phenoxy-5-(trifluoromethyl)benzoic acid

Scheme 7

a) 3-Nitro-4-phenoxy-5-(trifluoromethyl)benzoic acid

A round bottom flask was charged with 4-fluoro-3-nitro-5-(trifluoromethyl)benzoic acid (0.8700 g, 0.00344 mol), phenol (0.906 mL, 0.0133 mol), sodium bicarbonate (1.7325 g, 0.02062 mol) and water (20 mL) and the reaction heated to 85°C over night. The reaction was cooled to room temperature and acidified with 3N HCl and the solid precipitated was filtered and dried under vacuum to give the product as pale yellow solid (1.03 g).

MS m/z: 325.9 [M-CH₃]⁺, ¹H NMR (300 MHz, DMSO-d₆) δ 8.73 (d, J = 2.1 Hz, 1H), 8.51 (d, J = 2.1 Hz, 1H), 7.33 (t, J = 8.4 Hz, 2H), 7.11 (t, J = 7.8 Hz, 2H), 6.95 (d, J = 8.1 Hz, 2H).
b) Methyl 3-nitro-4-phenoxy-5-(trifluoromethyl)benzoate

A round bottom flask was charged with 3-nitro-4-phenoxy-5-(trifluoromethyl)benzoic acid (1.28 g, 3.91 mmol), methanol (40 mL) and thionyl chloride (0.856 mL, 11.74 mmol) was added slowly at room temperature. The reaction mixture was then heated to 60°C over night. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The resultant solid was dissolved in ethyl acetate and washed with saturated sodium bicarbonate. The solvents were removed to afford the product as yellow solid (1.28 g).

\[\text{[0655]} \text{H NMR (300 MHz, CDC13) } \delta 8.74 (d, J=2.1 Hz, 1H), 8.63 (d, J=2.1 Hz, 1H), 7.30 (t, J=8.4 Hz, 2H), 7.11 (t, J=7.8 Hz, 1H), 6.83 (d, J=8.1 Hz, 2H), 4.01 (s, 3H)\]

c) Methyl 3-amino-4-phenoxy-5-(trifluoromethyl)benzoate

A round bottom flask was charged with methyl 3-nitro-4-phenoxy-5-(trifluoromethyl)benzoate (1.28 g, 3.75 mmol) and ethanol (25 mL) and the reaction mixture was heated to 85°C and ammonium chloride (2.01 g, 37.51 mmol) in water (10 mL) was added and the reaction was continued at 85°C. Iron powder (0.84 g, 15 mmol) was then added in 3 portions with 5 minutes apart and heating was continued for another 2 hours. The reaction mixture was cooled to 60°C and poured into DCM (150 mL). The two layers formed were separated and the organic layer was washed with brine and dried over Na₂SO₄. The solvents were removed to give the product as brown solid (1.13g).

\[\text{[0657]} \text{MS m'/r. 312.2 [M+1] } ^1\text{H NMR (300 MHz, DMSO- d₆) } \delta 7.70 (d, J=2.1 Hz, 1H), 7.40 (d, J=2.1 Hz, 1H), 7.29 (t, J=7.5 Hz, 2H), 7.03 (t, J=7.5 Hz, 1H), 6.78 (d, J=7.5 Hz, 2H), 5.55 (bs, 2H), 3.86 (s, 3H)\]

d) Methyl 3-(dibutylamino)-4-phenoxy-5-(trifluoromethyl)benzoate and methyl 3-(butylamino)-4-phenoxy-5-(trifluoromethyl)benzoate

A reaction vial was charged with methyl 3-amino-4-phenoxy-5-(trifluoromethyl)benzoate (300 mg, 0.96 mmol), butyaldehyde (0.388 mL, 4.34 mmol) and 1,2-dichloroethane (5 mL) and the reaction was stirred for 15 minutes. Triacetoxyborohydride (0.508 g, 2.41 mmol) was added and the reaction was stirred at room temperature over night. There was still some amine left and so one more batch of NaB(OAc)₃H (2.5 eq) and butyaldehyde (4.5 eq) were added and the reaction was stirred for another day. LC/MS indicated both mono and di alkylated products. The reaction was quenched with water and extracted with ethyl acetate. The solvents were removed and the residue was purified by flash chromatography. \( ^1\text{H NMR indicated a mixture of both mono- and di-alkylated products. The mixture was taken to the next step without further purification. }\)

e) 3-(Butylamino)-4-phenoxy-5-(trifluoroniethyl)benzoic acid and 3-(dibutylamino)-4-phenoxy-5-
A round bottom flask was charged with a mixture of methyl 3-(dibutylamino)-4-phenoxy-5-(trifluoromethyl)benzoate and methyl 3-(butylamino)-4-phenoxy-5-(trifluoromethyl)benzoate (ratio 7:3, 300 mg), methanol (3mL), THF (3mL) and 1N lithium hydroxide (3 mL) was added and the reaction was stirred at room temperature over night. The organic solvents were removed under reduced pressure and the aqueous layer was acidified with 3N HCl and extracted with ethyl acetate. The solvents were removed under reduced pressure and the residue was purified by flash chromatography to give the dibutyl product as a white solid (78 mg) and the mono-butyl product as a white solid (67 mg).

**[0660]** MS m/z: 312.2 [M+1]VH NMR (300 MHz, DMSO- $d_6$) (mono butyl) δ 7.48 (d, $J=2.1$ Hz, 1H), 7.42 (d, $J=2.1$ Hz, 1H), 7.29 (t, $J=8.7$ Hz, 2H), 7.03 (t, $J=7.2$ Hz, 1H), 6.78 (d, $J=7.8$ Hz, 2H), 5.38 (t, $J=5.7$ Hz, 1H), 3.11-3.04 (m, 2H), 1.44-1.34 (m, 2H), 1.20-1.08 (m, 2H), 0.79 (t, $J=7.2$ Hz, 3H). $^1$H NMR (300 MHz, DMSO- $d_6$) (di-butyl) δ 8.02 (d, $J=1.8$ Hz, 1H), 7.91 (d, $J=1.8$ Hz, 1H), 7.23 (t, $J=7.5$ Hz, 2H), 7.01 (t, $J=7.2$ Hz, 1H), 6.75 (d, $J=7.8$ Hz, 2H), 3.08 (t, $J=7.5$ Hz, 4H), 1.29-1.19 (m, 4H), 1.13-1.03 (m, 4H), 0.80 (t, $J=7.5$ Hz, 6H).

**Compound 418**

3-(Dibutylamino)-4-phenoxybenzoic acid

Scheme 8
a) 3-Nitro-4-phenoxybenzoic acid

A round bottom flask was charged with 4-fluoro-3-nitrobenzoic acid (0.50 g, 2.70 mmol), phenol (1.27 g, 13.5 mmol), sodium bicarbonate (1.82 g, 21.6 mmol) and water (10 mL). The reaction mixture was heated to 85 °C for 6h and TLC indicated complete consumption of the starting material. After cooling, the reaction mixture was extracted with ethyl ether to remove the excess phenol. The aqueous phase was acidified with 3N HCl to pH=3 and extracted with ethyl acetate (3 x 30 mL). The combined EtOAc layers were washed with brine and dried over Na₂SO₄. The solvents were removed under reduced pressure to get a light yellow solid (0.70 g, 100%).

MS \( m/z \): 258.0 [M-1]⁺; \(^1\)H NMR (300 MHz, CDCl₃): \( \delta \) 8.69 (d, 1H, \( J = 2.1 \) Hz), 8.17 (dd, 1H, \( J = 9.0, 2.1 \) Hz), 7.47 (t, 2H, \( J = 8.1 \) Hz), 7.31 (t, 1H, \( J = 7.5 \) Hz), 7.15 (d, 2H, \( J = 8.1 \) Hz), 7.00 (d, 1H, \( J = 8.7 \) Hz).

b) Ethyl 3-amino-4-phenoxybenzoate

A round bottom flask was charged with ethyl 3-nitro-4-phenoxybenzoate (0.75 g, 2.61 mmol), ammonium chloride (1.40 g, 26.1 mmol), and THF-MeOH (1:1, 20 mL). Zinc (1.71 g, 26.1 mmol) was added under nitrogen and the reaction mixture was stirred at 60 °C for 3h. TLC and LC/MS indicated completion of the reaction. The reaction mixture was filtered through Celite and the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was treated with EtOAc and filtered again. The filtrate was concentrated in vacuo to afford the title compound as thick oil (0.67 g, 100%).

MS \( m/z \): 258.2 [M+1]⁺; \(^1\)H NMR (300 MHz, CDCl₃): \( \delta \) 7.52 (d, 1H, \( J = 2.1 \) Hz), 7.40 (dd, 1H, \( J = 8.4, 2.1 \) Hz), 7.37 (t, 2H, \( J = 8.4 \) Hz), 7.15 (t, 1H, \( J = 7.5 \) Hz), 7.03 (d, 2H, \( J = 7.5 \) Hz), 6.80 (d, 1H, \( J = 8.7 \) Hz), 4.36 (q, 2H, \( J = 7.2 \) Hz), 3.98 (s, 2H), 1.40 (t, 3H, \( J = 7.2 \) Hz).
c) Ethyl 3-(dibutylamino)-4-phenoxybenzoate

To a stirred solution of ethyl 3-amino-4-phenoxybenzoate (300 mg, 1.17 mmol) and butyraldehyde (0.52 mL, 5.83 mmol) in 1,2-dichloroethane (10 mL) was added sodium triacetoxyborohydride (1.24 g, 5.83 mmol) and the reaction mixture was stirred at 40 °C overnight. TLC and LC-MS indicated the reaction completed. The reaction was quenched with aq. Na₂CO₃ and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-20% EtOAc/hexane) to afford the product as colorless oil (400 mg, 93%).

MS m/z: 370.2 [M+1]+; ²H NMR (300 MHz, CDCl₃): δ 7.71 (d, 1H, J = 1.8 Hz), 7.57 (dd, 1H, J = 8.4, 2.1 Hz), 7.31 (t, 2H, J = 7.8 Hz), 7.08 (t, 1H, J = 7.5 Hz), 6.93 (d, 2H, J = 7.8 Hz), 6.89 (d, 1H, J = 8.7 Hz), 4.38 (q, 2H, J = 7.2 Hz), 3.16 (t, 4H, J = 7.5 Hz), 1.55-1.35 (m, 7H), 1.30-1.15 (m, 4H), 0.86 (t, 6H, J = 7.2 Hz).

d) 3-(Dibutylamino)-4-phenoxybenzoic acid

To a stirred solution of ethyl 3-(dibutylamino)-4-phenoxybenzoate (400 mg, 1.08 mmol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide monohydrate (363 mg, 8.66 mmol). The reaction mixture was stirred at 60 °C overnight, and then the mixture was concentrated in vacuo. The residue was treated with water and adjusted to pH=3 with 2N aq. HCl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to afford the product as off-white solid (370 mg, 100%).

MS m/z: 342.2 [M+1]+; ²H NMR (300 MHz, CDCl₃): δ 7.76 (d, 1H, J = 2.1 Hz), 7.64 (dd, 1H, J = 8.4, 2.1 Hz), 7.34 (t, 2H, J = 7.5 Hz), 7.11 (t, 1H, J = 7.5 Hz), 6.96 (d, 2H, J = 7.5 Hz), 6.90 (d, 1H, J = 8.4 Hz), 3.18 (t, 4H, J = 7.2 Hz), 1.53-1.40 (m, 4H), 1.33-1.17 (m, 4H), 0.88 (t, 6H, J = 7.2 Hz).

Compound 436

4-Phenoxy-3-(2-phenylacetamido)-5-(trifluoromethyl)benzoic acid

a) Methyl 4-phenoxy-3-(2-phenylacetamido)-5-(trifluoromethyl)benzoate
To a stirred solution of methyl 3-amino-4-phenoxy-5-(trifluoromethyl)benzoate (0.200 g, 0.00064 moles) in tetrahydrofuran (5.21 ml) was added 99.0% 2-phenylacetetyl chloride (0.25 ml) and N,N-diisopropylethyl amine (0.3186 ml) at room temperature and the mixture was stirred for 2 hours. The solution was quenched with water (10 mL), and tetrahydrofuran was removed under reduced pressure. The mixture was extracted with ethyl acetate (15 mL x 2). The organic layers were washed with sat. NaHCO₃(aq), brine, dried over MgSO₄(S) and concentrated to give a residue which was purified by flash chromatography (silical gel, EtOAc:Hexane=1:6) to give the title compound (0.23 g) as a white solid. MS m/z: 430.1 [M+1]⁺

b) 4-Phenoxy-3-(2-phenylacetamido)-5-(trifluoromethyl)benzoic acid

To a stirred solution of methyl 4-phenoxy-3-(2-phenylacetamido)-5-(trifluoromethyl)benzoate (0.23 g, 0.0005 moles) in 1,4-dioxane (3.9) and water (4.2) was added lithium hydroxide monohydrate (0.049 g, 0.0011 moles) and the mixture was stirred at 60 °C for 1 hour. The mixture was acidified to pH=2-3 with 2N HCl and extracted with ethyl acetate (10 mL x 2). The organic layers were dried over MgSO₄(S) and the ethyl acetate removed under reduced pressure to give the solid which was triturated with hexane (5 mL x 2) and dichloromethane (5 mL) to give the title compound (0.155 g, 72.3 %) as a white solid. ¹H NMR (CD₂OD, 400 MHz): δ 8.68 (d, J=2.0 Hz, 1H), 8.19 (d, J=1.6 Hz, 1H), 7.28 (t, J = 6.0 Hz, 2H), 7.18-7.09 (m, 4H), 6.94-6.92 (m, 2H), 6.75 (d, J = 8.8 Hz, 2H), 3.42 (s, 2H) MS m/z: 416 [M+1]⁺

Compound 469

3-Chloro-5-(dibutylamino)-4-phenoxybenzoic acid

Scheme 9
A round bottom flask was charged with 3-chloro-4-fluorobenzoic acid (2.50 g, 14.32 mmol) and sulfuric acid (10 mL), and nitric acid (0.91 mL, 2.148 mmol) was added slowly. The reaction mixture was stirred at rt for 30 min and then heated to 100 °C and stirred at that temperature for 2 h. After cooling to room temperature, the reaction mixture was poured into ice cold water and the precipitated solids were collected by filtration and washed with water and dried to afford a white powder (2.44 g, 78%).

\( ^1 \text{H} \text{NMR} \) (300 MHz, DMSO-d6): \( \delta \) 8.28 (d, 1H, J = 8.4 Hz), 8.14 (d, 1H, J = 7.2 Hz).

b) Ethyl 3-chloro-4-fluoro-5-nitrobenzoate

To a stirred mixture of 3-chloro-4-fluoro-5-nitrobenzoic acid (1.39 g, 6.33 mmol) and potassium carbonate (0.962 g, 6.96 mmol) in DMF (15 mL) was added iodoethane (0.557 mL, 6.96 mmol) and the reaction mixture was stirred at rt overnight. The mixture was partitioned between water and EtOAc and the aqueous phase was extracted with EtOAc. The combined EtOAc phases were washed with brine, dried over anhydrous \( \text{Na}_2\text{SO}_4 \), and concentrated in vacuo. The residue was purified by silica gel column (0-40% EtOAc/hexane) to afford the product as yellow oil which solidified in refrigerator (1.2 g, 77%).

\( ^1 \text{H} \text{NMR} \) (300 MHz, CDCl3): \( \delta \) 7.85 (d, 1H, J = 6.9 Hz), 7.73 (d, 1H, J = 7.8 Hz), 4.41 (q, 2H, J = 7.2 Hz), 1.39 (t, 3H, J = 7.2 Hz).

c) Ethyl 3-chloro-5-nitro-4-phenoxybenzoate

A mixture of ethyl 3-chloro-4-fluoro-5-nitrobenzoate (200 mg, 0.81 mmol), phenol (91 mg, 0.97 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.145 mL, 0.97 mmol) and N,N-dimethylacetamide (2
mL) was stirred at 90 °C for 5 h. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 20 mL). The combined EtOAc layers were washed with brine and dried over Na₂SO₄, and concentrated. The residue was purified by silica gel column (0-40% EtOAc/hexane) to afford the product as syrup (210 mg, 81%).

[0676] ¹H NMR (300 MHz, CDCl₃): δ 7.90 (s, 1H), 7.47 (t, 2H, J = 7.8 Hz), 7.30 (t, 1H, J = 7.8 Hz), 7.21 (s, 1H), 7.10 (d, 2H, J = 7.8 Hz), 4.39 (q, 2H, J = 7.2 Hz), 1.37 (t, 3H, J = 7.2 Hz).

**d) Ethyl 3-amino-5-chloro-4-phenoxybenzoate**

[0677] A round bottom flask was charged with ethyl 3-chloro-5-nitro-4-phenoxybenzoate (0.55 g, 1.71 mmol), ammonium chloride (0.915 g, 17.1 mmol), and THF-MeOH (1:1, 20 mL). Zinc (1.12 g, 17.1 mmol) was added and the reaction mixture was stirred under nitrogen at 60 °C for 3 h. Additional ammonium chloride (0.915 g, 17.1 mmol) and zinc (1.12 g, 17.1 mmol) were added and the reaction mixture was stirred at 60 °C for another hour. TLC and LC-MS indicated completion of the reaction. The reaction mixture was filtered through Celite and the filter cake was washed with EtOAc. The filtrate was concentrated under reduced pressure and the residue was treated with EtOAc and filtered again. The filtrate was concentrated in vacuo and the residue was purified by silica gel column (0-40% EtOAc/hexane) to afford the title compound as syrup (440 mg, 88%).

[0678] MS m/z: 291.9 [M⁺]⁺; ¹H NMR (300 MHz, CDCl₃): δ 7.96 (s, 1H), 7.40 (t, 2H, J = 7.8 Hz), 7.21 (t, 1H, J = 7.5 Hz), 7.07 (d, 2H, J = 7.5 Hz), 6.04 (s, 1H), 5.72 (s, 2H), 4.33 (q, 2H, J = 7.2 Hz), 1.41 (t, 3H, J = 7.2 Hz).

c) Ethyl (butylamino)-5-chloro-4-phenoxybenzoate

[0679] To a stirred solution of ethyl 3-amino-5-chloro-4-phenoxybenzoate (0.440 g, 1.51 mmol) and butyraldehyde (0.675 mL, 7.54 mmol) in 1,2-dichloroethane (20 mL) was added sodium triacetoxyborohydride (1.60 g, 7.54 mmol) and the reaction mixture was stirred at 40 °C overnight. TLC and LC-MS indicated the reaction was complete with only mono-alkylated product. The reaction was quenched with aq. Na₂C₀₃ and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-20% EtOAc/hexane) to afford the products as thick oil (525 mg, 100%).

[0680] MS m/z: 348.0 [M⁺]⁺; ¹H NMR (300 MHz, CDCl₃): δ 7.99 (s, 1H), 7.75 (bs, 1H), 7.39 (t, 2H, J = 8.1 Hz), 7.18 (t, 1H, J = 7.5 Hz), 7.06 (d, 2H, J = 8.1 Hz), 6.11 (s, 1H), 4.32 (q, 2H, J = 7.2 Hz), 3.00-2.91 (m, 2H), 1.63-1.50 (m, 2H), 1.45-1.28 (m, 5H), 0.91 (t, 3H, J = 7.2 Hz).

f) Ethyl 3-(N-butybutyramido)-5-chloro-4-phenoxybenzoate

[0681] To a stirred solution of ethyl 3-(butylamino)-5-chloro-4-phenoxybenzoate (240 mg, 0.69 mmol) and pyridine (0.5 mL) in CH₂Cl₂ (5 mL) was added butyryl chloride (0.215 mL, 2.07 mmol) and the
mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed sequentially with water, 2N aq. HCl and aq. Na₂CO₃, and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column (0-50% EtOAc/hexane) to afford the product as thick oil (270 mg, 94%).

**g) Ethyl 3-chloro-5-(dibutylamino)-4-phenoxybenzoate**

**[0683]** To a stirred solution of ethyl 3-(N-butylbutyramido)-5-chloro-4-phenoxybenzoate (270 mg, 0.65 mmol) in THF (5 mL) at 0 °C under nitrogen was slowly added borane-tetrahydrofuran complex (1.0M solution in THF, 3.23 mL, 3.23 mmol). The mixture was warmed to rt and stirred overnight. TLC indicated most starting material was consumed. The mixture was carefully quenched with water and 2N aq. HCl and stirred for 30 min at rt. The mixture was then adjusted to basic with solid K₂CO₃ and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-30% EtOAc/hexane) to afford an oil (200 mg, 77%).

**[0684]** MS m/z: 404.2 [M+1]+; ¹H NMR (300 MHz, CDCl₃): δ 7.74 (s, 1H), 7.37 (t, 2H, J = 8.1 Hz), 7.15 (t, 1H, J = 7.5 Hz), 7.01 (d, 2H, J = 8.1 Hz), 6.50 (s, 1H), 4.34 (q, 2H, J = 7.2 Hz), 3.01 (t, 4H, J = 7.2 Hz), 1.50-1.35 (m, 7H), 1.30-1.15 (m, 4H), 0.85 (t, 6H, J = 7.2 Hz).

