Title: PYRIDINES USEFUL AS MODULATORS OF ION CHANNELS

Abstract: The present invention relates to compounds of formulae I-A to I-D useful as inhibitors of voltage-gated sodium channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.
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PYRIDINES USEFUL AS MODULATORS OF ION CHANNELS

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compounds useful as inhibitors of ion channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION


Voltage gated Na channels comprise a gene family consisting of 9 different subtypes (Nav1.1-Nav1.9). As shown in Table 1, these subtypes show tissue specific localization and functional differences (See, Goldin, A. L. (2001) “Resurgence of sodium channel research” Annu Rev Physiol 63: 871-94). Three members of the gene family (Nav1.8, 1.9, 1.5) are resistant to block by the well-known Na channel blocker TTX, demonstrating subtype specificity within this gene family. Mutational analysis has identified glutamate 387 as a critical residue for TTX binding (See, Noda, M., H. Suzuki, et al. (1989) “A single point mutation confers tetrodotoxin and saxitoxin insensitivity on the sodium channel II” FEBS Lett 259(1): 213-6).

<table>
<thead>
<tr>
<th>Na isoform</th>
<th>Tissue</th>
<th>TTX IC50</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nav1.1</td>
<td>CNS, PNS soma of neurons</td>
<td>10nM</td>
<td>Pain, Epilepsy, neurodegeneration</td>
</tr>
<tr>
<td>Nav1.2</td>
<td>CNS, high in axons</td>
<td>10nM</td>
<td>Neurodegeneration</td>
</tr>
<tr>
<td>Nav1.3</td>
<td>CNS, embryonic, injured nerves</td>
<td>15nM</td>
<td>Pain</td>
</tr>
<tr>
<td>Nav1.4</td>
<td>Skeletal muscle</td>
<td>25nM</td>
<td>Myotonia</td>
</tr>
</tbody>
</table>

Table 1 (Abbreviations: CNS = central nervous system, PNS = peripheral nervous system, DRG = dorsal root ganglion, TG = Trigeminal ganglion):
<table>
<thead>
<tr>
<th>NaV1.5</th>
<th>Heart</th>
<th>2μM</th>
<th>Arrhythmia, long QT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaV1.6</td>
<td>CNS widespread, most abundant</td>
<td>6nM</td>
<td>Pain, movement disorders</td>
</tr>
<tr>
<td>NaV1.7</td>
<td>PNS, DRG, terminals neuroendocrine</td>
<td>25nM</td>
<td>Pain, Neuroendocrine disorders</td>
</tr>
<tr>
<td>NaV1.8</td>
<td>PNS, small neurons in DRG &amp; TG</td>
<td>&gt;50μM</td>
<td>Pain</td>
</tr>
<tr>
<td>NaV1.9</td>
<td>PNS, small neurons in DRG &amp; TG</td>
<td>1μM</td>
<td>Pain</td>
</tr>
</tbody>
</table>


[0006] Hyperalgesia (extreme sensitivity to something painful) that develops in the presence of tissue injury or inflammation reflects, at least in part, an increase in the excitability of high-threshold primary afferent neurons innervating the site of injury. Voltage sensitive sodium channels activation is critical for the generation and propagation of neuronal action potentials. There is a growing body of evidence indicating that modulation of NaV...
currents is an endogenous mechanism used to control neuronal excitability (See, Goldin, A. L. (2001) "Resurgence of sodium channel research" Ann Rev Physiol 63: 871-94.). Several kinetically and pharmacologically distinct voltage-gated sodium channels are found in dorsal root ganglion (DRG) neurons. The TTX-resistant current is insensitive to micromolar concentrations of tetrodotoxin, and displays slow activation and inactivation kinetics and a more depolarized activation threshold when compared to other voltage-gated sodium channels. TTX-resistant sodium currents are primarily restricted to a subpopulation of sensory neurons likely to be involved in nociception. Specifically, TTX-resistant sodium currents are expressed almost exclusively in neurons that have a small cell-body diameter; and give rise to small-diameter slow-conducting axons and that are responsive to capsaicin. A large body of experimental evidence demonstrates that TTX-resistant sodium channels are expressed on C-fibers and are important in the transmission of nociceptive information to the spinal cord.