**h) 3-Chloro-5-(dibutylamino)-4-phenoxybenzoic acid**

**[0685]** To a stirred solution of ethyl 3-chloro-5-(dibutylamino)-4-phenoxybenzoate (200 mg, 0.50 mmol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide monohydrate (166 mg, 3.96 mmol). The reaction mixture was stirred at 45 °C for 3 days, and then concentrated in vacuo. The residue was treated with water and adjusted to pH=3 with 2N aq. HCl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-50% EtOAc/hexane) to afford the product as an off-white solid (185 mg, 99%).

**[0686]** MS m/z: 376.2 [M+1]+; ¹H NMR (300 MHz, DMSO-d₆): δ 8.10 (s, 1H), 7.45-7.37 (m, 3H), 7.19 (t, 1H, J = 7.5 Hz), 7.02 (d, 2H, J = 8.1 Hz), 3.05 (t, 4H, J = 7.8 Hz), 1.36-1.12 (m, 8H), 0.80 (t, 6H, J ~ 7.2 Hz).

**Compound 511**

3-(Dibutylamino)-5-(N,N-diethylsulfamoyl)-4-(p-tolyloxy)benzoic acid

117
**a) 3-Nitro-5-sulfamoyl-4-(p-tolyloxy)benzoic acid**

[0687] A round bottom flask was charged with 4-chloro-3-nitro-5-sulfamoylbenzoic acid (2.50 g, 8.9 mmol), p-cresol (4.81 g, 44.5 mmol), sodium bicarbonate (5.98 g, 71.2 mmol) and water (50 mL). The reaction mixture was heated to 85 °C and stirred overnight. After cooling, the reaction mixture was extracted with ethyl ether to remove the unreacted p-cresol. The aqueous phase was acidified with 3N HCl to pH=3 and extracted with ethyl acetate (3 x 50 mL). The combined EtOAc layers were washed with brine and dried over Na₂SO₄. The solvents were removed under reduced pressure to get the title compound as a yellow solid (3.0 g). MS m/z: 351.0 [M-1] ; ¹H NMR (300 MHz, DMSO-d₆): δ 8.66 (d, 1H, J = 2.1 Hz), 8.59 (d, 1H, J = 2.1 Hz), 7.85 (s, 2H), 7.09 (d, 2H, J = 8.7 Hz), 6.79 (d, 2H, J = 8.7 Hz), 2.24 (s, 3H).

**b) Ethyl 3-(N,N-diethyIsulfamoyl)-5-nitro-4-(p-tolyloxy)benzoate**

[0688] To a stirred mixture of 3-nitro-5-sulfamoyl-4-(p-tolyloxy)benzoic acid (2.00 g, 5.7 mmol) and potassium carbonate (3.13 g, 22.7 mmol) in DMF (30 mL) was added iodoethane (1.81 ml, 22.7 mmol) and the reaction mixture was stirred at rt overnight. The mixture was partitioned between water and EtOAc and the aqueous phase was extracted with EtOAc. The combined EtOAc phases were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel
column (0-80% EtOAc/hexane) to afford the title product (1.4 g). ¹H NMR (300 MHz, CDC1₃): δ 8.94 (d, 1H, J = 2.1 Hz), 8.66 (d, 1H, J = 2.1 Hz), 7.09 (d, 2H, J = 8.4 Hz), 6.75 (d, 2H, J = 8.4 Hz), 4.48 (q, 2H, J = 7.2 Hz), 3.38 (q, 4H, J = 7.2 Hz), 2.31 (s, 3H), 1.46 (t, 3H, J = 7.2 Hz), 1.19 (t, 6H, J = 7.2 Hz).

c) Ethyl 3-amino-5-(N,N-diethylsulfamoyl)-4-(p-tolyloxy)benzoate

[0689] A round bottom flask was charged with ethyl 3-(N,N-diethylsulfamoyl)-5-nitro-4-(p-tolyloxy)benzoate (1.40 g, 3.2 mmol), ammonium chloride (1.71 g, 0.032 mmol), and THF-MeOH (1:1, 50 mL). Zinc (2.10 g, 0.032 mol) was added under nitrogen and the reaction mixture was stirred at rt overnight. TLC and LC/MS indicated the reaction was complete. The reaction mixture was filtered through Celite and the filter cake was washed with THF-MeOH (1:1). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column (0-50% EtOAc/hexane) to afford the title compound as an oil (0.75 g). MS m/z: 407.1 [M+1]; ¹H NMR (300 MHz, CDC1₃): δ 8.07 (d, 1H, J = 1.8 Hz), 7.64 (d, 1H, J = 2.1 Hz), 7.10 (d, 2H, J = 8.4 Hz), 6.77 (d, 2H, J = 8.4 Hz), 4.40 (q, 2H, J = 7.2 Hz), 3.82 (s, 2H), 3.32 (q, 4H, J = 7.2 Hz), 2.32 (s, 3H), 1.43 (t, 3H, J = 7.2 Hz), 1.15 (t, 6H, J = 7.2 Hz).

d) Ethyl 3-(dibutylamino)-5-(N,N-diethylsulfamoyl)-4-(p-tolyloxy)benzoate

[0690] A round bottom flask was charged with ethyl 3-amino-5-(N,N-diethylsulfamoyl)-4-(p-tolyloxy)benzoate (400mg, 0.98 mmol), butyraldehyde (0.44 mL, 4.9 mmol) and 1,2-dichloroethane (10 mL). The mixture was stirred for 15 minutes, and then sodium triacetoxyborohydride (0.63 g, 2.95 mmol) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with aq. NaHC<sub>4</sub> and extracted with ethyl acetate. The organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-40% EtOAc/hexane) to afford the product as a soft solid (230 mg). MS m/z: 519.3 [M+1]; ¹H NMR (300 MHz, CDC1₃): δ 8.26 (d, 1H, J = 2.1 Hz), 7.83 (m, 1H, J = 2.1 Hz), 7.03 (d, 2H, J = 8.7 Hz), 4.42 (q, 2H, J = 7.2 Hz), 3.31 (q, 4H, J = 7.2 Hz), 3.02 (t, 4H, J = 7.2 Hz), 2.29 (s, 3H), 1.44 (t, 3H, J = 7.2 Hz), 1.30-0.90 (m, 14H), 0.78 (t, 6H, J = 7.2 Hz).

e) 3-(Dibutylamino)-S-(N,N-diethylsulfamoyl)-4-(p-tolyloxy)benzoic acid

[0691] To a stirred solution of ethyl 3-(dibutylamino)-5-(N,N-diethylsulfamoyl)-4-(p-tolyloxy)benzoate (320 mg, 0.62 mmol) in THF (5 mL) and MeOH (5 mL) was added lithium hydroxide monohydrate (207 mg, 4.9 mmol). The reaction mixture was stirred at 60 °C overnight, and then the mixture was concentrated in vacuo. The residue was treated with water and adjusted to pH=3 with 2N aq. HCl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to afford the product as a light yellow foam (290 mg). MS m/z: 491.4 [M+1]; ¹H NMR (300 MHz, CDC3): δ 8.35 (d, 1H, J = 1.8 Hz), 7.87 (d, 1H, J = 2.1 Hz), 7.02 (d, 2H, J = 8.4 Hz), 6.64 (d, 2H, J = 8.4 Hz), 3.32 (q, 4H, J = 7.2 Hz), 3.04 (t, 4H, J = 7.2 Hz), 2.30 (s, 3H), 1.30-0.90 (m, 14H), 0.79 (t, 6H, J = 7.2 Hz).
**Compound 518**

3-(Piperidin-1-yl)-5-(pyrrolidin-1-ylsulfonyl)-4-(p-tolyloxy)benzoic acid

![Chemical Structure](image)

**Scheme 1**

**a) Ethyl 3-nitro-5-(pyrrolidin-1-ylsulfonyl)-4-(p-tolyloxy)benzoate**

A round bottom flask was charged with ethyl 3-nitro-5-sulfamoyl-4-(p-tolyloxy)benzoate (1.60 g, 0.0042 mol), potassium carbonate (1.74 g, 0.01262 mol), DMF (20 mL) and 1,4-diiodobutane (0.832 ml, 0.0063 mol). The reaction mixture was stirred at 40 °C overnight and then 70 °C for 2h. TLC indicated consumption of the starting material. The reaction was quenched with water and extracted with ethyl acetate (3 x ). The combined organic layers were washed with brine, dried over anhydrous Na2SO4, and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/hexane) to afford a yellow solid (600 mg, 33%). 1H NMR (300 MHz, CDC13): δ 8.94 (d, 1H, J = 2.1 Hz), 8.68 (d, 1H, J = 2.1 Hz), 7.09 (d, 2H, J = 8.1 Hz), 6.75 (d, 2H, J = 8.4 Hz), 4.48 (q, 2H, J = 7.2 Hz), 3.44 (t, 4H, J = 6.6 Hz), 2.31 (s, 3H), 1.92-1.84 (m, 4H), 1.46 (t, 3H, J = 7.2 Hz).

**b) Ethyl 3-amino-5-(pyrrolidin-1-ylsulfonyl)-4-(p-tolyloxy)benzoate**

A round bottom flask was charged with ethyl 3-nitro-5-(pyrrolidin-1-ylsulfonyl)-4-(p-tolyloxy)benzoate (550 mg, 0.0013 mol), ammonium chloride (677 mg, 0.012 mol), and THF-MeOH.
Zinc (827 mg, 0.012 mol) was added under nitrogen and the reaction mixture was stirred at 60 °C for 3h. TLC and LC/MS indicated the reaction was complete. The reaction mixture was filtered through Celite and the filter cake was washed with EtOAc. The filtrate was concentrated and the residue was dissolved in EtOAc and filtered again. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column (0-60% EtOAc/hexane) to afford the title compound as white foam (420 mg, 82%). MS m/z: 405.1 [M+1]+; 1H NMR (300 MHz, CDCl₃): δ 8.07 (d, 1H, J = 1.8 Hz), 7.66 (d, 1H, J = 1.8 Hz), 7.10 (d, 2H, J = 8.7 Hz), 6.78 (d, 2H, J = 8.4 Hz), 4.40 (q, 2H, J = 7.2 Hz), 3.86 (s, 2H), 3.37 (t, 4H, J = 6.6 Hz), 2.31 (s, 3H), 1.85-1.70 (m, 4H), 1.43 (t, 3H, J = 7.2 Hz).

c) Ethyl 3-(piperidin-1-yl)-5-(pyrrolidin-1-ylsulfonyl)-4-(p-tolyloxy)benzoate

A microwave vial was charged with ethyl 3-amino-5-(pyrrolidin-1-ylsulfonyl)-4-(p-tolyloxy)benzoate (160 mg, 0.0004 mol), potassium carbonate (0.328 g, 0.0024 mol), diiodopentane (0.088 ml, 0.0006 mol), and acetonitrile (2.5 ml). The reaction was heated in a microwave at 160 °C for 6h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (0-50% EtOAc/hexane) to afford the title product as syrup (100 mg). MS m/z: 473.2 [M+1]+; 1H NMR (300 MHz, CDCl₃): δ 8.32 (d, 1H, J = 1.8 Hz), 7.84 (d, 1H, J = 2.1 Hz), 7.02 (d, 2H, J = 8.7 Hz), 6.65 (d, 2H, J = 8.4 Hz), 4.41 (q, 2H, J = 7.2 Hz), 3.35 (t, 4H, J = 6.6 Hz), 2.93 (m, 4H), 2.31 (s, 3H), 1.69 (m, 4H), 1.50-1.20 (m, 9H).

d) 3-(Piperidin-1-yl)-5-(pyrrolidin-1-ylsulfonyl)-4-(p-tolyloxy)benzoic acid

To a stirred solution of ethyl 3-(piperidin-1-yl)-5-(pyrrolidin-1-ylsulfonyl)-4-(p-tolyloxy)benzoate (100 mg, 0.0002 mol) in THF (3 mL) and MeOH (3 mL) was added lithium hydroxide hydrate (46 mg, 0.0011 mol). The reaction mixture was stirred at 60 °C overnight, and then the mixture was concentrated in vacuo. The residue was treated with water and adjusted to pH=3 with 2N aq. HC1 solution, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo to afford the product as off-white foam (93 mg, 99%). MS m/z: 445.2 [M+1]+; 1H NMR (300 MHz, CDCl₃): δ 8.41 (d, 1H, J = 1.8 Hz), 7.89 (d, 1H, J = 1.8 Hz), 7.04 (d, 2H, J = 8.1 Hz), 6.68 (d, 2H, J = 8.4 Hz), 3.37 (t, 4H, J = 6.6 Hz), 2.95 (s, 4H), 2.32 (s, 3H), 1.71 (t, 4H, J = 6.6 Hz), 1.45-1.20 (m, 6H).

Compound 522

3-(Dibutylamino)-N,N-diethyl-5-(4-niethylpiperazine-1-carbonyl)-2-(p-tolyloxy)benzenesulfonamide
3-(Dibutylamino)-N,N-diethyl-5-(4-methylpiperazine-1-carbonyl)-2-(p-tolyloxy)benzenesulfonamide

Scheme 12

A mixture of 3-(dibutylamino)-5-(N,N-diethylsulfamoyl)-4-(p-tolyloxy)benzoic acid (40 mg, 0.00008 moi), HATU (46.50 mg, 0.00012 mol), N,N-diisopropylethylamine (0.028 ml, 0.00016 mol), and 1-methylpiperazine (0.018 ml, 0.00016 moi) in DMF (1.5 mL) was stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed with aq. Na₂CO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by flash chromatography to afford the product as a sticky syrup (42 mg, 90%). MS m/z: 573.3 [M+1]⁺; HPLC purity: 98.78%; ¹H NMR (300 MHz, CDCl₃): δ 7.62 (d, 1H, J = 1.8 Hz), 7.22 (d, 1H, J = 1.8 Hz), 7.01 (d, 2H, J = 8.7 Hz), 6.62 (d, 2H, J = 8.7 Hz), 3.82 (bs, 2H), 3.51 (bs, 2H), 3.27 (q, 4H, J = 7.2 Hz), 3.00 (t, 4H, J = 7.2 Hz), 2.52 and 2.45 (bs, 4H), 2.37 (s, 3H), 2.30 (s, 3H), 1.30-0.90 (m, 14H), 0.78 (t, 6H, J = 7.2 Hz).

Compound 601

3-(Dibutylamino)-5-(1,3,4-oxadiazol-2-yl)-2-phenoxybenzenesulfonamide

Scheme 13
A mixture of 3-(dibutylamino)-4-phenoxy-5-sulfamoylbenzoic acid (50 mg, 0.12 mmol) and (isocyanoimino)triphenylphosphorane (54 mg, 0.18 mmol) in CH₂Cl₂ (3 mL) was stirred at rt overnight. The mixture was concentrated and purified by silica gel column (0-70% EtOAc/hexane) to afford a light yellow solid (30 mg, 57%).

**[0698]** MS m/z: 445.2 [M+1]⁺; H NMR (300 MHz, CDCl₃): δ 8.52 (s, 1H), 8.21 (d, 1H, J = 2.1 Hz), 7.97 (d, 1H, J = 1.8 Hz), 7.28 (t, 2H, J = 7.5 Hz), 7.08 (t, 1H, J = 7.5 Hz), 6.86 (d, 2H, J = 7.5 Hz), 5.01 (s, 2H), 3.09 (t, 4H, J = 7.2 Hz), 1.30-1.15 (m, 4H), 1.15-0.98 (m, 4H), 0.80 (t, 6H, J = 7.2 Hz).

**Compound 603**

3-(Dibutylamino)-2-phenoxy-5-(1H-tetrazol-5-yl)benzenesulfonamide

**Scheme 14**
a) 3-(Dibutylamino)-4-phenoxy-5-sulfamoylbenzamide

A mixture of 3-(dibutylamino)-4-phenoxy-5-sulfamoylbenzoic acid (250 mg, 0.59 mmol), HATU (271 mg, 0.71 mmol), N,N-diisopropylethyl amine (0.2 mL, 1.2 mmol), 0.5 M 1,4-dioxane solution of ammonia (7 mL, 3.5 mmol) and DMF (10 mL) was stirred at room temperature overnight. The reaction was diluted with ethyl acetate and washed with aq. NaCl and brine, dried over anhydrous Na₂SO₄, and concentrated to afford the product as a white solid (250 mg, 100%).

b) 5-Cyano-3-(dibutylamino)-2-phenoxybenzenesulfonamide

To a solution of 3-(dibutylamino)-4-phenoxy-5-sulfamoylbenzamide (250 mg, 0.60 mmol) in 1,4-dioxane (10 mL) was added phosphorus oxychloride (0.56 mL, 6.0 mmol). The mixture was heated under reflux for 3h. LC-MS indicated completion of the reaction. The reaction was quenched with aq. K₂CO₃ and the mixture was stirred for 1h, and then extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column (0-60% EtOAc/hexane) to afford a brown solid (105 mg, 44%).

MS m/z: 402.2 [M+H]; 1H NMR (300 MHz, CDCl₃): δ 7.87 (d, 1H, J = 2.1 Hz), 7.39 (d, 1H, J = 2.1 Hz), 7.28 (t, 2H, J = 7.8 Hz), 7.09 (t, 1H, J = 7.5 Hz), 6.81 (d, 2H, J = 7.8 Hz), 4.97 (s, 2H), 3.04 (t, 4H, J = 2.1 Hz), 1.30-1.15 (m, 4H), 1.12-0.97 (m, 4H), 0.81 (t, 6H, J = 7.2 Hz).

c) 3-(Dibutylamino)-2-phenoxy-5-(IH-tetrazol-5-yl)benzenesulfonamide

A mixture 5-cyano-3-(dibutylamino)-2-phenoxybenzenesulfonamide (55 mg, 0.14 mmol), sodium azide (27 mg, 0.41 mmol) and ammonium chloride (29 mg, 0.55 mmol) in DMF (2 mL) was stirred at 120 °C for 6h. LC-MS indicated completion of the reaction. The reaction was diluted with EtOAc (30 mL) and washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column to afford a brown syrup (33 mg, 54%).
[0703] MS m/z: 445.2 [M+1]+; \textsuperscript{1}H NMR (300 MHz, CDC\textsubscript{3}D): \( \delta \) 8.10 (s, 1H), 8.02 (s, 1H), 7.23 (t, 2H, J = 7.8 Hz), 7.03 (t, 1H, J = 7.5 Hz), 6.84 (d, 2H, J = 8.1 Hz), 5.33 (bs, 2H), 3.08 (t, 4H, J = 7.2 Hz), 1.30-1.15 (m, 4H), 1.10-0.95 (m, 4H), 0.78 (t, 6H, J = 7.2 Hz).

**Compound 604**

\[
\text{N,N-Dibutyl-3-(methylsulfonyl)-2-phenoxy-5-(1H-tetrazol-5-yl)aniline}
\]

\[
\text{N=NN=}
\]

Scheme 15

a) \textit{1,4-Dibromo-2-(methylsulfonyl)benzene}

[0704] A suspension of 2,5-dibromobenzene-1-sulfonyl chloride (5.0 g, 15 mmol), sodium sulfite (2.3 g, 18 mmol) and sodium hydroxide (1.35 g, 34 mmol) in water (50 mL) was heated to 70 °C for 5h. To the cooled solution was added iodomethane (4.65 mL, 75 mmol) and methanol (50 mL). The bisphasic system was stirred vigorously at 50 °C overnight, and then concentrated and suspended in water. The solids were collected by filtration, washed with water and dried in air to give the product as white solids (4.2 g, 90%).
[0705] $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.33 (d, 1H, J = 2.1 Hz), 7.65 (AB, 1H, J = 8.1 Hz), 7.61 (AB, 1H, J = 8.4, 2.1 Hz), 3.31 (s, 3H).

b) 2,5-Dibromo-1-(methylsulfonyl)-3-nitrobenzene

[0706] A round bottom flask was charged with 1,4-dibromo-2-(methylsulfonyl)benzene (3.5 g, 11.5 mmol) and sulfuric acid (10 mL), and nitric acid (0.57 mL, 13 mmol) was added slowly. The reaction mixture was stirred at rt for 30 min and then heated to 100 °C and stirred at that temperature for 2h. After cooling to room temperature, the reaction mixture was poured into ice cold water and the precipitated solids were collected by filtration and washed with water and dried to afford the crude product as a white powder (4 g, 100%).