[0007] Intrathecal administration of antisense oligo-deoxynucleotides targeting a unique region of the TTX-resistant sodium channel (NaV1.8) resulted in a significant reduction in PGE2-induced hyperalgesia (See, Khasar, S. G., M. S. Gold, et al. (1998) "A tetrodotoxin-resistant sodium current mediates inflammatory pain in the rat" Neurosci Lett 256(1): 17-20). More recently, a knockout mouse line was generated by Wood and colleagues, which lacks functional NaV1.8. The mutation has an analgesic effect in tests assessing the animal’s response to the inflammatory agent carrageenan (See, Akopian, A. N., V. Souslova, et al. (1999) "The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways" Nat Neurosci 2(6): 541-8.). In addition, deficit in both mechanon- and thermoreception were observed in these animals. The analgesia shown by the Nav1.8 knockout mutants is consistent with observations about the role of TTX-resistant currents in nociception.

[0008] Immunohistochemical, in-situ hybridization and in-vitro electrophysiology experiments have all shown that the sodium channel NaV1.8 is selectively localized to the small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Akopian, A. N., L. Sivilotti, et al. (1996) "A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons" Nature 379(6562): 257-62.). The primary role of these neurons is the detection and transmission of nociceptive stimuli. Antisense and
immunohistochemical evidence also supports a role for NaV1.8 in neuropathic pain (See, Lai, J., M. S. Gold, et al. (2002) "Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, NaV1.8" *Pain* 95(1-2): 143-52, and Lai, J., J. C. Hunter, et al. (2000) "Blockade of neuropathic pain by antisense targeting of tetrodotoxin-resistant sodium channels in sensory neurons" *Methods Enzymol* 314: 201-13.). NaV1.8 protein is upregulated along uninjured C-fibers adjacent to the nerve injury. Antisense treatment prevents the redistribution of NaV1.8 along the nerve and reverses neuropathic pain. Taken together the gene-knockout and antisense data support a role for NaV1.8 in the detection and transmission of inflammatory and neuropathic pain.

[0009] In neuropathic pain states there is a remodeling of Na channel distribution and subtype. In the injured nerve, expression of NaV1.8 and NaV1.9 are greatly reduced whereas expression of the TTX sensitive subunit NaV1.3 is 5-10 fold upregulated (See, Dib-Hajj, S. D., J. Fjell, et al. (1999) "Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain." *Pain* 83(3): 591-600.) The timecourse of the increase in NaV1.3 parallels the appearance of allodynia in animal models subsequent to nerve injury. The biophysics of the NaV1.3 channel is distinctive in that it shows very fast repriming after inactivation following an action potential. This allows for sustained rates of high firing as is often seen in the injured nerve (See, Cummins, T. R., F. Aglieco, et al. (2001) "Nav1.3 sodium channels: rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons" *J Neurosci* 21(16): 5952-61.). NaV1.3 is expressed in the central and peripheral systems of man. NaV1.9 is similar to NaV1.8 as it is selectively localized to small sensory neurons of the dorsal root ganglion and trigeminal ganglion (See, Fang, X., L. Djouhri, et al. (2002). "The presence and role of the tetrodotoxin-resistant sodium channel Na(v)1.9 (NaN) in nociceptive primary afferent neurons." *J Neurosci* 22(17): 7425-33.). It has a slow rate of inactivation and left-shifted voltage dependence for activation (See, Dib-Hajj, S., J. A. Black, et al. (2002) "NaN/Nav1.9: a sodium channel with unique properties" *Trends Neurosci* 25(5): 253-9.). These two biophysical properties allow NaV1.9 to play a role in establishing the resting membrane potential of nociceptive neurons. The resting membrane potential of NaV1.9 expressing cells is in the −55 to −50mV range compared to −65mV for most other peripheral and central neurons. This persistent depolarization is in
large part due to the sustained low-level activation of NaV1.9 channels. This depolarization allows the neurons to more easily reach the threshold for firing action potentials in response to nociceptive stimuli. Compounds that block the NaV1.9 channel may play an important role in establishing the set point for detection of painful stimuli. In chronic pain states, nerve and nerve ending can become swollen and hypersensitive exhibiting high frequency action potential firing with mild or even no stimulation. These pathologic nerve swellings are termed neuromas and the primary Na channels expressed in them are NaV1.8 and NaV1.7 (see, Kretschmer, T., L. T. Happel, et al. (2002) “Accumulation of PN1 and PN3 sodium channels in painful human neuroma- evidence from immunocytochemistry” Acta Neurochir (Wien) 144(8): 803-10; discussion 810.). NaV1.6 and NaV1.7 are also expressed in dorsal root ganglion neurons and contribute to the small TTX sensitive component seen in these cells. NaV1.7 in particular my therefore be a potential pain target in addition to it’s role in neuroendocrine excitability (see, Klugbauer, N., L. Lacinova, et al. (1995) “Structure and functional expression of a new member of the tetrodotoxin- sensitive voltage-activated sodium channel family from human neuroendocrine cells” Embo J 14(6): 1084-90).