[0707] $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.53 (d, 1H, J = 2.1 Hz), 8.02 (d, 1H, J = 2.1 Hz), 3.38 (s, 3H).

c) 5-Bromo-1-(methylsulfonyl)-3-nitro-2-phenoxybenzene

[0708] A mixture of the crude 2,5-dibromo-1-(methylsulfonyl)-3-nitrobenzene (4.0 g, 11.1 mmol), phenol (1.26 g, 13.4 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (2.0 mL, 13.4 mmol) and N,N-dimethylacetamide (50 mL) was stirred at rt overnight. The reaction mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined EtOAc layers were washed with 1N aq. HCl, aq. Na$_2$CO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by silica gel column (0-70% CH$_2$Cl$_2$/hexane) to afford the product as a beige solid (2.1 g, 51%).

[0709] $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.51 (d, 1H, J = 2.4 Hz), 8.32 (d, 1H, J = 2.7 Hz), 7.32 (t, 2H, J = 7.8 Hz), 7.14 (t, 1H, J = 7.5 Hz), 6.89 (d, 2H, J = 8.4 Hz), 3.35 (s, 3H).

d) 5-Bromo-3-(methylsulfonyl)-2-phenoxyaniline

[0710] A round bottom flask was charged with 5-bromo-1-(methylsulfonyl)-3-nitro-2-phenoxy benzene (0.70 g, 1.88 mmol), ammonium chloride (1.0 g, 18.8 mmol), and THF-MeOH (1:1, 60 mL). Zinc (1.23 g, 18.8 mmol) was added and the reaction mixture was stirred under nitrogen at 60 °C for 2h. TLC and LC-MS indicated the reaction was complete. The reaction mixture was concentrated in vacuo. The residue was treated with EtOAc-C$_3$H$_7$OH -THF and filtered through Celite and the filter cake was washed with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by silica gel column (0-50% EtOAc/hexane) to afford the title compound as a white solid (0.55 g, 85%).

[0711] MS m/z: 342.0 [M+H$^+$]; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.55 (d, 1H, J = 2.1 Hz), 7.33 (t, 2H, J = 8.1 Hz), 7.19 (d, 1H, J = 2.1 Hz), 7.10 (t, 1H, J = 7.2 Hz), 6.93 (d, 2H, J = 8.4 Hz), 3.90 (s, 2H), 3.19 (s, 3H).

e) 5-Bromo-N-butyl-3-(methylsulfonyl)-2-phenoxyaniline

[0712] A reaction vial was charged with 5-bromo-3-(methylsulfonyl)-2-phenoxyaniline (500 mg, 1.46 mmol), butyraldehyde (0.393 mL, 4.38 mmol) and 1,2-dichloroethane (20 mL), and the reaction was stirred for 15 minutes. Sodium triacetoxyborohydride (929 mg, 4.38 mmol) was added and the reaction
was stirred at rt overnight. The reaction was quenched with aq. Na₂CO₃ and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-40% EtOAc/hexane) to afford the product as a white solid (500 mg, 86%).

[0713] MS m/z: 400.0 [M+1]+; ¹H NMR (300 MHz, CDCl₃): δ 7.45 (d, 1H, J = 2.4 Hz), 7.32 (t, 2H, J = 8.1 Hz), 7.09 (t, 1H, J = 7.5 Hz), 7.04 (d, 1H, J = 2.4 Hz), 6.90 (d, 2H, J = 7.8 Hz), 3.94 (t, 1H, J = 5.1 Hz), 3.17 (s, 3H), 3.06 (q, 2H, J = 6.3 Hz), 1.50-1.39 (m, 2H), 1.25-1.12 (m, 2H), 0.85 (t, 3H, J = 7.2 Hz).

f) 5-Bromo-N,N-dibutyl-3-(methylsulfonyl)-2-phenoxyaniline

[0714] A round bottom flask was charged with 5-bromo-N-butyl-3-(methylsulfonyl)-2-phenoxyaniline (840 mg, 2.1 mmol), butyraldehyde (0.756 mL, 8.44 mmol) and acetonitrile (10 mL), and the reaction was cooled to 0 °C and trifluoroacetic acid (1.57 mL, 21.1 mmol) was added slowly. The reaction was stirred at 0 °C for 30 minutes and triethylsilane (3.37 mL, 21.1 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 72h. The reaction mixture was diluted with water at 0 °C and basified with ammonium hydroxide to pH 9. The reaction mixture was stirred for 30 minutes and extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography (0-60% EtOAc/hexane) to afford the product as a syrup (940 mg, 98%).

[0715] MS m/z: 456.2 [M+1]+; ¹H NMR (300 MHz, CDCl₃): δ 7.75 (d, 1H, J = 2.1 Hz), 7.31 (d, 1H, J = 2.1 Hz), 7.25 (t, 2H, J = 8.1 Hz), 7.04 (t, 1H, J = 7.5 Hz), 6.79 (d, 2H, J = 8.1 Hz), 3.19 (s, 3H), 3.03 (t, 4H, J = 7.2 Hz), 1.30-1.16 (m, 4H), 1.12-0.95 (m, 4H), 0.81 (t, 6H, J = 7.2 Hz).

g) 3-(Dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzonitrile

[0716] A mixture of 5-bromo-N,N-dibutyl-3-(methylsulfonyl)-2-phenoxyaniline (550 mg, 1.21 mmol) and copper(I) cyanide (542 mg, 6.05 mmol) in NMP (5 mL) was heated in a microwave reactor at 200 °C for 1h. TLC indicated the reaction was complete. The mixture was filtered through Celite and the filter cake was washed with EtOAc. The filtrate was washed with aq. NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column (0-50% EtOAc/hexane) to afford a light yellow solid (450 mg, 93%).

[0717] MS m/z: 401.2 [M+1]+; ¹H NMR (300 MHz, CDCl₃): δ 7.92 (d, 1H, J = 2.1 Hz), 7.43 (d, 1H, J = 1.8 Hz), 7.27 (t, 2H, J = 7.8 Hz), 7.05 (t, 1H, J = 7.5 Hz), 6.79 (d, 2H, J = 7.8 Hz), 3.22 (s, 3H), 3.05 (t, 4H, J = 7.2 Hz), 1.30-1.16 (m, 4H), 1.12-0.98 (m, 4H), 0.81 (t, 6H, J = 7.2 Hz).

h) N,N-Dibutyl-3-(methylsulfonyl)-2-phenoxy-5-(1H-tetrazol-5-yl)aniline

[0718] A mixture 3-(dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzonitrile (160 mg, 0.40 mmol), sodium azide (78 mg, 1.20 mmol) and ammonium chloride (85 mg, 1.60 mmol) in DMF (5 mL) was stirred at 120 °C for 6h. LC-MS indicated the reaction was complete. The reaction was diluted with
EtOAc (50 mL), washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column (0-100% MeOH/CH₂Cl₂) to afford a beige solid (165 mg, 93%).

[0719] MS m/z: 444.2 [M+1]+; ¹H NMR (300 MHz, CDCl₃): δ 8.23 (d, 1H, J = 1.5 Hz), 8.13 (d, 1H, J = 1.8 Hz), 7.25 (t, 2H, J = 8.1 Hz), 7.05 (t, 1H, J = 7.5 Hz), 6.83 (d, 2H, J = 7.8 Hz), 3.35 (s, 3H), 3.13 (t, 4H, J = 7.2 Hz), 1.3-1.20 (m, 4H), 1.13-0.99 (m, 4H), 0.80 (t, 6H, J = 7.2 Hz).

**Compound 607**

N,N-Bibutyl-5-(1H-imidazol-1-yl)-3-(methylsulfonyl)-2-phenoxyaniline

Scheme 16

A microwave tube was charged with 5-bromo-N,N-dibutyl-3-(methylsulfonyl)-2-phenoxyaniline (80 mg, 0.18 mmol), imidazole (36 mg, 0.53 mmol), cesium carbonate (115 mg, 0.35 mmol), acetonitrile (3 mL), and copper(I) iodide (5 mg, 0.03 mmol). The mixture was flushed with nitrogen and heated in a microwave reactor at 180 °C for 2h. The mixture was filtered through Celite and the filler cake was washed with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by silica gel column (0-100% EtOAc/hexane) to afford the title compound as an off-white solid (55 mg, 71%).

[0720] MS m/z: 442.3 [M+1]+; ¹H NMR (300 MHz, DMSO-d₆): δ 8.32 (s, 1H), 7.83 (s, 1H), 7.53 (s, 2H), 7.26 (t, 2H, J = 7.8 Hz), 7.13 (s, 1H), 7.02 (t, 1H, J = 7.5 Hz), 6.79 (d, 2H, J = 8.1 Hz), 3.31 (s, 3H), 3.09 (t, 4H, J = 7.2 Hz), 1.28-1.12 (m, 4H), 1.08-0.92 (m, 4H), 0.74 (t, 6H, J = 7.2 Hz).

**Compound 609**

N,N-Dibutyl-5-(1H-imidazol-2-yl)-3-(methylsulfonyl)-2-phenoxyaniline

Scheme 17

128
A microwave tube was charged with 5-bromo-N,N-dibutyl-3-(methylsulfonyl)-2-phenoxyaniline (120 mg, 0.26 mmol), imidazole (27 mg, 0.40 mmol), palladium diacetate (3 mg, 0.01 mmol), N,N-dimethylacetamide (3 mL), and copper(I) iodide (100 mg, 0.53 mmol). The mixture was flushed with nitrogen and heated in a microwave reactor at 180 °C for 6 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with brine, and dried over anhydrous Na₂SO₄, concentrated in vacuo. The residue was purified by silica gel column (0-100% EtOAc/hexane) to afford the title compound as a light brown solid (40 mg, 34%).

**Compound 619**

N,N-Dibutyl-3-(methylsulfonyl)-2-phenoxy-5-(1H-pyrazol-4-yl)aniline

Scheme 18

To a solution of 5-bromo-N,N-dibutyl-3-(methylsulfonyl)-2-phenoxyaniline (100 mg, 0.22 mmol), 1H-pyrazole-4-boronic acid (49 mg, 0.44 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (8.4 mg, 0.02 mmol), potassium phosphate (93 mg, 0.44 mmol), and 1-butanol (3 mL) under nitrogen was added tris(dibenzylideneacetone)dipalladium(0) (4.0 mg, 0.02 eq.). The mixture was purged with nitrogen and stirred at 100 °C overnight. After cooling, the mixture was filtered through...
Celite and the filter cake was washed with EtOAc. The filtrate was concentrated and the residue was purified by silica gel column (0-70% EtOAc/hexane) to afford the product as a soft solid (36 mg, 37%).

\[ \text{MS } m/z: 442.2 [M+1]^+; \text{ } ^1H\text{ NMR (300 MHz, DMSO-d}_6): \delta 13.04 (br s, 1H), 8.32 (br s, 1H), 7.97 (br s, 1H), 7.59 (d, 1H, J = 1.8 Hz), 7.52 (d, 1H, J = 1.5 Hz), 7.24 (t, 2H, J = 7.8 Hz), 6.99 (t, 1H, J = 7.5 Hz), 6.76 (d, 2H, J = 7.8 Hz), 3.25 (s, 3H), 3.04 (t, 4H, J = 7.2 Hz), 1.26-1.12 (m, 4H), 1.08-0.92 (m, 4H), 0.74 (t, 6H, J = 7.2 Hz).

**Compound 620**

**N,N-Dibutyl-3-(methylsulfonyl)-2-phenoxy-5-(1H-pyrazol-3-yl)aniline**

Scheme 19

![Reaction scheme](image)

[0725] To a solution of 5-bromo-N,N-dibutyl-3-(methylsulfonyl)-2-phenoxyaniline (100 mg, 0.22 mmol), potassium 1H-pyrazole-3-trifluoroborate (77 mg, 0.44 mmol), 2-dicyclohexylphosphino-2'4'6'-triisopropylbiphenyl (8.4 mg, 0.02 mmol), potassium phosphate (93 mg, 0.44 mmol), and 1-butanol (3 mL) under nitrogen was added tris(dibenzylideneacetone)dipalladium(0) (4 mg, 0.02 eq.). The mixture was purged with nitrogen and stirred at 100 °C overnight. After cooling, the mixture was filtered through Celite and the filter cake was washed with EtOAc. The filtrate was concentrated and the residue was purified by silica gel column (0-70% EtOAc/hexane) to afford a while foam (63 mg, 65%).

[0727] MS m/z: 442.3 [M+1]^+; ^1H NMR (300 MHz, DMSO-d_6): \delta 13.01 (br s, 1H), 7.88 (s, 1H), 7.83 (s, 1H), 7.75 (s, 1H), 7.24 (t, 2H, J = 7.8 Hz), 7.00 (t, 1H, J = 7.5 Hz), 6.83-6.73 (m, 3H), 3.26 (s, 3H), 3.05 (t, 4H, J = 7.2 Hz), 1.26-1.12 (m, 4H), 1.08-0.93 (m, 4H), 0.74 (t, 6H, J = 7.2 Hz).

**Compound 622**

**N,N-Dibutyl-3-(methylsulfonyl)-5-morpholino-2-phenoxyaniline**

Scheme 20

130
A round bottom flask was charged with morpholine (0.02 mL, 0.22 mmol), 5-bromo-N,N-dibutyl-3-(methylsulfonyl)-2-phenoxyaniline (85 mg, 0.19 mmol), xantphos (4.3 mg, 0.01 mmol), toluene (5 mL), and sodium tert-butoxide (27 mg, 0.28 mmol). The mixture was degassed and filled with nitrogen, and then tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.01 mmol) was added and the reaction was stirred under nitrogen at 100 °C overnight. After cooling, the mixture was diluted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column (0-60% EtOAc/hexane) to afford the title compound as a light yellow solid (75 mg, 87%).

**Compound 624**

3-(3-(Dibutylamino)-5-(methylsulfonyl)-4-phenoxyphenyl)-1,2,4-oxadiazol-5(4H)-one

**Scheme 21**

A mixture of 3-(dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzonitrile (100 mg, 0.25 mmol), hydroxylamine hydrochloride (35 mg, 0.50 mmol), methanol (5 mL), and sodium bicarbonate (42 mg, 0.50 mmol) was stirred at 80 °C overnight, and then the volatiles were evaporated. The residue was treated...
with aq. NaHCO$_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated to afford a white foam (130 mg). The crude hydroxybenzamidine (130 mg) was dissolved in THF (10 mL) and 1.1'-carbonyldiimidazole (49 mg, 0.30 mmol) was added. The mixture was heated at 100 °C under reflux for 3h. After cooling, the mixture was treated with water and adjusted to pH 3 with 1N HCl. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by silica gel column (0-100% EtOAc/hexane) to afford the title compound as a white solid (75 mg, 65%).

[0731] MS m/z: 460.4 [M+1]$^+$; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.99 (d, 1H, J = 2.1 Hz), 7.79 (d, 1H, J = 1.8 Hz), 7.26 (t, 2H, J = 7.8 Hz), 7.07 (t, 1H, J = 7.5 Hz), 6.81 (d, 2H, J = 7.8 Hz), 3.38 (s, 3H), 3.09 (t, 4H, J = 7.2 Hz), 1.30-1.17 (m, 4H), 1.13-0.97 (m, 4H), 0.81 (t, 6H, J = 7.2 Hz).

**Compound 625**

**N,N-Dibutyl-5-(1H-imidazol-5-yl)-3-(methylsulfonyl)-2-phenoxyaniline**

![Chemical structure](image)

**Scheme 22**

a) **N,N-Dibutyl-3-(methylsulfonyl)-2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline**

[0732] To a mixture of 5-bromo-N,N-dibutyl-3-(methylsulfonyl)-2-phenoxyaniline (250 mg, 0.55 mmol), bis(pinacolato)diboron (210 mg, 0.83 mmol), and potassium acetate (162 mg, 1.65 mmol) in 3,4-dioxane (10 mL) and DMSO (0.1 mL) under nitrogen was added Pd(dppf)Cl$_2$ (15 mg). The mixture was heated at 85 °C overnight and TLC indicated the reaction was complete. The mixture was filtered through
Celite and the filter cake was washed with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by silica gel column (0-50% EtOAc/hexane) to afford the title compound as a syrup (100 mg).

**[0733]** MS m/z: 502.4 [M+H]+; 1H NMR (300 MHz, CDCl₃): δ 8.11 (s, 1H), 7.64 (s, 1H), 7.22 (t, 2H, J = 8.1 Hz), 7.01 (t, IH, J = 7.5 Hz), 6.79 (d, 2H, J = 8.4 Hz), 3.17 (s, 3H), 3.02 (t, 4H, J = 7.2 Hz), 1.38 (s, 12H), 1.35-1.14 (m, 7H), 1.11-0.96 (m, 4H), 0.79 (t, 6H, J = 7.2 Hz).

**b) N,N-Dibutyl-5-(1H-imidazol-5-yl)-3-(methylsulfonyl)-2-phenoxyaniline**

**[0734]** To a solution of N,N-dibutyl-3-(methylsulfonyl)-2-phenoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (55 mg, 0.11 mmol), 4-bromo-1H-imidazole (64 mg, 0.44 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (4 mg, 0.01 mmol), potassium phosphate (47 mg, 0.22 mmol), and 1-butanol (2 mL) under nitrogen was added tris(dibenzylideneacetone)dipalladium(0) (2 mg). The mixture was purged with nitrogen and heated in a microwave reactor at 150 °C for 2h. After cooling, the mixture was filtered through Celite and the filter cake was washed with EtOAc. The filtrate was concentrated and the residue was purified by silica gel column (0-100% EtOAc/hexane) to afford a light brown foam (12 mg, 25%).

**[0735]** MS m/z: 442.2 [M+H]+; 1H NMR (300 MHz, DMSO-δ6):  δ 12.27 (br s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 7.75 (s, IH), 7.73 (s, 1H), 7.24 (t, 2H, J = 7.8 Hz), 6.99 (t, IH, J = 7.5 Hz), 6.76 (d, 2H, J = 8.1 Hz), 3.24 (s, 3H), 3.03 (t, 4H, J = 6.9 Hz), 1.30-1.12 (m, 4H), 1.08-0.93 (m, 4H), 0.74 (t, 6H, J = 7.2 Hz).

**Compound 626**

5-(3-(Dibutylamino)-5-(methylsulfonyl)-4-phenoxyphenyl)-1,3,4-oxadiazol-2(3H)-one

**Scheme 23**

[0736] A mixture of ethyl 3-(dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzoate (150 mg, 0.34 mmol) and hydrazine (0.16 mL, 5.0 mmol) in EtOH (2 mL) was heated in a microwave reactor at 180 °C for 1h. The mixture was concentrated in vacuo to afford the crude hydride (150 mg). MS m/z: 434.3
To a solution of the crude hydride in THF (10 mL) was added 1,1’-carbonyldiimidazole (217 mg, 1.34 mmol). The mixture was heated under reflux for 2 h. LC-MS indicated the reaction was complete. After cooling, the mixture was treated with water and adjusted to pH=3 with IN HCl. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na$_3$SO$_4$ and concentrated. The residue was purified by silica gel column (0-100% EtOAc/hexane) to afford the title compound as light yellow foam (65 mg, 42%).

**Scheme 24**

3-(Bibutylamino)-N,5-bis(methylsulfonyl)-4-

Phenoxybenzamide

![Phenoxybenzamide](image)

To a stirred mixture of 3-dibutylamino-5-methanesulfonyl-4-phenoxy-benzamide (60 mg, 0.14 mmol) in THF (5 mL) was added 60% sodium hydride in mineral oil (23 mg, 0.57 mmol). The mixture was stirred at rt for 2 h and then methanesulfonyl chloride (98 mg, 0.86 mmol) was added. The mixture was stirred at rt overnight and then quenched with water. The mixture was extracted with EtOAc and the EtOAc layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by silica gel column (0-70% EtOAc/hexane) to afford the product as a white solid (10 mg) and recover some starting material.

**Compound 630**

![Compound 629](image)

**Compound 629**

3-(Bibutylamino)-N,5-bis(methylsulfonyl)-4-

Phenoxybenzamide

![Phenoxybenzamide](image)

To a stirred mixture of 3-dibutylamino-5-methanesulfonyl-4-phenoxy-benzamide (60 mg, 0.14 mmol) in THF (5 mL) was added 60% sodium hydride in mineral oil (23 mg, 0.57 mmol). The mixture was stirred at rt for 2 h and then methanesulfonyl chloride (98 mg, 0.86 mmol) was added. The mixture was stirred at rt overnight and then quenched with water. The mixture was extracted with EtOAc and the EtOAc layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by silica gel column (0-70% EtOAc/hexane) to afford the product as a white solid (10 mg) and recover some starting material.

**Compound 630**

![Compound 630](image)

134
4-(3-(Dibutylamino)-5-(methylsulfonyl)-4-phenoxyphenyl)-3H-1,2,3,5-oxathiadiazole 2-oxide

Scheme 25

A mixture of 3-(dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzonitrile (310 mg, 0.77 mmol), hydroxylamine hydrochloride (108 mg, 1.55 mmol), methanol (15 mL), and sodium bicarbonate (130 mg, 1.55 mmol) was stirred at 90°C for 4h, and then the volatiles were evaporated. The residue was treated with aq. NaHCO₃ and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated to afford the crude 3-(dibutylamino)-N-hydroxy-5-(methylsulfonyl)-4-phenoxybenzimidamide (315 mg) as a white foam.

Compound 635

N,N-Dibutyl-6-(methylsulfonyl)-4-(1H-tetrazol-5-yl)-4'-(trifluoromethyl)-11'-biphenyl-2-amine

[0740] MS m/z: 480.4 [M+1]+; ¹H NMR (300 MHz, CDCI₃): δ 8.87 (br s, 1H), 7.89 (d, 1H, J = 1.8 Hz), 7.85 (d, 1H, J = 2.1 Hz), 7.27 (t, 2H, J = 7.8 Hz), 7.07 (t, 1H, J = 7.5 Hz), 6.81 (d, 2H, J = 7.8 Hz), 3.28 (s, 3H), 3.09 (t, 4H, J = 7.2 Hz), 1.30-1.18 (m, 4H), 1.13-0.98 (m, 4H), 0.81 (t, 6H, J = 7.2 Hz).
a) Methyl 2-(raethylsulfonyl)-6-nitro-4'-[(trifuoromethyl)-[1,1'-biphenyl]-4-carboxylate

[0742] A round bottom flask was charged with 4-chloro-3-(methylsulfonyl)-5-nitrobenzoic acid (3.00 g, 0.01073 mol), 4-(trifluoromethyl)phenylboronic acid (3.002 g, 0.01581 mol), tetrakis(triphenylphosphine)palladium(0) (0.620 g, 0.0005 mol), sodium bicarbonate (3.60 g, 0.043 mol) and degassed DMF/water (5:2) (40 mL); and the whole flask was evacuated and back-filled with nitrogen. The reaction mixture was heated to 100°C overnight. The reaction mixture was cooled to room temperature and diluted with dichloromethane and washed with water. The aqueous layer was acidified and extracted with ethyl acetate. Ethyl acetate was removed under reduced pressure and the residue was
used in the next reaction without further purification.

A round bottom flask was charged with 2-(methylsulfonyl)-6-nitro-4-((trifluoromethyl)-[1,l'-biphenyl]-4-carboxylic acid from the previous step, methanol (40 mL) and thionylchloride (2.63 ml, 0.0361 mol) was added slowly at room temperature. The reaction mixture was then heated to 50°C over night. The reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was purified by flash chromatography to give the product as yellow solid (2.1 g). $^1$H NMR (CDCl$_3$, 300 MHz): δ 9.09 (d, J=1.5 Hz, 1H), 8.66 (d, J=1.8 Hz, 1H), 7.75 (d, J=8.1 Hz, 2H), 7.53 (d, J=7.8 Hz, 2H), 4.06 (s, 3H), 2.72 (s, 3H).

b) Methyl 2-(methylsulfonyl)-6-nitro-4'-(trifluoromethyl)-[1,l'-biphenyl]-4-carboxylate

A round bottom flask was charged with methyl 2-(methylsulfonyl)-6-nitro-4'-(trifluoromethyl)-[1,l'-biphenyl]-4-carboxylate (2.10 g, 0.005 mol), ammonium chloride (3.025 g, 0.0567 mol), and THF-MeOH (1:1, 10 mL). Zinc (3.670 g, 0.05656 mol) was added under nitrogen and the reaction mixture was stirred at room temperature for 30 min, and then at 60°C for 2h. TLC and LC-MS indicated the reaction was complete. The reaction mixture was concentrated in vacuo. The residue was treated with EtOAc and filtered through Celite and the filter cake was washed with EtOAc. The filtrate was concentrated in vacuo and the residue (a white solid, 1.9 g) was used in the next reaction without further purification. MS m/z: 374.1 (M+1). $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 7.83 (d, J=8.4 Hz, 2H), 7.78 (d, J=1.8 Hz, 1H), 7.67 (d, J=1.8 Hz, 1H), 7.49 (d, J=8.1 Hz, 2H), 5.23 (bs, 2H), 3.88 (s, 3H), 2.83 (s, 3H).

c) Methyl 2-(dibutylamino)-6-(methylsulfonyl)-4'-(trifluoromethyl)-[1,l'-'biphenyl]-4-carboxylate

A round bottom flask was charged with methyl 2-amino-6-(methylsulfonyl)-4'-(trifluoromethyl)-[1,l'-biphenyl]-4-carboxylate (1.90 g, 0.005 mol), butyraldehyde (4.56 ml, 0.051 mol) and 1,2-dichloroethane (35 ml) and stirred at room temperature for 15 minutes. Sodium triacetoxyborohydride (10.73 g, 0.051 mol) was added and the reaction stirred at room temperature over night. The reaction was heated to 50°C for 4h. The reaction was quenched with water and extracted with DCM (3X100 ML) and the combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash chromatography (0-60% ethyl acetate/hexanes) to give the product as white solid (1.02g). MS m/z: 486.2 (M+1).

d) 2-(Dibutylamino)-6-(methylsulfonyl)-4'-(trifluoromethyl)-[1,l'-biphenyl]-4-carboxylic acid

To a stirred solution of methyl 2-(dibutylamino)-6-(methylsulfonyl)-4'-(trifluoromethyl)-[1,l'-biphenyl]-4-carboxylate (1.002 g, 0.0021 mol) in THE (15 mL) and MeOH (15 mL) was added lithium hydroxide monohydrate (0.592 g, 0.0141 mol). The reaction mixture was stirred at room temperature for 1 hour and the mixture was concentrated in vacuo. The residue was treated with water and adjusted to pH=3 with 6N aq. HCl solution, and extracted with EtOAc. The organic layer was washed with brine, dried over
anhydrous MgSO₄, and concentrated in vacuo to get the product. MS m/z: 4\[M+1\]^+. ¹H NMR (CDCl₃, 300 MHz): δ 8.62 (d, J=1.8 Hz, 1H), 8.10 (d, J=1.8 Hz, 1H), 7.73 (d, J=8.7 Hz, 2H), 7.53 (d, J=8.4 Hz, 2H), 2.77 (t, J=7.2 Hz, 4H), 2.55 (s, 3H), 1.14-1.11 (m, 8H), 0.82 (t, J=6.9 Hz, 6H).

e) 2-(Dibutylamino)-6-(methylsulfonyl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-4-carboxamide

[0747] A mixture of 2-(dibutylamino)-6-(methylsulfonyl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylic acid (952 mg, 0.002 mol), HBTU (1148 mg, 0.003 mol), N,N-diisopropylethyl amine (0.67 ml, 0.004 mol) and DMF (30 mL) was stirred at room temperature for 20 min and then cooled by placing the flask in a bath filled with dry ice. Ammonia was bubbled into the mixture for 5 minutes. The reaction was sealed and stirred at room temperature overnight. The reaction was diluted with water and extracted with ethyl acetate. The organic layers were washed with aq. Na₂CO₃ and brine, dried over anhydrous Na₂SO₄, and concentrated to afford the crude product as a beige solid (0.95g). MS m/z: 471.2 [M+1]^+.

f) 2-(Dibutylamino)-6-(methylsulfonyl)-4'-trifluoromethyl)-[1,1'-biphenyl]-4-carbonitrile

[0748] To a stirred solution of crude 2-(dibutylamino)-6-(methylsulfonyl)-4-(trifluoromethyl)biphenyl-4-carboxamide (450 mg, 0.001 mol) and N,N-diisopropylethyl amine (0.63 ml, 0.004 mol) and pyridine (0.77 ml, 0.010 mol) in THF (20 mL) was slowly added trifluoro acetic anhydride (0.40 ml, 0.003 mol). The reaction was stirred at 60 °C for 3h. The reaction was quenched with cold water and diluted with ethyl acetate and washed with aq. Na₂CO₃, brine, dried over anhydrous Na₂SO₄, and concentrated. The residue was purified by silica gel flash chromatography (0-50% EtOAc/hexane) to afford the product as a yellow solid (290 mg). MS m/z: 453.3 [M+1]^+; ¹H NMR (300 MHz, CDC1₃): δ 8.18 (d, 1H, J = 1.2 Hz), 7.75 (d, 2H, J = 8.1 Hz), 7.58 (d, 1H, J = 1.2 Hz), 7.52 (d, 2H, J = 8.4 Hz), 2.75 (t, 4H, J = 7.2 Hz), 2.50 (s, 3H), 1.24-1.02 (m, 8H), 0.83 (t, 6H, J = 6.9 Hz).

g) N^'-Dibutyl-e-fmethylsulfonyl]J^'-ilH-ietrazol-S-yli^'-itrifluoromethyO-Cl,l'-biphenyy^-aim^e

[0749] A mixture 2-(dibutylamino)-6-(methylsulfonyl)-4'-(trifluoromethyl)biphenyl-4-carbonitrile (140 mg, 0.0003 mol), sodium azide (100 mg, 0.0015 mol) and ammonium chloride (99 mg, 0.002 mol) in DMF (10 mL) was stirred at 120 °C for 6h. LC-MS indicated the reaction was complete. The reaction was treated with water and acidified with 1N aq. HCl to pH3-4 and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel flash chromatography (0-10% MeOH/C₃Cl) to afford a yellow foam (135 mg, 88%). MS m/z: 496.1 [M+1]^+; ¹H NMR (300 MHz, CDC1₃): δ 8.53 (s, 1H), 8.28 (s, 1H), 7.75 (d, 2H, J = 7.8 Hz), 7.57 (d, 2H, J = 7.8 Hz), 2.82 (t, 4H, J = 7.2 Hz), 2.62 (s, 3H), 1.30-1.00 (m, 8H), 0.82 (t, 6H, J = 7.2 Hz).

Compound 701

3-(N IV-Diethyisulfamoyl)-4-phenoxy-5-(piperidin-1-yl)benzoic acid
a) 3-Nitro-4-phenoxy-5-sulfamoyl benzoic acid

[0750] A round bottom flask was charged with 4-chloro-3-nitro-5-sulfamoyl-benzoic acid (2.0 g, 7.12 mmol), sodium bicarbonate (2.45 g, 29.2 mmol), phenol (1.47 g, 15.6 mmol) and water (20 mL) and heated at 85°C over night. The reaction mixture was cooled to room temperature and acidified with 3N HCl. The product precipitated out which was filtered and dried to give the product as yellow solid (1.9 g). MS m/z: 337 [M-1].

b) 3-Nitro-4-phenoxy-5-sulfamoyl benzoic acid methyl ester

[0751] A round bottom flask was charged with 3-nitro-4-phenoxy-5-sulfamoyl benzoic acid methyl ester (1.9 g, 5.637 mmol) and methanol (50 mL). Thionyl chloride (2.012 g, 16.91 mmol) was added slowly at room temperature and the reaction mixture was heated to 50°C overnight. The solvent was removed under reduced pressure and the residue redissolved in ethyl acetate and washed with saturated sodium bicarbonate solution, water and brine. The organic solvent was removed under reduced pressure and the residue purified by flash chromatography to give the product as pale yellow solid (1.72 g).

c) 3-(Dimethylaminomethylene-sulfamoyl)-5-nitro-4-phenoxy-benzoic acid methyl ester

[0752] A reaction flask was charged with 3-nitro-4-phenoxy-5-sulfamoyl benzoic acid methyl ester
(1.65 g, 4.68 mmol), acetonitrile (20 mL) and N,N-dimethyl formamide dimethyl acetal (0.65 mL, 4.917 mmol) and stirred at room temperature over night. The solvent was removed under reduced pressure and the resultant gummy residue was treated with ice cold water to give yellow solid. The solid was filtered and dried to give the product (1.9 g). MS m/z: 408 [M+1]+.

d) 5-Amino-3-(dimethylaminomethylene-sulfamoyl)-4-phenoxy-benzoic acid methyl ester

A round bottom flask was charged with 3-(dimethylaminomethylene-sulfamoyl)-5-nitro-4-phenoxy-benzoic acid methyl ester (1.0 g, 2.457 mmol), ethanol (50 mL) and the reaction mixture heated to 85°C. Ammonium chloride (1.3 g, 24.57 mmol) in water (25 mL) was added. Iron powder (541 mg, 9.828 mmol) was added in three portions 3 minutes apart. The heating was continued for another 1 h. The reaction mixture was cooled to 600°C and poured into dichloromethane (150 mL). The organic layer was separated and washed with water, brine and dried over sodium sulfate. The solvents were removed under reduced pressure to give the product as off white solid (690 mg). MS m/z: 378[M+1]+.

e) Methyl 3-(N-((dimethylamino)methylene)sulfamoyl)-4-phenoxy-5-(piperidin-1-yl)benzoate

A microwave vial was charged with 5-Amino-3-(dimethylaminomethylene-sulfamoyl)-4-phenoxy-benzoic acid methyl ester (600 mg, 0.0016 moles), potassium carbonate (1.32 g, 0.0095 moles), diiodopentane (0.35 ml, 0.0024 moles), Acetonitrile and the reaction heated in a microwave for 6h at 160°C. The reaction mixture was filtered to remove excess K₂CO₃ and solvents removed under reduced pressure. The residue was purified by flash chromatography to afford the product as an off white solid (450 mg). MS m/z: 446 [M+1]+.

f) 4-Phenoxy-3-(piperidin-1-yl)-5-sulfamoylbenzoic acid

A round bottom flask was charged with methyl 3-(N-((dimethylamino)methylene)sulfamoyl)-4-phenoxy-5-(piperidin-1-yl)benzoate (460 mg, 0.00103 moles), methanol (20 mL) and Sodium hydroxide (4.0 mL of a 2M aqueous solution) and the reaction mixture was heated to 50°C for 1 hour. LC/MS indicated completion of reaction. The reaction was cooled to room temperature and the organic solvents mostly removed under reduced pressure and the aqueous residue was acidified with 6 N HCl and extracted with ethyl acetate. The organic solvents were removed to afford the product as pale yellow solid. MS m/z: 377.1 [M+1]+.

g) 3-(N,N-diethylsulfamoyl)-4-phenoxy-5-(piperidin-1-yl)benzoic acid

A round bottom flask was charged with 4-phenoxy-3-(piperidin-1-yl)-5-sulfamoylbenzoic acid (90 mg, 0.00024 moles), sodium hydride in mineral oil (24 mg, 0.00096 moles) and THF (10 mL) was added under nitrogen. The reaction was stirred at room temperature for 20 minutes. Iodoethane (0.11 mL, 0.00143 moles) was added and the reaction heated to 50°C over night. Starting material was consumed according to the LC/MS. The reaction was cooled to room temperature and diluted with water and extracted with ethyl acetate. The solvents were removed under reduced pressure and the residue purified
by flash chromatography to afford the product as pale brown viscous oil.  'H NMR (CDCl₃, 300 MHz): δ 8.40 (d, J=2.1 Hz, 1H), 7.87 (d, J=1.8 Hz, 1H), 7.26 (t, J = 8.1 Hz, 2H), 7.03 (t, J=7.2 Hz, 1H), 6.77 (d, J=8.4 Hz, 2H), 3.29 (q, J=7.5 Hz, 4H), 2.91 (t, J=4.5 Hz, 4H), 1.34-1.32 (m, 2H), 1.26-1.22 (m, 4H), 1.11 (t, J=6.9 Hz, 6H). MS m/z: 433.2 (M+1).

**Compound 801**

![Chemical Structure of Compound 801](image)

[0757] The compound is prepared following the method described in WO2010085352. The PCT publication is incorporated herein by reference in its entirety.

**Compound 1A**

3-(N,N-Dibutylamino)-4-phenoxy-5-methylsulfonylbenzoic acid, sodium salt

![Chemical Structure of Compound 1A](image)

[0758] A suspension of 3-(dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzoic acid (1 g) in water is stirred at room temperature for 15-30 min. and treated with NaHCO₃ solution (1.1 eq. in 5 mL of water). The mixture is stirred for 15 min. at room temperature. NaCl is added and the mixture is heated to 75-80 °C until it is clear. The clear solution is then cooled to room temperature over 12 hrs to obtain the sodium salt as a white powder. The salt is collected by filtration and air dried.

[0759] The corresponding potassium, magnesium, and calcium salts may be prepared following the method described for preparation of the sodium salt.

**Compound IB**

3-(yy,Dibutylamino)-4-phenoxy-5-methylsulfonylbenzoic acid, ammonium salt
A suspension of 3-(dibutylamino)-5-(methylsulfonyl)-4-phenoxybenzoic acid (1 g) in acetone is stirred at room temperature for 15-30 min.s and treated with NH₄OH solution (1.1 eq., 25%). The mixture is stirred for 15 hr. at room temperature. The solvent is evaporated and the residue is treated with heptanes (5 mL). The stirring continued for another 12 hrs to obtain the ammonium salt as a white powder. The salt is collected by after the complete evaporation of the solvents.

Compound 1C
Sodium 2-(dibutylamino)-6-(methylsulfonyl)-4′-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate

Scheme 27

A round bottom flask was charged with 2-(dibutylamino)-6-(methylsulfonyl)-4′-(trifluoromethyl)-[1, 1′-biphenyl]-4-carboxylic acid (517 mg, 0.0011 mol) and THF (5 mL) and the mixture was stirred at room temperature. 0.474 mL of a sodium hydroxide solution (1.19 g in 10 mL methanol and 2 mL water) was added (43.8 mg, 0.0011 mol NaOH) and the mixture was stirred for 30
minutes at room temperature. The solvents were removed at reduced pressure and the resultant semi-solid was taken up in diethyl ether where upon a white solid precipitated out upon standing. This mixture was allowed to sit at room temperature overnight. The diethyl ether was decanted and the solid dried under reduced pressure give a white solid (507 mg). MS m/z: 472.2 [M+1]⁺ of free acid. ¹H NMR (DMSO-d₆, 300 MHz): δ 8.28 (d, J=0.9 Hz, 1H), 8.00 (d, J=0.9 Hz, 1H), 7.73 (d, J=8.4 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 2.73 (s, 3H), 2.66 (t, 4H), 1.03-1.00 (m, 8H), 0.73 (t, J=6.9 Hz).

**Compound 1D**

Sodium 5-(2-(dibutylamino)-6-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)tetrazol-1-ide

![Scheme 28](image)

[0762] To a stirred solution of N,N-dibutyl-6-(ethylsulfonyl)-4-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-2-amine (870 mg, 0.0019 mol) in MeOH (20 mL) was added a solution of Sodium hydroxide (78 mg, 0.0019 mol) in MeOH. The mixture was stirred for 30 min at rt and then filtered through cotton. The filtration was concentrated and the residue was triturated with hexane and dried to afford the product as beige powder (915 mg). MS m/z: 442.1 [M+1]⁺; HPLC purity: 99.25%; ¹H NMR (300 MHz, CDC1₃): δ 8.32 (s, 1H), 7.94 (s, 1H), 7.40-7.15 (m, 5H), 2.63 (s, 4H), 2.30 (m, 2H), 0.97 (s, 8H), 0.76 (t, 3H, J = 7.2 Hz), 0.68 (s, 6H).

[0763] The title corresponding substituted phenoxy compounds are or may be prepared using the appropriate substituted phenols and following the procedures described above.

[0764] The following examples were or can be prepared using the appropriate reagents and starting materials, and following the procedures described herein or with slight modifications thereof, and following procedures familiar to one of ordinary skill in the art.
Table 1: Compounds According to Embodiments of the Invention

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Further embodiments of the present invention will now be described with reference to the following examples. The examples contained herein are offered by way of illustration and not by any way of limitation.

EXEMPLARY EXAMPLES 1-4
Assessment of Therapeutic Potential of Compounds in Alleviating Anxiety

EXAMPLE 1
Fear Potentiated Startle Paradigm

Design. FPS model is a commonly used assessment of therapeutic value of anxiolytic compounds in the rat. Animals are trained and tested in stabilimeter devices (Med-Associates). Briefly, each rat is placed in a small Plexiglas cylinder. The floor of each stabilimeter consists of four 6-mm-diameter stainless steel bars spaced 18 mm apart through which shock can be delivered. Cylinder movements result in displacement of an acccelerometer where the resultant voltage is proportional to the velocity of the cage displacement. Startle amplitude is defined as the maximum accelerometer voltage that occurs during the first 0.25 seconds after the startle stimulus is delivered. The analog output of the accelerometer is amplified, digitized on a scale of 0-4096 units and stored on a microcomputer. Each stabilimeter is enclosed in a ventilated, light- and sound-attenuating box.