[00011] Antagonists for NaV1.5 have been developed and used to treat cardiac arrhythmias. A gene defect in NaV1.5 that produces a larger noninactivating component to the current has been linked to long QT in man and the orally available local anesthetic mexiletine has been used to treat this condition (see, Wang, D. W., K. Yazawa, et al. (1997) “Pharmacological targeting of long QT mutant sodium channels.” J Clin Invest 99(7): 1714-20).

bladder syndrome (see, Yoshimura, N., et al., J Neurosci. 2001; 21(21):8690-6); interstitial
cystitis (IC) (see, Giannakopoulos & Campilomatos, Arch Ital Urol Nefrol Androl. 1992;
64(4):337-9; Boucher, M., et al., J Urol. 2000; 164(1):203-8); and prostatitis (see, Mayersak,

Calcium channels are membrane-spanning, multi-subunit proteins that allow
Ca entry from the external milieu and concurrent depolarization of the cell's membrane
potential. Traditionally calcium channels have been classified based on their functional
characteristics such as low voltage or high voltage activated and their kinetics (L,T,N,P,Q).
The ability to clone and express the calcium channel subunits has lead to an increased
understanding of the channel composition that produces these functional responses. There
are three primary subunit types that make up calcium channels - α1, α2δ, and β. The α1 is
the subunit containing the channel pore and voltage sensor, α2 is primarily extracellular and
is disulfide linked to the transmembrane δ subunit, β is nonglycosylated subunit found bound
to the cytoplasmic region of the α1 subunit of the Ca channel. Currently the various calcium
channel subtypes are believed to made up of the following specific subunits:

- L-type, comprising subunits α4C, α4D, α4F, or α4S, α2δ and β3α
- N-Type, comprising subunits α4B, α2δ, β4b
- P-Type, comprising subunits α4A, α2δ, β4a
- Q-Type, comprising subunits α4A (splice variant) α2δ, β4a
- R-Type, comprising subunits α4E, α2δ, β4b
- T-Type, comprising subunits α4C, α4D, or α4

Calcium channels play a central role in neurotransmitter release. Ca influx
into the presynaptic terminal of a nerve process binds to and produces a cascade of protein-
protein interactions (syntaxin 1A, SNAP-25 and synaptotagmin) that ultimately ends with the
fusion of a synaptic vesical and release of the neurotransmitter packet. Blockade of the
presynaptic calcium channels reduces the influx of Ca and produces a cubic $X^3$ decrease in
neurotransmitter release.

The N type Ca channel (CaV2.2) is highly expressed at the presynaptic nerve
terminals of the dorsal root ganglion as it forms a synapse with the dorsal horn neurons in
lamina I and II. These neurons in turn have large numbers of N type Ca channels at their presynaptic terminals as they synapse onto second and third order neurons. This pathway is very important in relaying pain information to the brain.

Pain can be roughly divided into three different types: acute, inflammatory, and neuropathic. Acute pain serves an important protective function in keeping the organism safe from stimuli that may produce tissue damage. Severe thermal, mechanical, or chemical inputs have the potential to cause severe damage to the organism if unheeded. Acute pain serves to quickly remove the individual from the damaging environment. Acute pain by its very nature generally is short lasting and intense. Inflammatory pain on the other hand may last for much longer periods of time and its intensity is more graded. Inflammation may occur for many reasons including tissue damage, autoimmune response, and pathogen invasion. Inflammatory pain is mediated by an “inflammatory soup” that consists of substance P, histamines, acid, prostaglandin, bradykinin, CGRP, cytokines, ATP, and neurotransmitter release. The third class of pain is neuropathic and involves nerve damage that results in reorganization of neuronal proteins and circuits yielding a pathologic “sensitized” state that can produce chronic pain lasting for years. This type of pain provides no adaptive benefit and is particularly difficult to treat with existing therapies.

Pain, particularly neuropathic and intractable pain is a large unmet medical need. Millions of individuals suffer from severe pain that is not well controlled by current therapeutics. The current drugs used to treat pain include NSAIDS, COX2 inhibitors, opioids, tricyclic antidepressants, and anticonvulsants. Neuropathic pain has been particularly difficult to treat, as it does not respond well to opioids until high doses are reached. Gabapentin is currently the favored therapeutic for the treatment of neuropathic pain although it works in only 60% of patients where it shows modest efficacy. The drug is however very safe and side effects are generally tolerable although sedation is an issue at higher doses.