All sound level measurements are made with a Precision Sound Level Meter. The noise of a ventilating fan attached to a sidewall of each wooden box produces an overall background noise level of 64 dB. The startle stimulus is a 50 ms burst of white noise (5 ms rise-decay time) generated by a white noise generator. The visual conditioned stimulus ("CS") used is illumination of a light bulb adjacent to the white noise source. The unconditioned stimulus is a 0.6 mA foot shock with duration of 0.5 seconds, generated by constant-current shockers located outside the chamber. The presentation and sequencing of all stimuli is under the control of the microcomputer. FPS procedures may consist of 5 days of testing; during days 1 and 2 baseline startle responses are collected, days 3 and 4 light/shock pairings are delivered, day 5 testing for fear potentiated startle was conducted. Rats are receive a 30 min period of habituation to the FPS apparatus. 24-hr later baseline startle amplitudes are collected. The rats are be divided into two matched groups based on baseline startle amplitudes. Following baseline startle

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amplitude collection, 20 light/shock pairings are delivered on 2 sessions over 2 consecutive days (i.e., 10 light/shock pairings per day). On the final day, one group of rats receives an injection (i.v.) of a test compound and the other group receives vehicle only. Immediately following injections, startle amplitudes are assessed during startle alone trials and startle plus fear (light followed by startle) trials. Fear potentiated startle (light+startle amplitudes minus startle alone amplitudes) are compared between the treatment groups.

Testing. Rats are placed in the same startle boxes where they are trained and after 3 min are presented with 18 startle-eliciting stimuli (all at 105 dB). These initial startle stimuli are used to again habituate the rats to the acoustic startle stimuli. Thirty seconds after the last of these stimuli, each animal will receive 60 startle stimuli with half of the stimuli presented alone (startle alone trials) and the other half presented 3.2 seconds after the onset of the 3.7 seconds CS (CS-startle trials). All startle stimuli are presented at a mean 30 second interstimulus interval, randomly varying between 20 and 40 seconds.

Measures. The treatment groups are compared based on the difference in startle amplitude between CS-startle and startle-alone trials (fear potentiation). In general, the compounds described herein will affect the startle amplitude where the greater the reduction in fear-potentiated startle, the more anxiolytic the test compound.

Compounds described herein that show activity in a fear potentiated startle paradigm may be used in methods of treating anxiety (e.g., anxiolytics).

EXAMPLE 2

Contextual Fear Conditioning Model

Design. Contextual fear conditioning involves pairing an aversive event, in this case moderate foot shock, with a distinctive environment. The strength of the fear memory is assessed using freezing, a species-typical defensive reaction in rats that is marked by complete immobility, except for breathing. If rats are placed into a distinctive environment and are immediately shocked, they do not learn to fear the context. However, if they are allowed to explore the distinctive environment sometime before the immediate shock, they show intense anxiety and fear when placed back into the same environment. By procedurally dividing contextual fear conditioning into two phases, one can separately study effects of treatments on memory for the context (specifically a hippocampus based process) from learning the association between context and shock or experiencing the aversiveness of the shock (which depend upon emotional response circuitry including amygdala). Post-Traumatic Distress Syndrome (PTSD) in humans has been shown to be related to emotional response circuitry in the amygdala; for this reason contextual memory conditioning is a widely accepted model for PTSD. A typical experiment will use 24 rats.

Methods. In a typical experiment, 4 identical chambers (20x20x15 cm) are used. All aspects of the timing and control of events are under microcomputer control. Measurement of freezing is accomplished through an overhead video camera connected to the microcomputer and is automatically scored using a specialty piece of software, FreezeFrame. In Phase I, rats are placed individually into the
chambers for 5 minutes. Phase 2 begins 72 hours later, when again rats are placed individually into the same chambers but they receive an immediate foot shock \( \text{e.g.,} \) 1 mA for 2 s. Thirty seconds later they are removed from the chambers. Phase 3, 24 hours later, the rats are returned to the chambers for 8 minutes, during which time freezing, the index of conditioning fear is scored. Total freezing time may be analyzed in a one-way ANOVA with drug dose as the within-groups factor.

[0773] The compounds described herein which show significant anxiolytic effect in this model system may be used in a method for treating anxiety including post-traumatic stress disorder. For example, the compounds described herein may be used as anxiolytics. Further, the compounds used in this example, and derivatives thereof, may be used to treat anxiety including post-traumatic stress disorder (PTSD). Exemplary use of this model system are described in U.S. Patent Application Publication Nos. 2006/0089350 and 2009/0215754.

**EXAMPLE 3**

**Elevated Plus Maze**

[0774] **Design.** The elevated plus maze (EPM) is commonly used to assess anxiety levels in rodents. The EPM takes advantage of the fact that when a normal rat is feeling anxious in a novel environment it will seek out and hide in enclosed spaces. A normal rat will venture out into open spaces within the new environment only when it feels less anxious. Drugs like diazepam and buspirone show anxiolytic effects in this task, and hence rats treated with such drugs spend more time within the open areas of the maze.

[0775] A first group of the rats receives an injection (i.v) of test compound, and a second group receives an injection of vehicle. Each rat will immediately be placed on the elevated plus maze.

[0776] The elevated plus maze consists of two opposing open arms, 50X10 cm, crossed with two opposing enclosed arms of the same dimensions but with walls 40 cm high. Each of the four arms is connected to one side of a central square (10X10 cm) giving the apparatus a plus-sign appearance. The maze is elevated 50 cm above the floor in a normally illuminated room. The rats are placed individually on the central square of the plus maze facing an enclosed arm. The entire 3-minute session is videotaped and later scored. The time spent and the number of entries into the open and closed arms, and the number of trips made to at least the midpoint down the open arms is recorded. An arm entry is defined as placement of all four paws onto the surface of the arm. Time spent in the open arms of the maze are compared between treatment groups. Where the test compound reduces anxiety in rat, the group that received the test compound will spend more time in the open arms than the rats that received vehicle.

[0777] The compounds described herein which show significant anxiolytic effect in this model system may be used in a method for treating anxiety. For example, the compounds described herein may be used as anxiolytics.

**EXAMPLE 4**

**Marble Burying Test**

[0778] This method, which detects anxiolytic/tranquillizing activity, follows that described by

Mice were individually placed in transparent plastic cages with 5 cm of sawdust on the floor and 25 marbles grouped in the centre of the cage. The cage was covered with an inverted plastic cage. Each test cage, together with the marbles, was impregnated with mouse odor before-hand by leaving 10 mice in the cage for 15 minutes. These mice then play no further role in the experiment. The number of marbles covered by sawdust (2/3 or more) is counted at the end of a 30 minute test. The test was performed partially blind (apart from positive control). The test substances were each evaluated at 3 doses, administered i.p. 30 minutes before the test, and compared vehicle control group. Data was analyzed by comparing treated groups with vehicle control using unpaired ANOVA followed by post-hoc tests. Data with the reference substance was compared with vehicle control using unpaired Student’s t tests. A decrease in the number of marbles buried is indicative of a reduction in anxiety. Several of the compounds described herein decrease the number of marbles buried by mice as compared to the vehicle control, and thus, exhibit anxiolytic activity. See FIGURE 1.

This data demonstrates that the compounds described herein may be used in methods of treating anxiety. In particular, the compounds used in this Example, and derivatives thereof, may be used in methods of treating anxiety (e.g., anxiolytics).

Example 5
Animal Model of Amphetamine Sensitization (Addiction)

The therapeutic usefulness of compounds in the treatment of behavior disorders may be examined by measuring the ability of a compound to reverse the symptoms of amphetamine sensitization in rats. See Peleg-Raibstein, et al. (2008) "Amphetamine sensitization in rats as an animal model of schizophrenia." Behav. Brain Res. 191(2): 190-201.

Amphetamine sensitization is induced in animals. Following three days of handling, the animals receive daily intraperitoneal (i.p.) injections of 1.5 mg/kg amphetamine hydrochloride (injection volume 1.0 ml/kg) for 5 days (amphetamine-amphetamine group). The fifth day of treatment with amphetamine is followed by withdrawal for 48 h. Following the 48 hours withdrawal, one group of the rats receive an injection of compounds (i.v) and the others receive an injection of vehicle (i.v). The rats then receive a challenge injection of amphetamine (1.5 mg/kg) and are monitored for locomotor activity in an open field. All injections except the challenge injection are administered in the rats' home cage.

Locomotor activity is measured in an open field for 120 minute following the amphetamine challenge. Total distance traveled and number of rears are automatically recorded and compared between groups using one-way analysis of variance. When a compound reduces or blocks amphetamine sensitization, the group that received that compound prior to the amphetamine challenge exhibits shorter distances and fewer total rears.
[0784] This data demonstrates that the compounds described herein may be used in methods of treating schizophrenia. In particular, the compounds used in this Example, and derivatives thereof, may be used in methods of treating schizophrenia (e.g., antipsychotics).

EXAMPLE 6

Mouse model of Mesial Temporal Lobe Epilepsy (MTLE)

[0785] A group of adult mice were injected with kainite and implanted with a bipolar electrode in the dorsal hippocampus using stereotaxic techniques under general anesthesia. Between 4 and 6 weeks following KA injection, the mice were injected with drugs in a random order (two injections per week). Drug conditions were counter-balanced, the animals were used as their own controls. Digital EEG recordings were performed in freely moving animals for 20 minutes preinjection and 20 minutes between 20 and 40 minutes post-injection. The effects of the injected compound were compared versus reference period. This model is also described in U.S. Patent No. 6,495,601 and Sharma, et al. (2007) Toxicologic Pathology 35: 984-999.

[0786] Several compounds described herein decreased the number of seizures in this model of mesial temporal lobe epilepsy. See FIGURE 2.

[0787] This data demonstrates that the compounds described herein may be used in methods of treating seizures. For example, the compounds described herein may be used in methods for suppressing the occurrence or lessening the severity of seizures. In particular, the compounds used in this Example, and derivatives thereof, may be used in methods of treating seizures (e.g., anticonvulsant). For example, the compounds described herein may be used in methods to treat and/or prevent (prophylactic) for seizures, seizure disorders, epilepsy, epileptic seizures, and other neurodegenerative disorders (e.g., those neurodegenerative disorders which involve seizures).

EXAMPLE 7

Epileptiform Discharges in Hippocampal Slices

[0788] Spontaneous epileptiform activity may be elicited by a variety of treatments. To perform hippocampal slice studies, Sprague-Dawley rats (males and females; 25-35 days old) are decapitated, the top of the skull is rapidly removed, and the brain chilled with ice-cold oxygenated slicing medium. Sucrose-based artificial cerebrospinal fluid (aCSF) consisting of 220 mM sucrose, 3 mM KCl, 1.25 mM Na₃P0₄, 2 mM MgSO₄, 26 mM NaHCO₃, 2 mM CaCl₂, and 10 mM dextrose (295-305 mOsm) may be used as the slicing medium. A hemisphere of brain containing hippocampus is blocked and glued (cyanoacrylate adhesive) to the stage of a Vibroslicer (Frederick Haer, Brunsick, ME). Horizontal or transverse slices 400 μm thick are cut in 4°C, oxygenated (95% O₂; 5% CO₂) slicing medium. The slices are then immediately transferred to a holding chamber where they remained submerged in oxygenated
bathing medium (ACSF) consisting of 124 mM NaCl, 3 mM KCl, 1.25 mM NaH₂PO₄, 2 mM MgSO₄, 26 mM NaHCO₃, 2 mM CaCl₂, and 10 mM dextrose (29-305 mOsm). The slices can be held at room temperature for at least 45 minutes before being transferred to a submersion-style recording chamber. In the recording chamber, the slices may be perfused with oxygenated recording medium at 34-35°C. All animal procedures are conducted in accordance with NTH animal care guidelines. In most slice experiments, simultaneous extracellular field electrode recordings are obtained from CA1 and CA3 as described in U.S. Patent Nos. 6,495,601 and 7,214,711.

[0789] Hippocampal slices treated with the test compounds exhibit less epileptiform activity, indicative of anti-seizure properties. Therefore, compounds described herein showing activity in this model may be used in methods of treating seizures. For example, the compounds described herein may be used in methods for suppressing the occurrence or lessening the severity of seizures or in methods to treat and/or prevent (prophylactic) for seizures, seizure disorders, epilepsy, epileptic seizures, and other neurodegenerative disorders (e.g., those neurodegenerative disorders which involve seizures).

EXAMPLE 8

In vitro Hippocampal Recordings of miniature and spontaneous inhibitory post-synaptic currents (mIPSCs and sIPSCs)

[0790] Compounds may be tested for their ability to increase GABA_A inhibitory drive, such as a marked increase in spontaneous IPSCs or in miniature IPSCs in a hippocampal slice model, where the compound consistently shows a significant decrease in the time between inhibitory events (e.g., increased frequency of events). Ion flux in neuronal cells are measured using standard techniques. Kandel and Schwartz Principles of Neural Science, 2nd Edition (1985), see, e.g., pages 128-131. Recording is performed in vitro in hippocampal slices (CA1 pyramidal cell layer). For recording GABA_A-IPSCs, glutamatergic and GABA_A transmission is blocked by adding DNOX (50 µM) [6,7-Dinitroquinoxaline-2,3-dione]; AP-5 [2-Amino-5-phosphonopentanoic acid] (50 µM), and SCH50911 [(2S)-(+)5,5-dimethyl-2-morpholineacetic acid] (20 mM) into the medium. The intracellular solution comprised CsCl and 0X31 4.

[0791] Data demonstrating that the interval between miniature and/or spontaneous inhibitory post-synaptic currents (mIPSCs and sIPSCs, respectively) events are substantially decreased in the presence of the compound indicate a highly significant increase in the frequency of inhibitory events. Such data suggest a potentially selective pre-synaptic mechanism increasing the release of GABA from the neurons by the action of compounds described herein.

[0792] Compounds described herein which act parasynaptically may be administered at high doses (e.g., 100 mg/kg) without the unwanted side effects usually associated with GABAergic compounds (e.g., sedation from benzodiazepines).
Therefore, compounds described herein showing activity in this model may be used in methods of treating seizures. For example, the compounds described herein may be used in methods for suppressing the occurrence or lessening the severity of seizures or in methods to treat and/or prevent (prophylactic) for seizures, seizure disorders, epilepsy, epileptic seizures, and other neurodegenerative disorders (e.g., those neurodegenerative disorders which involve seizures).

**EXAMPLES 9-12**

**Experimental Models of Pain**

Experimental models of pain include tests of response thresholds to high intensity stimuli (acute pain tests) and changes in spontaneous or evoked behavioral responses in animals with peripheral injury or inflammation (persistent pain models). Acute thermal pain is modeled by the hot-plate and tail-flick test, while persistent pain can be modeled by the formalin test. See Bannon and Malmberg "Models of Nociception: Hot-Plate, Tail-Flick, and Formalin Tests in Rodents." *Curr. Protoc. Neurosci.* 41:8.9.1-8.9.16 for protocols for all three of these tests, including preparation of animals (rats or mice), administration of a compound being tested for its analgesic properties and data collection.

**EXAMPLE 9**

**Formalin Paw Test (late phase and early/late phase)**

The formalin paw method described herein detects analgesic/anti-inflammatory activity, generally used to test compounds for pain relief, in particular diabetic neuropathy or nociceptive neuropathy. See Wheeler-Aceto, et al. (1991) *Psychopharmacology* 104: 35-44. The formalin paw model allows for testing antinociceptive effects in persistent pain in both the early phase, which reflects direct activation of nociceptors, and in the late phase, which is indicative of inflammatory pain. Mice are given an intraplantar injection of 5% formalin (25 μl) into the posterior left paw. This treatment induces paw licking in control animals. Mice are briefly observed at 1 minute intervals between 15 and 50 minutes after the injection of formalin and the number of occasions that the mice are observed licking the injected paw is recorded. The test is performed “blind” (i.e., the observers do not know which mice received test compounds).

Test substances were administered to groups of 8 ICR male mice weighing 23 +/- 3 g. Test substances and vehicle were each administered by IP injection 30 minutes before subplantar injection of formalin. Formalin-induced hind paw licking time was recorded at 5-minute intervals for 35 minutes after formalin injection. Reduction of the formalin-induced hind paw licking time by 50 percent or more (> 50% in-house criteria) indicates significant analgesic activity. Also, statistical analysis was performed by using one-way ANOVA followed by Dunnett's test to compare the test compound-treated and vehicle control groups. P<0.05 is considered statistically significance. Data for early and late phase (acute and inflammatory pain) is shown in Figure 3A-D.
The compounds to be evaluated (125 µmole/kg) were administered i.p. 30 minutes before the test (i.e. 15 minutes before formalin), and compared with a vehicle control group. Gabapentin (100 mg/kg i.p.), administered under the same experimental conditions, was used as reference substance. Data was analyzed by comparing treated groups with vehicle control using unpaired Mann-Whitney U tests. Late phase data (inflammatory pain) is shown in Figure 4. The compounds which show a reduction in this test described herein may be used in methods to treat and/or prevent (prophylactic) for pain for both acute and/or inflammatory pain.

This data demonstrates that the compounds described herein may be used in methods of treating pain. For example, the compounds described herein may be used in methods for suppressing the occurrence or lessening the severity of pain. In particular, the compounds used in this Example, and derivatives thereof, may be used in methods of treating pain (e.g., analgesics). For example, the compounds described herein may be used in methods to treat acute and/or inflammatory pain.

**EXAMPLE 10**

**Taxol® (paclitaxel) Induced Neuropathy Model**

Peripheral neuropathies are chronic conditions that arise when nerves are damaged by trauma, disease, metabolic insufficiency, or by certain drugs and toxins. The sensory disturbances associated with chemotherapeutic agents, such as paclitaxel (Taxol®), range from mild tingling to spontaneous burning, typically in the periphery such as the hands and feet. Symptoms become more intense with continued therapy and can lead to weakness, ataxia, numbness and pain, limiting the dose and/or treatment with the chemotherapeutic agent.

Gabapentin, 100 mg/kg, IP is able to mitigate the mechanical allodynia seen as a result of the Taxol-induced neuropathic pain. Similarly, rats treated with compounds described herein are believed to show a significant improvement in allodynia when compared to the vehicle control group.

Test articles are administered intraperitoneally in dose volumes of 10 mL/kg body weight. Preparations are made freshly for each day of administration. The reference article, Gabapentin, is formulated in saline to a concentration of 100 mg/mL and delivered subcutaneously at a dose volume of 1 mL/kg body weight (for a dosing concentration of 100 mg/kg). Male Sprague Dawley rats may be used.

For inclusion into the study (first portion), the animals have a baseline thermal paw test, which is measured prior to Taxol® (paclitaxel) injections. Animals with a thermal paw score greater than 15 seconds are excluded from study.

All animals that will receive Taxol® (paclitaxel) are tested for thermal hyperalgesia. Animals need to have at least a 20% drop from baseline for inclusion into the treatment segment of the study. All animals undergo a baseline pre-dose von Frey test, which is measured prior to Taxol® (paclitaxel) injection. See, e.g., Bennett, et al. (2003) Models of Neuropathic Pain in the Rat Current Protocols in
Neuroscience. For inclusion into the study, the animals need to have a baseline von Frey score above 12.

All animals administered Taxol® (paclitaxel) are tested for mechanical allodynia using von Frey. See, e.g., Bennett, et al. (2003) Models of Neuropathic Pain in the Rat Current Protocols in Neuroscience. Animals receiving a score of 13 or below are allocated to treatment groups. The mechanical allodynia scores for each group are reviewed to ensure the mean values and standard deviations are homogeneous. Rats are allocated to treatment groups.

All animals are administered Taxol® (paclitaxel), 2 mg/kg, I.P. at a dose volume of 1 mL/kg, on Days 1, 3, 5 and 7.

All animals will receive a single intraperitoneal injection of test compound. All animals will receive an I.P. injection of vehicle or test compound 30 minutes prior to mechanical allodynia testing. Animals are dosed at a volume of 10 mL/kg.

Control animals will receive an I.P. injection of gabapentin 90 minutes prior to mechanical allodynia testing. Animals are dosed at a volume of 1 mL/kg.

Twice prior to baseline testing, the animals undergo acclimation to the mechanical allodynia apparatus. This habituates the rats to the testing devices, so they are calm at the time of testing.

All animals undergo von Frey testing for mechanical allodynia. On testing days, the animals are returned to the chambers and allowed approximately 15 minutes to explore their surroundings prior to testing. A filament is applied to the left hind paw.

The group mean results are analyzed versus the vehicle control group using a two way ANOVA, followed by a Bonferroni post-hoc test. Individual groups are tested pre and post dose using a paired t-test.

Compounds described herein act parasympathetically and may be administered to treat neuropathic pain without the unwanted side effects usually associated with GABAergic compounds (e.g., sedation from benzodiazepines). Further treatment with compounds described herein may be expected to have similar effects.

Compounds described herein that show activity in this experimental model may be used in methods of treating neuropathic pain. For example, the compounds described herein may be used in methods for lessening the severity of neuropathic pain.

EXAMPLE 11

Tail Flick Test Model of Nociception

The mouse tail-flick model is a well-accepted model of acute thermal pain in which a number of clinically relevant opioid analgesics produce moderate to full efficacy on several different pain-related measures. See, e.g., Bannon & Malberg (2007) Curr. Protoc. Neurosci., 41: 8.9.1-8.9. 16.

Efficacy of the test compounds are assessed using the 52°C warm water tail-flick test. The latency to the first sign of a rapid tail-flick is taken as the behavioral endpoint (Jannsen, et al. 1963). Each
mouse is first tested for baseline latency by immersing its tail in the water and recording the time to response. Mice not responding within 5 seconds are excluded from further testing. Test compounds are then injected, and the mice are rested for thermal latencies at 10, 20, 30, 45, 60, 90, 120, and 180 minutes post-injection (if a drug effect dropped below 20% for the group average then the testing is halted for that group). Antinociception is calculated by the following formula: % Antinociception = 100 x (test latency-control latency)/(10-control latency). A maximum score is assigned (100%) to animals not responding within 10 seconds to avoid tissue damage.

[0815] Each experimental group consisted of 8 mice with a total of approximately 260 mice. On the morning of Day 1, mice were marked and weighed, and then baselined for thermal latencies in the 52°C tail-flick assay. Test compounds are then injected and the mice are tested for thermal latencies at 10, 20, 30, 45, 60, 90, 120 and 180 minutes post-injection (if a drug effect drops below 20% for the group average then the testing is halted for that group). A technician blinded to the specific treatments administered the test compounds by the intraperitoneal route and tested for thermal latencies.

[0816] Evidence of the ability of compounds described herein to alleviate pain may be seen as a higher pain threshold than the group that received vehicle as tested (e.g., an increase in the mean % antinociception) and results are shown in Figure 5A-H. Several of the compounds (e.g., NTP-8001, NTP-8002, NTP-8009, NTP-8010, NTP-8012, NTP-8013, NTP-8014, NTP-8014, and NTP-8015) exhibit an alleviation of pain as a function of a higher pain threshold than the group that received the vehicle. Therefore, the compounds described herein exhibit analgesic effects in pain (e.g., acute pain).

[0817] This data demonstrates that the compounds described herein may be used in methods of treating pain. For example, the compounds described herein may be used in methods for suppressing the occurrence or lessening the severity of pain. In particular, the compounds used in this Example, and derivatives thereof, may be used in methods of treating pain (e.g., analgesics). For example, the compounds described herein may be used in methods to treat acute and/or inflammatory pain.

**EXAMPLE 12**

**Chung model of neuropathy**

[0818] **Design.** Spinal nerve ligation is performed under isofluorane anesthesia with animals placed in the prone position to access the left L4-L6 spinal nerves. Under magnification, approximately one-third of the transverse process is removed. The L5 spinal nerve is identified and carefully dissected free from the adjacent L4 spinal nerve and then tightly ligated using a 6-0 silk suture. The wound is treated with an antiseptic solution, the muscle layer is sutured, and the incision is closed with wound clips. Behavioral testing of mechanical paw withdrawal threshold takes place within a 3-7 day period following the incision. Briefly, animals are placed within a Plexiglas chamber (20x10.5x40.5 cm) and allowed to habituate for 15 minutes. The chamber is positioned on top of a mesh screen so that mechanical stimuli
can be administered to the plantar surface of both hindpaws. Mechanical threshold measurements for each hindpaw are obtained using an up/down method with eight von Frey monofilaments (5, 7, 13, 26, 43, 64, 106, and 202 mN). Each trial begins with a von Frey force of 13 mN delivered to the right hindpaw for approximately 1 seconds, and then the left hindpaw. If there is no withdrawal response, the next higher force is delivered. If there is a response, the next lower force is delivered. This procedure is performed until no response is made at the highest force (202 mN) or until four stimuli are administered following the initial response. The 50% paw withdrawal threshold for each paw is calculated using the following formula: \[ \text{Thresh} = [\text{vFr}] \log \frac{1}{k} \] where \([vFr]\) is the force of the last von Frey used, \(k=0.2268\) which is the average interval (in log units) between the von Frey monofilaments, and \(y\) is a value that depends upon the pattern of withdrawal responses. If an animal does not respond to the highest von Frey hair (202 mN), then \(y=1.00\) and the 50% mechanical paw withdrawal response for that paw is calculated to be 340.5 mN. Mechanical paw withdrawal threshold testing is performed three times and the 50% withdrawal values are averaged over the three trials to determine the mean mechanical paw withdrawal threshold for the right and left paw for each animal. This model is described in Kim & Chung (1992) Pain, 50: 355-363.

[0819] Compounds described herein that show activity in this experimental model may be used in methods of treating neuropathic pain. For example, the compounds described herein may be used in methods for lessening the severity of neuropathic pain.

**EXAMPLE 13**

Amphetamine-induced HA Test for Antipsychotic and Antiparkinson Activity

[0820] The method, which detects antipsychotic and antiparkinson activity, follows that described by Costal, et al. (1977) Brain Res. 123: 89-111, and uses an activity meter similar to that described by Boissier and Simon (1965) Arch. Int. Pharmacodyn. Ther. 158(1): 212-221. Amphetamine induces hyperactivity in this test situation. Hyperactivity is antagonized by classical and atypical antipsychotics acting on dopaminergic systems at the limbic level, and is potentiated by antiparkinson drugs.

[0821] Mice were injected with amphetamine and are immediately placed in the activity meter. The activity meter consists of 24 covered Plexiglas cages contained within a darkened cabinet and connected to silent electronic counters. Each cage is equipped with four photocell assemblies (two at each end of the cage) 2.5 cm above the floor, in order to measure the number of movements by each animal (one per cage) in the horizontal plane. Seven additional photocell assemblies are placed at even intervals 9.5 cm above the floor along the long wall to record rearing. The number of (horizontal) crossings by each animal (one per cage) from one pair of photocells to the other is recorded by computer in 10-minute intervals for 30 minutes. A similar procedure is utilized for recording of rearing, except that individual photobeam breaks are recorded. The scores for activity and rearing are recorded by computer over 10-minute intervals and cumulated over a 30-minute period. The test was performed blind.
Each test substance was evaluated at 1 dose, administered i.p. 30 minutes before amphetamine, and compared with a vehicle control group. The experiment also included a control group not treated with amphetamine.

Data with the test substance was analyzed by comparing treated groups with appropriate control using one-way ANOVA followed by post-hoc Dunnett’s tests for total cumulated activity. Data with the reference substance was analyzed using unpaired Student’s t tests. Results are shown in Figure 6 which demonstrates that several of the compounds described herein show antipsychotic activity and thus may be useful for the treatment of neuropsychiatric disorders and Parkinson’s disease.

This data demonstrates that the compounds described herein may be used in methods of treating neuropsychiatric disorders and Parkinson’s disease. In particular, the compounds used in this Example, and derivatives thereof, may be used in methods of treating neuropsychiatric disorders (e.g., antipsychotics).

Example 14

In vitro Molecular Tests of Compounds of Invention on GABA<sub>A</sub> Receptor Isoforms

Experimental design for selectivity screen

The addition of GABA to GABAergic cells activates the recombinant expressed GABA<sub>A</sub> receptors, creating an ion movement through the ion channel in the GABA<sub>A</sub> receptor. The electrical current generated by the movement of chloride ions into the cells can be quantified.

The effects of NTP compounds on the activity of specific GABA<sub>A</sub> receptors were assessed in human embryonic kidney 293 cells (HEK-293). Cells were transiently transfected with rat, specific GABA<sub>A</sub> receptor subunit constructs and whole cell electrophysiology recordings were performed in the presence or absence of NTP compounds (Fisher, 2004). Whole-cell patch clamp recording was performed at -50 mV, GABA or GABA + NTP compounds was applied for 5 sec. NTP compounds were diluted from a freshly made stock in DMSO, GABA was prepared from a frozen stock. The 100% inhibition denotes complete inhibition of GABA<sub>A</sub> receptors in response to GABA. Any value above 0% was indicative of inhibition of GABA<sub>A</sub> receptors by a test compound. Compounds described herein were tested at 10 µM GABA concentrations against receptors containing the α<sub>1</sub>, ọ<sub>1</sub>, ọ<sub>4</sub>, and ọ<sub>3</sub> GABA<sub>A</sub> receptor subunits. Table 2 shows the deviation from the baseline GABA effect caused by the indicated compounds (e.g., inhibition of the receptor response to GABA).

Classic GABAergic drugs

Classic GABAergic drugs (e.g., benzodiazepines) are non-selective agonists that increase both the amplitude and time course of inhibitory currents in GABA<sub>A</sub> receptor. FRJISIUM (clobazam) an anticonvulsant, AMBIEN (Zolpidem) a sleep aid, and VALIUM (diazepam) an anxiolytic drug, all increase both the amplitude and time course of inhibitory currents in GABA<sub>A</sub> receptor. GABA<sub>A</sub> receptor
agonists activate GABA<sub>A</sub> receptors at low GABA concentrations, and while effective, also induce CNS side effects including sedation, decreased respiration, decreased cognition, and impaired motor function.

**Compounds of the Invention**

[0828] Compounds described herein were tested at 10 µM GABA concentrations against multiple GABA<sub>A</sub> receptor isoforms (e.g., α<sub>2</sub>β<sub>3</sub>γ<sub>2</sub>, α<sub>1</sub>β<sub>2</sub>γ<sub>2</sub>, α<sub>3</sub>β<sub>2</sub>γ<sub>2</sub>). Several of compounds described herein have some selectivity for blocking the α<sub>4</sub> GABA<sub>A</sub> receptor isoform by inhibiting currents in the α<sub>4</sub> GABA<sub>A</sub> receptor isoform. See Table 2. Several of the compounds may act as noncompetitive inhibitors.

Further, particular compounds of the present invention appear not to be active at post-synaptic GABA<sub>A</sub> receptors that are most commonly comprised of a<sub>1</sub> GABA<sub>A</sub> receptor subunits, indicating that they show presynaptic-selectivity.

**α<sub>1</sub>β<sub>2</sub>γ<sub>2</sub> GABA<sub>A</sub> receptor isoform**

[0829] The α<sub>1</sub> subunit is the predominant a subunit in GABA<sub>A</sub> receptors in the adult brain. The α<sub>1</sub> containing receptors showed no significant activation in response many of the compounds described herein. In general, the amplitude of the current associated with GABA activation of these receptors is not affected by preferred compounds, with a mixture of increased decay time and decreased amplitude seen at the highest concentration (10 µM) but no alteration at lower concentrations. This is in contrast to the significantly increased positive modulation seen with action of benzodiazepines and other classic GABA-ergic agents.

**Compounds described herein appear to have a different mechanism of action upon the GABA<sub>A</sub> receptors than traditional GABA agonist drugs.** The primary effect is an inhibition of chloride current reducing total GABA "drive", especially after prolonged administrations of GABA. It is seen best at α<sub>4</sub> and α<sub>6</sub>, α<sub>3</sub> and the inhibition is consistent with noncompetitive antagonism, i.e., open channel block.

[0830] Compounds described herein appear to have a different mechanism of action upon the GABA<sub>A</sub> receptors than traditional GABA agonist drugs. The primary effect is an inhibition of chloride current reducing total GABA "drive", especially after prolonged administrations of GABA. It is seen best at α<sub>4</sub> and α<sub>6</sub>, α<sub>3</sub> and the inhibition is consistent with noncompetitive antagonism, i.e., open channel block.

**The activity of compounds described herein appear to exhibit two features:** (a) higher potency inhibition of GABA<sub>A</sub> receptors containing specific subunits, e.g., α<sub>4</sub>, and (b) a lack of positive modulation of receptors containing α<sub>4</sub>, e.g., targets of traditional GABAergic mechanisms such as benzodiazepines. Therefore, some compounds described herein appear to act in a presynaptic-specific manner by increasing GABA release at synapses leading to increased neuronal inhibition through a pre-synaptic mechanism and thus would be expected to decrease in anxiety and seizure frequency. Compounds whose activity shows these features may also reduce pain, especially neuropathic pain. Inhibition of prolonged GABA-evoked currents is the primary effect observed at α<sub>4</sub>, α<sub>6</sub>, and α<sub>5</sub>-containing receptors. These effects may require a γ subunit, as 5-containing receptors are believed to be unaffected by compounds described herein.

[0832] **Table 2: Inhibition of the GABAA Receptor Response to GABA by Compounds of the Invention**
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### Example 15

**In vitro** Molecular Tests of Compounds of Invention on NKCC1 Receptor

The compounds described herein may show NKCC1 selective activity. To test for this activity, the compounds may be tested for NKCC1 activation. Three days before the experiment, NHDF (Normal Human Dermal Fibroblast) are seeded at 3000 cells/well in 96 well white culture plate and stored at 37°C (incubator 5% CO2). Two days before the experiment the cells are starved in 0.2% FCS. One hour before the experiment, bFGF is added to the medium at 1ng/ml. After washing, medium is then replaced by a preincubation buffer with bFGF, Ouabaine (Na+/K+ ATPase inhibitor) and without NaCl (replaced by choline chloride) during 15 minutes at 37°C. Preincubation buffer is then replaced by the assay buffer with bFGF, Ouabaine and NaCl. 5 µCi/ml 86Rb is then added in the absence or presence of test compounds at 10µM or Bumetanide at 30µM (positive control) for 20 minutes at 37°C. After washing with cold MgCl2, Microscint 40 is added in each well and incubated for at least 1 hour at RT before reading with Topcount. Bumetanide concentration response is determined for each plate tested. All compounds responses may be represented as the percent inhibition of Bumetanide-sensitive Rubidium (86Rb+) influx.

**Table 3: Inhibition of NKCC by Compounds**

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Although the invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims. Modifications of the above-described modes for carrying out the invention that are obvious to persons of skill in medicine, pharmacology, microbiology, and/or related fields are intended to be within the scope of the following claims.

Although the invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the appended claims. Modifications of the above-described modes for carrying out the invention that are obvious to persons of skill in medicine, pharmacology, microbiology, and/or related fields are intended to be within the scope of the following claims.

All publications (e.g., Non-Patent Literature), patent application publications, and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All such publications (e.g., Non-Patent Literature), patent application publications, and patent applications are herein incorporated by reference to the same extent as if each individual publication, patent, patent application publication, or patent application is specifically and individually indicated to be incorporated by reference.

It should be understood that factors such as the differential cell penetration capacity of the various compounds can contribute to discrepancies between the activity of the compounds in the in vitro biochemical and cellular assays.

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 Open Eye 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 either ChemDraw® or ISIS®/DRAW. 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.
WE CLAIM:

I. A compound of the formula I:

\[ \text{I} \]

wherein:

- \( \text{Cy} \) is aryl or heteroaryl;

- \( \text{L}^2 \) is a single bond, or \(-0-\);

(a) \( \text{L}^1 \) is substituted or unsubstituted alkyene, or \(-\text{C}(=\text{O})-\) and \( \text{R}^1 \) is selected from the group consisting of hydroxy, amino, substituted amino, substituted or unsubstituted \( \text{N} \) containing heterocycloalkyi, and substituted or unsubstituted alkoxy, or

(b) \( \text{L}^1 \) is a single bond or substituted or unsubstituted alkyene, and \( \text{R}^1 \) is selected from the group consisting of \( \text{H} \), halo, \( \text{CN} \), substituted or unsubstituted 5-12 membered heteroaryl, and substituted or unsubstituted 4-8 membered heterocycloalkyi;

- \( \text{R}^{2b} \) is \( \text{H} \), substituted or unsubstituted alkyi, substituted or unsubstituted arylalkyl, or substituted or unsubstituted heteroarylalkyl;

- \( \text{R}^{3b} \) is substituted or unsubstituted acyl, substituted or unsubstituted alkyi, substituted or unsubstituted arylalkyl, or substituted or unsubstituted heteroarylalkyl;

\( \text{R}^{2a} \) and \( \text{R}^{2b} \) may join together to form a 4-7 membered heterocycloalkyi ring;

- \( \text{R}^3 \) is selected from the group consisting of halo, alkyi, substituted or unsubstituted haloalkyl, \( \text{CN} \), and \( \text{S}(0)=\text{R}^{3a} \), wherein

  - the subscript \( \text{x} \) is 0, 1, or 2; and

(a) \( \text{R}^{3a} \) is substituted or unsubstituted alkyi, substituted or unsubstituted cycloalkyi, aryl or heteroaryl;

(b) \( \text{R}^{3b} \) is substituted or unsubstituted amino, or substituted or unsubstituted \( \text{N} \)-containing heterocycloalkyi, wherein the \( \text{N} \) of the heterocycle is bonded to \( \text{S} \) via a single bond; provided that \( \text{L}^1 \) is other than \(-\text{C}(=\text{O})-\), or

(c) \( \text{R}^{3c} \) is substituted or unsubstituted amino, or substituted or unsubstituted \( \text{N} \)-containing heterocycloalkyi, and wherein the \( \text{N} \) of the heterocycle is bonded to \( \text{S} \) via a single bond; provided
that \( R^{2a} \) is other than H and the subscript \( n \) is other than 0; and

each \( R^4 \) is independently selected from the group consisting of substituted or unsubstituted alkyl, substituted or unsubstituted acyl, substituted or unsubstituted acylamino, substituted or unsubstituted alkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkoxy carbonyl, substituted or unsubstituted alkylarylamino, substituted or unsubstituted amino, substituted or unsubstituted aroyl, substituted or unsubstituted aryloxy, substituted or unsubstituted aroyloxy, hydroxy, substituted or unsubstituted alkoxy, substituted sulfanyl, substituted sulfinyl, substituted sulfanyl, substituted or unsubstituted aminosulfonyl, substituted or unsubstituted carboxyl, cyano, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl, substituted or unsubstituted dialkylamino, halo, nitro, and thiol; or two adjacent \( R^3 \)'s may join together to form cycloalkyl or heterocycloalkyl, and the subscript \( n \) is 0, 1, 2, or 3; or a pharmaceutically acceptable salt, or solvate thereof; or stereoisomers, isotopic variants or tautomers thereof; provided that

i) when \( R^3 = S(0) - R^{3a} \), x is 2, \( L^1 = -C(=O)K \), \( R^1 \) is OH, \( R^{3a} \) is unsubstituted alkyl, \( L^2 = -O-, \) \( R^{2a} \) is H, and \( R^{2b} \) is unsubstituted benzyl; then n is other than 0; and

ii) when \( R^3 = S(0) - R^{3a} \), x is 2, \( L^1 = -C(S)O- \), \( R^1 \) is OH, \( R^{3a} \) is unsubstituted alkyl, \( L^2 = -O-, \) one of \( R^{2a} \) and \( R^{2b} \) is n-Bu, and the other is H, unsubstituted alkyl, unsubstituted aralkyl, or unsubstituted heteroarylalkyl; then n is other than 0;

iii) when \( L^1 = -CH_2 - \), \( R^1 \) is OH, \( R^3 \) is Br, \( L^2 \) is a single bond, and \( R^{2a} \) is Me; then \( R^{2b} \) is other than Me;

iv) when \( R^3 = S(0) - R^{3a} \), x is 2, \( L^1 = -C(=O)K \), \( R^1 \) is OH, \( R^{3a} \) is methoxymethyl, \( L^2 = -O-, \) one of \( R^{2a} \) and \( R^{2b} \) is n-Bu, and the other is H; then n is other than 0;

v) when \( R^3 = S(0) - R^{3a} \), x is 2, \( L^1 = -C(S)O- \), \( R^1 \) is OH, \( R^{3a} \) is Me, \( L^2 = -O-, \) the \( NR^{2a} \) group is unsubstituted pyrrolin-1-yl; then n is other than 0;

vi) when \( R^3 = S(0) - R^{3a} \), x is 2, \( L^1 \) is a single bond, \( R^1 \) is tetrazolyl, and \( L^2 = -O-; \) then n is other than 0;

vii) when \( L^1 \) is a single bond or alkylene, \( R^1 \) is Cl, \( R^{2a} \) is H or Me, and \( R^{2b} \) is Me; then \( R^3 \) is other than Cl;

viii) when \( L^1 \) is a single bond or substituted or unsubstituted alkylene, \( R^1 \) is H, and \( R^3 \) is Cl; then \( R^{2a} \) is other than H;

ix) when \( R^{2b} \) is substituted or unsubstituted acyl, \( L^1 = -C(=O)K \), and \( R^1 \) is OH; then \( R^3 \) is selected from the group consisting of halo, alkyl, substituted or unsubstituted haloalkyl, CN, and \( S(0) - R^{3a}; \) the subscript \( x \) is 0, 1, or 2; and \( R^{3a} \) is substituted or unsubstituted alkyl, substituted or...
unsubstituted cycloalkyl, ary] or heteroaryl; and
x) the compound is other than

2. A compound according to claim 1, wherein
Cy, L², R̃², R̃²b, R⁴, and n are as in claim 1;
L¹ is substituted or unsubstituted alkylene;
R¹ is selected from the group consisting of hydroxy, amino, substituted or unsubstituted amino,
substituted or unsubstituted N containing heterocycloalkyl, and substituted or unsubstituted alkoxy;
or L¹ is a single bond or substituted or unsubstituted alkylene, and R¹ is selected from the group
consisting of H, halo, CN, substituted or unsubstituted 5-12 membered heteroaryl, and substituted or
unsubstituted 4-8 membered heterocycloalkyl;
R³ is §(0)ₖ R₃⁰;
the subscript x is 0, 1, or 2;
R₃⁰ is substituted or unsubstituted amino, or substituted or unsubstituted N- containing
heterocycloalkyl, and wherein the N of the heterocycle is bonded to S via a single bond;
or a pharmaceutically acceptable salt, or solvate thereof; or stereoisomers, isotopic variants or
tautomers thereof;
provided that
i) when R³ is 8(0) R³, x is 2, L¹ is a single bond, R¹ is tetrazolyl, and L² is -0-; then n is other
than 0.
3. The compound of claim 1, wherein L¹ is -C(=0)-.
4. The compound of any one of claims 1-3, wherein L¹ is C₁⁻C₄ alkylene, unsubstituted or substituted
with halo.
5. The compound of any one of claims 1-3, wherein L¹ is -CH₂⁻, -C(Me)H⁻, or -CH⁻CH⁻.
6. The compound of any one of claims 1-3, wherein L¹ is a single bond or C₁⁻C₄ alkylene; and R¹ is
CN.
7. The compound of any one of claims 1-3, wherein L¹ is a single bond or C₁⁻C₄ alkylene; and R¹ is 5-
12 membered heteroaryl.
8. The compound of any one of claims 1-3, wherein L¹ is a single bond or C₁⁻C₄ alkylene; and R¹ is
substituted or unsubstituted pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl,
furanyl, triazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, tetrazolyl, pyridyl, pyrimidyl, or
quinolinyl.
9. The compound of any one of claims 1-3, wherein L is a single bond or C-C alkylene; and R is substituted or unsubstituted 4-8 membered heterocycloalkyl.