The N type Ca channel has been validated in man by intrathecal infusion of the toxin Ziconotide for the treatment of intractable pain, cancer pain, opioid resistant pain, and neuropathic and severe pain. The toxin has an 85% success rate for the treatment of pain in humans with a greater potency than morphine. An orally available N type Ca channel antagonist would garner a much larger share of the pain market. Ziconotide causes mast cell
degranulation and produces dose-dependent central side effects. These include dizziness, nystagmus, agitation, and dysmetria. There is also orthostatic hypotension in some patients at high doses. The primary risk for this target involves the CNS side effects seen with Ziconotide at high dosing. These include dizziness, nystagmus, agitation, and dysmetria. There is also orthostatic hypotension in some patients at high doses. It is believed that this may be due to Ziconotide induced mast cell degranulation and/or its effects on the sympathetic ganglion that like the dorsal root ganglion also expresses the N type Ca channel. Use-dependent compounds that block preferentially in the higher frequency range >10Hz should be helpful in minimizing these potential side-effect issues. The firing rate in man of the sympathetic efferents is in the 0.3 Hz range. CNS neurons can fire at high frequencies but generally only do so in short bursts of action potentials. Even with the selectivity imparted by use-dependence intrinsic selectivity against the L type calcium channel is still necessary as it is involved in cardiac and vascular smooth muscle contraction.

[00020] Unfortunately, as described above, the efficacy of currently used sodium channel blockers and calcium channel blockers for the disease states described above has been to a large extent limited by a number of side effects. These side effects include various CNS disturbances such as blurred vision, dizziness, nausea, and sedation as well more potentially life threatening cardiac arrhythmias and cardiac failure. Accordingly, there remains a need to develop additional Na channel and Ca channel antagonists, preferably those with higher potency and fewer side effects. Unfortunately, as described above, the efficacy of currently used sodium channel blockers and calcium channel blockers for the disease states described above has been to a large extent limited by a number of side effects. These side effects include various CNS disturbances such as blurred vision, dizziness, nausea, and sedation as well more potentially life threatening cardiac arrhythmias and cardiac failure. Accordingly, there remains a need to develop additional Na channel and Ca channel antagonists, preferably those with higher potency and fewer side effects.

**SUMMARY OF THE INVENTION**

[00021] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are useful as inhibitors of voltage-gated sodium channels
and calcium channels. These are compounds of formula IA, formula IB, formula IC, and formula ID:

![Chemical structures](image)

or a pharmaceutically acceptable salt thereof.

[00022] These compounds and pharmaceutically acceptable compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain.

**DETAILED DESCRIPTION OF THE INVENTION**

[00023] *I. General Description of Compounds of the Invention:*
In one embodiment, the present invention provides compounds of formula IA, formula IB, formula IC, and formula ID:

or a pharmaceutically acceptable salt thereof,

wherein:

W is OR', SR', NR'2, CHF2, or CH2F;

R1 and R2, taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8-membered monocyclic, saturated or partially unsaturated ring having 0-3 additional heteroatoms independently selected from nitrogen, sulfur, or oxygen; wherein the ring formed by R1 and R2 taken together, are each optionally and independently substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with z independent occurrences of -R4, wherein z is 0-5;

y is 0-5;

R3a is hydrogen or XR0, wherein X is a C1-C6 alkylidene chain wherein up to two non-adjacent methylene units of X other than the carbon atom directly attached to the pyridinyl ring are optionally and independently replaced by -NR-, -S-, -O-, -CS-, -CO2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO2-, -SO2NR-, -NRSO2-, -CONRNR-, -NRCO-, -OCONR-, -NRNR-, -NRSO2NR-, -SO-, -SO2-, -PO-, -PO2-, -OP(O)(OR)-, or -POR-;

R0 is independently selected from -R', =O, =NR', halogen, -NO2, -CN, -OR', -SR', -N(R')2, -NR'COR', -NR'CON(R')2, -NR'CO2R', -COR', -CO2R', -OCOR', -CON(R')2, -
OCON(R')_2, -SOR', -SO_2R', -SO_2N(R')_2, -NR'SO_2R', -NR'SO_2N(R')_2, -COCOR', -COCH_2COR', -OP(O)(OR')_2, -P(O)(OR')_2, -OP(O)OR', -PO(R')_2, or -OPO(R')_2;