10. The compound of claim 9, wherein L' is a single bond or C-C alkylene; and R is substituted or unsubstituted piperidinyl, piperazinyl, or morpholiny.

11. The compound of any one of claims 1-10, wherein Cy is aryl.

12. The compound of any one of claims 1-10, wherein Cy is heteroaryl.

13. The compound of any one of claims 1-10, wherein Cy is phenyl.

14. The compound of any one of claims 1-10, wherein Cy is pyridyl.

15. The compound of any one of claims 1-14, wherein R is amino, or substituted amino.

16. The compound of any one of claims 1-14, wherein R is hydroxyl or substituted or unsubstituted alkoxy.

17. The compound of claim 1, wherein the compound is according to formula IIa, lib, Ile, or fid:

and wherein R, R, R, n, and L are as in claim 1; and R is independently H, or substituted or unsubstituted alkyl; R is substituted or unsubstituted acyl, or substituted or unsubstituted alkyl; or or may join together to form a 4-7 membered heterocycloalkyl ring; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

18. The compound of claim 1, wherein the compound is according to formula IIia, IIib, IIic, or IIId:

and wherein R, R, R, n, and L are as in claim 1; R is as in claim 1 or claim 2; and R is independently H, or substituted or unsubstituted alkyl; R is substituted or unsubstituted acyl, or
substituted or unsubstituted alkyl; or $R^{2a}$ and $R^{2b}$ may join together to form a 4-7 membered heterocycloalkyl ring; 
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

19. The compound of either of claim 17 or claim 18, wherein $R^{1a}$ is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.

20. The compound of any of claims 17-19, wherein $R^{1b}$ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu; or $R^{1c}$ and $R^{1b}$ are joined together to form piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, or azetidinyl.

21. The compound of claim 1, wherein the compound is according to formula IVa, IVb, IVc, or IVd:

and wherein $R^{2a}$, $R^{2b}$, $R^{1c}$, n, and $L^2$ are as in claim 1; and $R^3$ is as in claim 1 or claim 2; and $X$ is F, Cl, Br, or I;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;
provided that
i) when the compound is according to formula IVc, $X$ is Cl, $R^{2a}$ is H or Me, and $R^{2b}$ is Me; then $R^3$ is other than Cl; and
ii) when the compound is according to formula IVd, and $R^3$ is Cl; then $R^{2a}$ is other than H.

22. The compound of claim 1, wherein the compound is according to formula IVe, or IVf:

and wherein $R^{2a}$, $R^{2b}$, $R^{1c}$, n, and $L^2$ are as in claim 1; $R^3$ is as in claim 1 or claim 2; and $R^1$ is substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8
membered heterocycloalkyl;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

23. The compound of any one of claims 1-22, wherein R₃ is F, Cl, Br, or I.
24. The compound of any one of claims 1-22, wherein R₃ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.
25. The compound of any one of claims 1-22, wherein R₃ is CF₃.
26. The compound of any one of claims 1-22, wherein R₃ is CN.
27. The compound of any one of claims 1-22, wherein R₃ is S(0)ₓ-R₃⁰; x is 1 or 2; and R₃⁰ is as in claim 1.
28. The compound of any one of claims 1-22, wherein R₃ is S(0)ₓ-R₃⁰; x is 1 or 2; and R₃⁰ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.
29. The compound of any one of claims 1-22, wherein R₃ is SOMe, SOEt, SO-i-Pr, SO-n-Bu, SO₂Me, SO₂Et, SO₂-i-Pr, or SO₂-n-Bu.
30. The compound of any one of claims 1-22, wherein R₃ is S(0)ₓ-R₃⁰; x is 1 or 2; and R₃⁰ is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
31. The compound of any one of claims 1-22, wherein R₃ is SO-cyclopropyl, SO-cyclobutyl, SO-cyclopentyl, SO-cyclohexyl, SO₂-cyclopropyl, SO₂-cyclobutyl, SO₂-cyclopentyl, or SO₂-cyclohexyl.
32. The compound of any one of claims 1-22, wherein R₃ is S(0)ₓ-R₃⁰; x is 1 or 2; and R₃⁰ is substituted or unsubstituted amino.
33. The compound of any one of claims 1-22, wherein R₃ is S(0)ₓ-R₃⁰; x is 1 or 2; and R₃⁰ is NH₂, NMe₂, NEt₂, piperidinyl, morpholinyl, pyrrolidinyl, or piperazinyl.
34. The compound of claim 1, wherein the compound is according to formula Va, Vb, Vc, Vd, Ve, Vf, or Vg:
35. 

and wherein $R^{2a}, R^{3b}, R^4, n,$ and $L^3$ are as in claim 1; and $R^3$ is substituted or unsubstituted amino, or substituted or unsubstituted N-containing heterocycloalkyl, and wherein the N of the heterocycle is bonded to S via a single bond; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that 

i) when the compound is according to formula Vd or Ve, $L^2$ is -0-, $R^{2a}$ is H, and $R^{2b}$ is unsubstituted benzyl, then n is other than 0; and

ii) when the compound is according to formula Vd or Ve, $L^2$ is -0-, one of $R^{2a}$ and $R^{2b}$ is n-Bu, and the other is H, unsubstituted alkyl, unsubstituted aralkyl, or unsubstituted heteroarylalkyl; then n is other than 0;

iii) when the compound is according to formula Vg, then n is other than 0; and

iv) when the compound is according to formula Vg, then $R^{2b}$ is other than substituted or unsubstituted acyl.

36. The compound of claim 1, wherein the compound is according to formula Via, Vlb, Vic, Vld, Vie, Vlf, or Vlg:
and wherein \( R^{2a}, R^{2b}, R^4, n, \) and \( L^2 \) are as in claim 1; and \( R^1 \) is CN, substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;

provided that

i) when the compound is according to formula VIg, \( L^2 \) is -0-, \( R^1 \) is tetrazolyl, then \( n \) is other than 0.

37. The compound of any one of claims 1-36, wherein \( L^2 \) is a single bond.

38. The compound of any one of claims 1-36, wherein \( L^2 \) is -0-.

39. The compound of claim 1, wherein the compound is according to formula Vila, VIlb, VIIc, VIlld, Vile, or VIlf:
Vila, Vllb, Vile, Vlld, Vile, or Vllf

and wherein R\textsuperscript{2a}, R\textsuperscript{2b}, R\textsuperscript{4}, n, and \( \mathcal{L} \) are as in claim 1;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;
provided that
when the compound is according to formula Vila, R\textsuperscript{2a} is other than H.

40. The compound of claim 1, wherein the compound is according to formula Vila, Vllb, VIIc, Vlld, Vile, or VIIf:
and wherein \( R^2, R^{3b}, R^4, n, \) and \( L^2 \) are as in claim 1; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

41. The compound of claim 1, wherein the compound is according to formula \( \text{VEIa, VIIib, VIIIc, VIIIId, VIIIe, or VIIIIf:} \)

![Chemical structures]

and wherein \( R^{2a}, R^{2b}, R^4, \) and \( n \) are as in claim 1;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;
provided that

i) when the compound is according to formula Villa, \( R^{2a} \) is other than \( H \); and

ii) when the compound is according to formula \( \text{VIIIId or VIIIIf, one of } R^{2a} \) and \( R^{2b} \) is unsubstituted benzyl, or \( \text{n-Bu} \), and the other is \( H \), unsubstituted alkyl, unsubstituted aralkyl, or unsubstituted heteroaryalkyl; then \( n \) is other than 0.

42. The compound of claim 1, wherein the compound is according to formula \( \text{IXa, IXb, IXc, IXd, IXe, IXf, or IXg:} \)
and wherein $R^2$, $R^3$, $R^4$, $n$, and $L^2$ are as in claim 1; and $R^1$ is $CN$, substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

43. The compound of claim 1, wherein the compound is according to formula Xa, Xb, Xc, Xd, Xe, Xf, or Xg:
and wherein $R^{2a}$, $R^{2b}$, $R^4$, $n$, and $L^2$ are as described for formula I; and $R^1$ is F, Cl, Br, I, CN, substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof;
provided that
i) when the compound is according to formula Xg, $R^4$ is tetrazolyi; then $n$ is other than 0; and
ii) when the compound is according to formula Xb, $R^{2a}$ is H or Me, and $R^{2b}$ is Me; then $R^1$ is other than Cl.

44. The compound of any one of claims 36, 42, or 43, wherein $R^1$ is CN.
45. The compound of any one of claims 36, 42, or 43, wherein $R^1$ is pyrazolyl, imidazolyl, triazolyl, oxazolyl, oxadiazolyl, oxathiazolyl, pyridyl, tetrazolyl; provided that when the compound is according to formula VIII or Xg, and $R^1$ is tetrazolyl; then $n$ is other than 0.
46. The compound of any one of claims 36, 42, or 43, wherein $R^4$ is piperidinyl or morpholinyl.
47. The compound of any one of claims 1-46, wherein $R^{2a}$ is H, alkyl, or aralkyl.
48. The compound of any one of claims 1-46, wherein $R^{2a}$ is alkyl, unsubstituted or substituted with hydroxyl, substituted or unsubstituted amino, cyano, substituted or unsubstituted alkoxy, or halo.
49. The compound of any one of claims 1-46, wherein $R^{2a}$ is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, benzyl, or phenethyl.
50. The compound of any one of claims 1-46, wherein $R^{3a}$ is -CH$_2$-CF$_3$, -CH$_2$-CH$_2$-NM$_2$, -CH$_2$-CH$_2$-OH,
or -C¼-CH₂-CN.

51. The compound of any one of claims 1-46, wherein R² is H.

52. The compound of any one of claims 1-46, wherein R² is

\[ \text{and wherein } m \text{ is } 0, \ 1, \ 2, \ \text{or } 3; \ \text{and } R^2c \text{ is independently selected from the group consisting of halo, cyan, alkyl, haloalkyl, alkoxy, and haloalkoxy.} \]

53. The compound according to claim 52, wherein m is 1 or 2; and each R²c is independently selected from the group consisting of Cl, F, Br, OMe, Me, CN, i-Pr, CF₃, or OCF₃.

54. The compound of any one of claims 1-53, wherein R²b is acyl, alkyl, or aralkyl.

55. The compound of any one of claims 1-53, wherein R²b is alkyl, unsubstituted or substituted with hydroxyl, substituted or unsubstituted amino, cyan, substituted or unsubstituted alkoxy, or halo.

56. The compound of any one of claims 1-53, wherein R²b is acetyl, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, benzyl, or phenethyl.

57. The compound of any one of claims 1-53, wherein R²b is -CH₂-CF₃, -CH₂CH₂-NMe₂, -CH₂CH₂OH, -CH₂CH₂OMe, -CH₂CH₂CH₂OMe, or -CH₂-C¼-CN.

58. The compound of any one of claims 1-53, wherein R²b is

\[ \text{and wherein } m \text{ is } 0, \ 1, \ 2, \ \text{or } 3; \ \text{and } R^2c \text{ is independently selected from the group consisting of halo, cyan, alkyl, haloalkyl, alkoxy, and haloalkoxy.} \]

59. The compound of claim 56, wherein m is 1 or 2; and each R²c is independently selected from the group consisting of Cl, F, Br, OMe, Me, CN, i-Pr, CF₃, or OCF₃.

60. The compound of any one of claims 1-46, wherein R²b and R²b are joined together to form a 4-7 membered heterocyclic ring.

61. The compound of any one of claims 1-46, wherein the group -NR²a R²b is

\[ \text{and wherein } R^2d \text{ is H or alkyl.} \]

62. The compound of any one of claims 1-46, wherein each of R²a and R²b is n-Bu.
63. The compound of claim 1, wherein the compound is according to formula XIa, Xlb, XIc, Xld, Xle, or Xlf:

![Chemical structures](attachment:image.png)

and wherein R₄ and n are as in claim 1; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof; provided that when the compound is according to formula Xld or Xle, n is other than 0.

64. The compound of claim 1, wherein the compound is according to formula XIIa, XIIb, XIIc, XIIId, XIIe, XIIf, or XIIg:
and wherein $R^4$ and $n$ are as in claim 1; and $R^1$ is substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and
tautomers thereof;
provided that

i) when the compound is according to formula $X_{llg}$, and $R^1$ is tetrazolyl; then $n$ is other than 0.

65. The compound of claim 64, wherein $R^1$ is pyrazolyl, imidazolyl, triazolyl, oxazolyl, oxadiazolyl,
oxathiadiazolyl, pyridyl, tetrazolyl, piperidinyl or morpholinyl, unsubstituted or substituted with alkyl,
hydroxy, or oxo; provided that when the compound is according to formula $X_{llg}$ and $R^1$ is tetrazolyl;
then $n$ is other than 0.

66. The compound of claim 1, wherein the compound is according to formula $X_{llla}$, $X_{lllb}$, $X_{lllc}$, $X_{llld}$,
$X_{lle}$, $X_{llf}$, or $X_{llg}$:
The compound of any one of claims 1-66, wherein n is 0.

The compound of any one of claims 1-66, wherein n is 1, 2, or 3.

The compound of any one of claims 1-66, wherein n is 1 or 2; and \( R^4 \) is as in claim 1.

The compound of any one of claims 1-66, wherein n is 1 or 2; and \( R^4 \) is independently alkyl, alkoxy, haloalkyl, halo, CN, hydroxyl, alkylsulfonyl, arylsulfonyl, \( \text{SO}_3 \text{OH} \), amido, substituted amido, carboxyl, carbalkoxy, amino, or substituted amino.

The compound of any one of claims 1-70, wherein each \( R^4 \) is independently Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.

The compound of any one of claims 1-70, wherein each \( R^4 \) is independently F, Cl, Br, I, CN, or \( \text{CF}_3 \).

The compound of any one of claims 1-70, wherein each \( R^4 \) is independently OMe, OEt, OCF_3, or O-i-Pr.

The compound of any one of claims 1-70, wherein each \( R^4 \) is independently \( \text{SO}_2 \text{Me} \) or \( \text{SO}_2 \text{Et} \).

The compound of any one of claims 1-70, wherein each \( R^4 \) is independently is Cl, Me, or OMe.

The compound of claim 1, wherein the compound is according to formula XIVa, XIVb, XIVc, XIVd, or XIVe:
The compound of claim 1, wherein the compound is according to formula XVa, XVb, XVc, XVd, XVe, or XVf:

or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

77. The compound of claim 1, wherein the compound is according to formula XVa, XVb, XVc, XVd, XVe, or XVf:
and R¹ is substituted or unsubstituted 5-12 membered heteroaryl or substituted or unsubstituted 4-8 membered heterocycloalkyl;
or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof;
provided that
i) when the compound is according to formula XVf, and R¹ is tetrazolyl; then n is other than 0.

78. The compound of claim 77, wherein R¹ is pyrazolyl, imidazolyl, triazolyl, oxazolyl, oxadiazoyl, oxathiadiazolyl, pyridyl, tetrazolyl, piperidinyl or morpholinyl, unsubstituted or substituted with alkyl, hydroxy, or oxo; provided that when the compound is according to formula XVf, and R¹ is tetrazolyl; then n is other than 0.

79. The compound of claim 1, wherein the compound is according to formula XVIa, XVIb, XVIc, XVId, XVIe, or XVII:
or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

80. The compound of claim 1, wherein the compound is according to formula XVIa, XVIb, XVIc, XVIId, XVIe, XVIIe, XVIIIg, XVIIIh, or XVIIIi:
and wherein $R_3$, $R_4$, and $n$ are as in claim 1 or 2;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and
tautomers thereof;
provided that
81. The compound of claim 80, wherein R³ is F, Cl, Br, or I.
82. The compound of claim 80, wherein R³ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.
83. The compound of claim 80, wherein R³ is CF₃.
84. The compound of claim 80, wherein R³ is CN.
85. The compound of claim 80, wherein R³ is S(0)ₓ-R³ₓ; x is 1 or 2; and R³ₓ is as in claim 1.
86. The compound of claim 80, wherein R³ is S(0)ₓ-R³ₓ; x is 1 or 2; and R³ₓ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.
87. The compound of claim 80, wherein R³ is SOMe, SOEt, SO-i-Pr, SO-n-Bu, S0₂Me, S0₂El, S0₂-i-Pr, or S0₂-n-Bu.
88. The compound of claim 80, wherein R³ is S(0)ₓ-R³ₓ; x is 1 or 2; and R³ₓ is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
89. The compound of claim 80, wherein R³ is SO-cyclopropyl, SO-cyclobutyl, SO-cyclopentyl, SO-cyclohexyl, SO₂-cyclopropyl, SO₂-cyclobutyl, SO₂-cyclopentyl, or SO₂-cyclohexyl.
90. The compound of claim 80, wherein R³ is S(0)ₓ-R³ₓ; x is 1 or 2; and R³ₓ is substituted or unsubstituted amino.
91. The compound of claim 80, wherein R³ is S(0)ₓ-R³ₓ; x is 1 or 2; and R³ₓ is NH₂.
92. The compound of any one of claims 80-91, wherein n is 0.
93. The compound of any one of claims 80-91, wherein n is 1, 2, or 3.
94. The compound of any one of claims 80-91, wherein n is 1, 2; and R⁴ is as in claim 1.
95. The compound of any one of claims 80-91, wherein n is 1, 2; and R⁴ is independently alkyl, alkoxy, haloalkyl, halo, CN, hydroxy, alkylsulfonyl, arylsulfonyl, SO₂OH, amido, substituted amido, carboxy, carbalkoxy, amino, or substituted amino.
96. The compound of any one of claims 80-95, wherein each R⁴ is independently Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu.
97. The compound of any one of claims 80-95, wherein each R⁴ is independently Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CF₃.
98. The compound of any one of claims 80-95, wherein each R⁴ is independently OMe, OEt, OCF₃, or O-i-Pr.
99. The compound of any one of claims 80-95, wherein each R⁴ is independently SO₂Me, or SO₂Et.
100. The compound of any one of claims 80-95, wherein each R⁴ is independently Cl, Me, or OMe.
101. The compound of any one of claims 80-95, wherein each R⁴ is independently 4-Cl, 4-Me, 4-F, 4-CN, 4-CF₃, or 4-OMe.
102. A compound of the formula XVIII:

i) when the compound is according to formula XVIIa; then n is other than 0.
wherein:
each $R^3$ and $R^b$ is independently unsubstituted $C_1$-$C_4$ alkyl or unsubstituted benzyl;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and
tautomers thereof;
provided that when $R^3$ is Me, and $R^b$ is n-Bu at the same time; then the compound is in a form of a
sodium, potassium, calcium, ammonium or magnesium salt.

103. The compound of claim 102, wherein $R^3$ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, or t-Bu.
104. The compound of claim 102, wherein $R^3$ is Me.
105. The compound of claim 102, wherein the compound is according to formula XIX:

and wherein $R^b$ is as in claim 1;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and
tautomers thereof;
provided that when $R^b$ is n-Bu; then the compound is in a form of a sodium, potassium, calcium,
ammonium or magnesium salt.

106. The compound of any one of claims 102-105, wherein $R^b$ is Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu,
or benzyl.
107. The compound of claim 102, wherein the compound is according to formula XXa, XXb, XXc, or
XXd:
or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants thereof; provided that when the compound is according to formula Hid; then the compound is in a form of a sodium, potassium, calcium, ammonium or magnesium salt.

108. The compound of claim 102, wherein the compound is 3-(W-benzyl-4-butyI)amino-4-phenoxy-5-methylsulfonyl-benzoic acid.

109. The compound of claim 102, wherein the compound is a pharmaceutically acceptable salt of 3-(N-benzyl-W-butyI)amino-4-phenoxy-5-methylsulfonyl-benzoic acid.

110. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-8034.

111. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8034.

112. The compound of claim 1, wherein the compound is the sodium salt of NTP-8034.

113. The compound of claim 1, wherein the compound is the potassium salt of NTP-8034.

114. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-8055.

115. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8055.
116. The compound of claim 1, wherein the compound is the sodium salt of NTP-8055.
117. The compound of claim 1, wherein the compound is the potassium salt of NTP-8055.
118. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-8067.
119. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8153.
120. The compound of claim 1, wherein the compound is the sodium salt of NTP-8067.
121. The compound of claim 1, wherein the compound is the potassium salt of NTP-8067.
122. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-8069.
123. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8069.
124. The compound of claim 1, wherein the compound is the sodium salt of NTP-8069.
125. The compound of claim 1, wherein the compound is the potassium salt of NTP-8069.
126. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-8081.
127. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8081.
128. The compound of claim 1, wherein the compound is the sodium salt of NTP-8081.
129. The compound of claim 1, wherein the compound is the potassium salt of NTP-8081.
130. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-8097.
131. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8097.
132. The compound of claim 1, wherein the compound is the sodium salt of NTP-8097.
133. The compound of claim 1, wherein the compound is the potassium salt of NTP-8097.
134. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-8147.
135. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8147.
136. The compound of claim 1, wherein the compound is the sodium salt of NTP-8 147.
137. The compound of claim 1, wherein the compound is the potassium salt of NTP-8147.
138. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-8153.
139. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-8 153.
140. The compound of claim 1, wherein the compound is the sodium salt of NTP-8153.

141. The compound of claim 1, wherein the compound is the potassium salt of NTP-8153.

142. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-16031.

143. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-16031.

144. The compound of claim 1, wherein the compound is the sodium salt of NTP-16031.

145. The compound of claim 1, wherein the compound is the potassium salt of NTP-16031.

146. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-16033.

147. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-16033.

148. The compound of claim 1, wherein the compound is the sodium salt of NTP-16033.

149. The compound of claim 1, wherein the compound is the potassium salt of NTP-16033.

150. The compound of claim 1, wherein the compound is a pharmaceutically acceptable salt of NTP-16035.

151. The compound of claim 1, wherein the compound is the sodium, potassium, calcium, or magnesium salt of NTP-16035.

152. The compound of claim 1, wherein the compound is the sodium salt of NTP-16035.

153. The compound of claim 1, wherein the compound is the potassium salt of NTP-16035.

154. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof, according to any one of claims 102-153, and a pharmaceutically acceptable carrier.

155. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound selected from the group consisting of the sodium, potassium, calcium, or magnesium salt(s) of NTP-8034, NTP-8055, NTP-8067, NTP-8069, NTP-8081, NTP-8097, NTP-8147, NTP-8153, NTP-16031, NTP-16033, NTP-16035, or mixtures thereof.

156. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-8034.

157. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of NTP-8034.

158. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-8034.

159. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of NTP-8034.

160. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-8055.
161. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of NTP-8055.
162. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-8055.
163. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of NTP-8055.
164. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-8067.
165. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of NTP-8067.
166. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-8067.
167. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of NTP-8067.
168. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-8069.
169. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of NTP-8069.
170. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-8069.
171. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of NTP-8069.
172. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-8081.
173. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of NTP-8083.
174. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-8081.
175. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of NTP-8081.
176. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-8097.
177. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of NTP-8097.
178. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-8097.
379. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of
NTP-8097.
180. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-
8147.
181. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of
NTP-8147.
182. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-
8147.
183. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of
NTP-8153.
184. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-
8153.
185. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of
NTP-8153.
186. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-
8153.
187. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of
NTP-8153.
188. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-
16033.
189. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of
NTP-16033.
190. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-
16033.
191. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of
NTP-16033.
192. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-
16033.
193. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of
NTP-16033.
194. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-
16033.
195. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of
NTP-16033.
196. The pharmaceutical composition of claim 155, wherein the compound is the sodium salt of NTP-
16035.
197. The pharmaceutical composition of claim 155, wherein the compound is the potassium salt of NTP-16035.
198. The pharmaceutical composition of claim 155, wherein the compound is the calcium salt of NTP-16035.
199. The pharmaceutical composition of claim 155, wherein the compound is the magnesium salt of NTP-16035.
200. A compound selected from the group consisting of compounds listed in Table 1.
201. The compound of claim 1, wherein the compound is according to formula XXIa, XXIb, or XXIc:

\[
\begin{align*}
\text{XXIa} & \quad \text{XXIb} & \quad \text{XXIc}
\end{align*}
\]

and wherein each \( R^3 \) is independently \( \text{NH}_2, \text{NMe}_2, \text{NEt}_2, \text{Me}, \text{n-Pr}, \text{i-Pr}, \text{or} \text{n-Bu}; \) and each \( R^4 \) is independently alkyl, haloalkyl, halo, alkoxy, or haloalkoxy;
or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.
202. The compound of claim 201, wherein \( R^3 \) is Me.
203. The compound of claim 201, wherein \( R^3 \) is Et.
204. The compound of claim 201, wherein \( R^3 \) is \( \text{NH}_2 \).
205. The compound of claim 201, wherein \( R^3 \) is \( \text{NMe}_2 \).
206. The compound of claim 201, wherein \( R^3 \) is \( \text{NEt}_2 \).
207. The compound of any one of claims 201-206, wherein each \( R^4 \) is independently \( \text{Me}, \text{Cl}, \text{F}, \text{CF}_3, \) or \( \text{OCF}_3 \).
208. The compound of any one of claims 201-206, wherein each \( R^4 \) is independently \( \text{Cl}, \text{F}, \text{CF}_3, \) or \( \text{OCF}_3 \).
209. The compound of any one of claims 201-206, wherein each \( R^4 \) is F.
The compound of claim 1, wherein the compound is NTP-8034, NTP-8055, NTP-8067, NTP-8069, NTP-8081, NTP-8097, or NTP-8153.


The compound of claim 1, wherein the compound is NTP-15001, NTP-15002, NTP-15003, NTP-15004, NTP-15005, NTP-15006, NTP-15007, NTP-15008, NTP-15009, NTP-15010, NTP-15011, NTP-15012, NTP-15013, NTP-15014, NTP-15015, NTP-15016, NTP-15017, NTP-15018, NTP-15019, NTP-15020, NTP-35023 or NTP-15022.
The compound of claim 1, wherein the compound is according to formula XXIIa, or XXIIb:

and wherein each $R^3$ is independently $\text{NH}_2$, $\text{NMe}^n$, $\text{NEt}_2$, $\text{Me}$, $\text{Et}$, $\text{n-Pr}$, $\text{i-Pr}$, or $\text{n-Bu}$; and each $R^4$ is independently $\text{H}$, alkyl, haloalkyl, halo, alkoxy, or haloalkoxy; or a pharmaceutically acceptable salt, or solvate thereof; and stereoisomers, isotopic variants and tautomers thereof.

215. The compound of claim 214, wherein $R^3$ is Me.

216. The compound of claim 214, wherein $R^3$ is Et.

217. The compound of claim 214, wherein $R^3$ is $\text{NH}_2$, $\text{NMe}^n$, or $\text{NEt}_2$.

218. The compound of any one of claims 214-217, wherein $R^4$ is $\text{H}$, $\text{Cl}$, $\text{F}$, $\text{CF}_3$, or $\text{OCF}_3$.

219. The compound of any one of claims 214-217, wherein $R^4$ is $\text{H}$.

220. The compound of any one of claims 214-217, wherein each $R^4$ is independently $\text{Cl}$, $\text{F}$, $\text{CF}_3$, or $\text{OCF}_3$.

221. The compound of any one of claims 214-217, wherein each $R^4$ is $\text{F}$.


223. A compound according to formula:
or a pharmaceutically acceptable salt, or solvate thereof; and isotopic variants and tautomers thereof.

224. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-223, and a pharmaceutically acceptable carrier.

225. The pharmaceutical composition according to claim 223, wherein the carrier is a parenteral carrier.

226. The pharmaceutical composition according to claim 223, wherein the carrier is an oral carrier.

227. The pharmaceutical composition according to claim 223, wherein the carrier is a topical carrier.

228. A method for treating a disease or a condition in a mammal comprising administering to said mammal an effective amount of a compound or a pharmaceutical salt thereof of any one of claims 1-227.

229. The method of claim 228, wherein said condition is selected from the group consisting of addictive disorders, Alzheimer's Disease, anxiety disorders, ascites, autism, bipolar disorder, cancer, depression, endothelial corneal dystrophy, edema, epilepsy, glaucoma, Huntington's Disease, inflammatory pain, insomnia, ischemia, migraine, migraine with aura, migraine without aura, neuropathic pain, nociceptive neuralgia, nociceptive pain, ocular diseases, pain, itch, excessive itch, Pruritis, neuropathic pruritis, Parkinson's disease, personality disorders, postherpetic neuralgia, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.

230. A method for treating NKCC mediated disease or condition in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition according to any one of claims 1-227.

231. The method of claim 230, wherein said condition is selected from the group consisting of addictive disorders, Alzheimer's Disease, anxiety disorders, ascites, autism, bipolar disorder, cancer, depression, endothelial corneal dystrophy, edema, epilepsy, glaucoma, Huntington's Disease, inflammatory pain, insomnia, ischemia, migraine, migraine with aura, migraine without aura, neuropathic pain, nociceptive neuralgia, nociceptive pain, ocular diseases, pain, itch, excessive itch, Pruritis, neuropathic pruritis, Parkinson's disease, personality disorders, postherpetic neuralgia, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.

232. A method for treating GABA\textsubscript{A} receptor mediated disease or condition in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition according to any one of claims 1-227.

233. The method of claim 232, wherein said condition is selected from the group consisting of
addictive disorders, Alzheimer's Disease, anxiety disorders, ascites, autism, bipolar disorder, cancer, depression, endothelial corneal dystrophy, edema, epilepsy, glaucoma, Huntington's Disease, inflammatory pain, insomnia, ischemia, migraine, migraine with aura, migraine without aura, neuropathic pain, nociceptive neuralgia, nociceptive pain, ocular diseases, pain, Parkinson's disease, personality disorders, postherpetic neuralgia, psychosis, schizophrenia, seizure disorders, tinnitus, and withdrawal syndromes.

234. The method of claim any of claims 228-233, wherein the disease is epilepsy.

235. A method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound or a pharmaceutical composition according to any one of claims 1-227.

236. Use of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-227 in the manufacture of a medicament for the treatment of a disease or condition.

237. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any of claims 1-227 for the manufacture of a medicament for treating a condition involving GABA_A receptor.

238. A method to treat epilepsy in a mammal comprising the step of administering to said mammal a compound selected from the group consisting of the sodium, potassium, calcium, or magnesium salt(s) of NTP-8034, NTP-8055, NTP-8067, NTP-8069, NTP-8081, NTP-8097, NTP-8147, NTP-8153, NTP-16031, NTP-16033, NTP-16035, or mixtures thereof or a pharmaceutical composition comprising a pharmaceutically acceptable carrier and said compound.

239. The method of claim 238, wherein the compound is the sodium salt of NTP-8034.

240. The method of claim 238, wherein the compound is the potassium salt of NTP-8034.

241. The method of claim 238, wherein the compound is the calcium salt of NTP-8034.

242. The method of claim 238, wherein the compound is the magnesium salt of NTP-8034.

243. The method of claim 238, wherein the compound is the sodium salt of NTP-8055.

244. The method of claim 238, wherein the compound is the potassium salt of NTP-8055.

245. The method of claim 238, wherein the compound is the calcium salt of NTP-8055.

246. The method of claim 238, wherein the compound is the magnesium salt of NTP-8055.

247. The method of claim 238, wherein the compound is the sodium salt of NTP-8067.

248. The method of claim 238, wherein the compound is the potassium salt of NTP-8067.

249. The method of claim 238, wherein the compound is the calcium salt of NTP-8067.

250. The method of claim 238, wherein the compound is the magnesium salt of NTP-8067.

251. The method of claim 238, wherein the compound is the sodium salt of NTP-8069.

252. The method of claim 238, wherein the compound is the potassium salt of NTP-8069.

253. The method of claim 238, wherein the compound is the calcium salt of NTP-8069.

254. The method of claim 238, wherein the compound is the magnesium salt of NTP-8069.

255. The method of claim 238, wherein the compound is the sodium salt of NTP-8081.

256. The method of claim 238, wherein the compound is the potassium salt of NTP-8081.

245
257. The method of claim 238, wherein the compound is the calcium salt of NTP-8081.
258. The method of claim 238, wherein the compound is the magnesium salt of NTP-8081.
259. The method of claim 238, wherein the compound is the sodium salt of NTP-8097.
260. The method of claim 238, wherein the compound is the potassium salt of NTP-8097.
261. The method of claim 238, wherein the compound is the calcium salt of NTP-8097.
262. The method of claim 238, wherein the compound is the magnesium salt of NTP-8097.
263. The method of claim 238, wherein the compound is the sodium salt of NTP-8147.
264. The method of claim 238, wherein the compound is the potassium salt of NTP-8147.
265. The method of claim 238, wherein the compound is the calcium salt of NTP-8147.
266. The method of claim 238, wherein the compound is the magnesium salt of NTP-8147.
267. The method of claim 238, wherein the compound is the sodium salt of NTP-8153.
268. The method of claim 238, wherein the compound is the potassium salt of NTP-8153.
269. The method of claim 238, wherein the compound is the calcium salt of NTP-8153.
270. The method of claim 238, wherein the compound is the magnesium salt of NTP-16031.
271. The method of claim 238, wherein the compound is the sodium salt of NTP-16031.
272. The method of claim 238, wherein the compound is the potassium salt of NTP-16031.
273. The method of claim 238, wherein the compound is the calcium salt of NTP-16031.
274. The method of claim 238, wherein the compound is the magnesium salt of NTP-16031.
275. The method of claim 238, wherein the compound is the sodium salt of NTP-16031.
276. The method of claim 238, wherein the compound is the potassium salt of NTP-16031.
277. The method of claim 238, wherein the compound is the calcium salt of NTP-16031.
278. The method of claim 238, wherein the compound is the magnesium salt of NTP-16031.
279. The method of claim 238, wherein the compound is the sodium salt of NTP-16031.
280. The method of claim 238, wherein the compound is the potassium salt of NTP-16031.
281. The method of claim 238, wherein the compound is the calcium salt of NTP-16031.
282. The method of claim 238, wherein the compound is the magnesium salt of NTP-16031.
283. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an epilepsy-
treating amount of a compound according to formula XXIIIa, or XXIIIb:
284. The pharmaceutical composition of claim 283, wherein the epilepsy-treating amount is about 0.5 mg/kg body weight/day to about 100 mg/kg body weight/day.

285. The pharmaceutical composition of claim 283, wherein the epilepsy-treating amount is about 1 mg/kg body weight/day to about 50 mg/kg body weight/day.

286. The pharmaceutical composition of claim 283, wherein the epilepsy-treating amount is about 1 mg/kg body weight/day to about 10 mg/kg body weight/day.

287. A unit dosage form of the pharmaceutical composition of claim 283 comprising about 1 to 2000 mg of the compound according to formula XXIIIa or XXIIIb.

288. A unit dosage form of the pharmaceutical composition of claim 283 comprising about 1 to 1700 mg of the compound according to formula XXIIIa or XXIIIb.

289. A unit dosage form of the pharmaceutical composition of claim 283 comprising about 1 to 1000 mg of the compound according to formula XXIIIa or XXIIIb.

290. A unit dosage form of the pharmaceutical composition of claim 283 comprising about 1 to 750 mg of the compound according to formula XXIIIa or XXIIIb.

291. A unit dosage form of the pharmaceutical composition of claim 283 comprising about 250 to 750 mg of the compound according to formula XXIIIa or XXIIIb.

292. A unit dosage form of the pharmaceutical composition of claim 283 comprising about 500 to 750 mg of the compound according to formula XXIIIa or XXIIIb.

293. A compound, or a pharmaceutically acceptable salt thereof, according to any of claims 1-227 for use as a medicament.

294. A composition for the treatment of a condition involving at least one GABA \(_A\) receptor comprising an effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to any of claims 1-227.

295. Use of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-227 in a manufacture of a medicament for the treatment of a disease or condition.

296. A method for treating a disease or condition comprising administering an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-227.
297. A composition for the treatment of a disease or condition comprising an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-227.

298. The use, method, or composition of any one of claims 295-297, wherein said disease or condition is selected from the group consisting of Alzheimer's Disease (AD), addictive disorders, optionally compulsive disorders, eating disorders, optionally obesity, anorexia nervosa, bulimia, addiction to narcotics/physical dependence, alcohol addiction, narcotic addiction, cocaine addiction, heroin addiction, opiate addiction, alcoholism, and smoking; anxiety disorders, optionally anxiety, acute anxiety, panic disorder, social anxiety disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), generalized anxiety disorder, and specific phobia; autism, optionally Autism spectrum disorder (ASD); bipolar disorder, optionally manic-depressive illness, manic phase, depressive phase, mixed bipolar state, bipolar I disorder, bipolar II disorder, rapid-cycling bipolar disorder, bipolar I disorder, bipolar II disorder; depression, optionally psychotic depression, postpartum depression, seasonal affective disorder (SAD), cortical spreading depression, dysthymia (mild depression); epilepsy, optionally seizures, epileptic seizures, a seizure cluster, an acute seizure, optionally status epilepticus, seizure disorder, and other neurological disorders involving seizures, optionally cerebral palsy, Ohtahara Syndrome; Huntington's Disease (HD); insomnia, itch, excessive itch, Pruritis, neuropathic pruritis, migraine, optionally migraine including headache, migraine variant, migraine headache, cervical migraine syndrome, acute confusional migraine, migraine with aura, migraine without aura, chronic migraine, transformed migraine; neuropathic pain, optionally diabetic neuropathy, cluster headache, nerve injury, nerve tract injury, neuropathic pain associated with visceral and/or somatic pain, peripheral neuropathy, chemotherapy-induced neuropathy, chemotherapy-induced peripheral neuropathy, HIV-treatment induced neuropathy, HIV-treatment induced neuralgia, neuralgia, polyneuropathy, mononeuropathy, mononeuritis multiplex, autonomic neuropathy, symmetrical peripheral neuropathy, radiculopathy, large Fiber peripheral neuropathy, small fiber peripheral neuropathy, idiopathic neuropathic pain; nociceptive pain; pain, optionally acute pain, acute inflammatory pain, chronic inflammatory pain, pain associated with arthritis, fibromyalgia, back pain, cancer-associated pain, chemotherapy-induced neuropathy, chemotherapy-induced peripheral neuropathy, pain associated with digestive disease, pain associated with Crohn's disease, pain associated with autoimmune disease, pain associated with endocrine disease, pain associated with diabetic neuropathy, pain associated with shingles or herpes zoster, phantom limb pain, spontaneous pain, chronic post-surgical pain, chronic temporomandibular pain, causalgia, postherpetic neuralgia, AIDS-related pain, complex regional pain syndromes type I and II, trigeminal neuralgia, chronic back pain, pain associated with spinal cord injury, incisional post operative, trauma associated, burns, recurrent acute pain, head pain, headache, nonmigrainous, specific non-migraine head pains, tic doloureux, postherpetic neuralgia, ice pick headache; Parkinson's disease, personality disorders, psychosis, seizure disorders, personality disorders, schizophrenia, tinnitus, and withdrawal
syndromes, optionally alcohol withdrawal syndrome, nicotine withdrawal syndrome, opioid withdrawal syndrome, benzodiazepine withdrawal syndrome, methadone withdrawal syndrome, SSRI discontinuation syndrome, hydrocodone withdrawal syndrome, cocaine withdrawal syndrome, or heroin withdrawal syndrome.
Data presented as number of crossings +/ SEM.

-- Figure 6 --

Number of Crossings (0-30)
### INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/US 12/61100

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC(8) -** A01N 35/00 (201 2.01)

**USPC -** 514/677

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/677

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

Electronic Database Searched: PUBWEST (PGPB,USPT,USOC,EPAB,JPAB).

Search Terms Used 2,3,5 trisubstituted aryl, heteroaryl amino, sulfonamide, amino

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

**Date of the actual completion of the international search**

8 December 2012 (8.12.2012)

**Date of mailing of the international search report**

8 JAN 2013

**Name and mailing address of the ISA/US**

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Form PCT/ISA/210 (second sheet) (July 2009)
**INTERNATIONAL SEARCH REPORT**

**Box No. II**  Observations where certain claims were found unsearchable (Cont. of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 11-16, 20, 23-33, 37-38, 47-62, 67-75, 96-101, 224, 228-237, 293-298 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III**  Observations where unity of invention is lacking (Cont. of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☒ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)