each occurrence of \( R^{3b}, R^{3c}, R^4, \) and \( R^5 \) is independently \( Q-R^X \); wherein Q is a bond or is a C_1-C_6 alkyldiene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by -NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO_2-, -SO_2NR-, -NRSO_2-, -CONNR-, -NRCONR-, -OCNR-, -NRRNR-, -NRSO_2NR-, -SO-, -SO_2-, -PO-, -PO_2-, -OP(O)(OR)-, or -POR-; and each occurrence of \( R^X \) is independently selected from -R', halogen, -NO_2, -CN, -OR', -SR', -N(R')_2, -NR'COR', -NR'CON(R')_2, -NR'CO_2R', -COR', -CO_2R', -OCOR', -CON(R')_2, -OCOCON(R')_2, -SO_2R', -SO_2N(R')_2, -NR'SO_2R', -NR'SO_2N(R')_2, -COCOR', -COCH_2COR', -OP(O)(OR')_2, -P(O)(OR')_2, -P(O)OR', -PO(R')_2, or -OPO(R')_2;

each occurrence of \( R \) is independently hydrogen or an optionally substituted C_1-C_6 aliphatic group;

each occurrence of \( R' \) is independently hydrogen or an optionally substituted C_1-C_6 aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12

membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or \( R' \) and R, two occurrences of \( R \), or two occurrences of \( R' \), are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

i) in formula \( I-D \), when \( R^{3a}, R^{3b}, \) and \( R^{3c} \) are hydrogen, and \( R^1 \) and \( R^2 \), together with the nitrogen atom form a 4-morpholinyl ring, then \( W \) is not SR' wherein R' is methyl or 1H-benzimidazol-2-yl;

ii) in formula \( I-A \), when \( R^{3a}, R^{3b}, \) and \( R^{3c} \) are hydrogen, and \( R^1 \) and \( R^2 \), together with the nitrogen atom form a 4-morpholinyl ring, then \( W \), together with \( R^5 \) and the phenyl ring, is not:
iii) in formula I-B, when \( y = 0 \), \( R_3a \) and \( R_3b \) are both hydrogen, \( R_1 \) and \( R_2 \) taken together form 4-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl, then \( R^{2c} \) is not \(-\text{NRCO-R}^X \) or \(-\text{NRCOR}^Y \).

2. **Compounds and Definitions:**

Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March’s Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase “optionally substituted” is used interchangeably with the phrase “substituted or unsubstituted.” In general, the term “substituted”, whether preceded by the term “optionally” or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some
embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[00028] The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “carbocycle” “cycloaliphatic” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. In some embodiments, “cycloaliphatic” (or “carbocycle” or “cycloalkyl”) refers to a monocyclic or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[00029] The term “heteroaliphatic”, as used herein, means aliphatic groups wherein one or two carbon atoms are independently replaced by one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon. Heteroaliphatic groups may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and include “heterocycle”, “heterocyclyl”, “heterocycloaliphatic”, or “heterocyclic” groups.

[00030] The term “heterocycle”, “heterocyclyl”, “heterocycloaliphatic”, or “heterocyclic” as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members are an independently selected heteroatom. In some embodiments, the “heterocycle”, “heterocyclyl”, “heterocycloaliphatic”, or “heterocyclic” group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[00031] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a
heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR+ (as in N-substituted pyrrolidinyl)).

[00032] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[00033] The term “alkoxy”, or “thioalkyl”, as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen (“alkoxy”) or sulfur (“thioalkyl”) atom.

[00034] The terms “haloalkyl”, “haloalkenyl” and “haloalkoxy” means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term “halogen” means F, Cl, Br, or I.

[00035] The term “aryl” used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring”. The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

[00036] The term “heteroaryl”, used alone or as part of a larger moiety as in “heteroaralkyl” or “heteroaryloxyalkyl”, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term “heteroaryl” may be used interchangeably with the term “heteroaryl ring” or the term “heteroaromatic”.

[00037] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroaryloxyalkyl and the like) group may contain one or more substituents and thus may be “optionally substituted”. Unless otherwise specified herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are generally selected from halogen; -R; -OR; -SR; phenyl (Ph) optionally substituted with R; -O(Ph) optionally substituted with R; -(CH₂)₁₋₃(Ph), optionally substituted with R; -CH=CH(Ph), optionally substituted with R; -NO₂; -CN; -N(R)₂; -NR²C(O)R⁰; -NR²C(S)R⁰; -NR²C(O)N(R)₂; -NR²C(S)N(R)₂; -NR²CO₂R⁰; -NR²NR²C(O)R⁰; -NR²NR²C(O)N(R)₂; -NR²NR²CO₂R⁰; -C(O)C(O)R⁰; -C(O)CH₂C(O)R⁰; -CO₂R; -
C(O)R^o; -C(S)R^o; -C(O)N(R^o)2; -C(S)N(R^o)2; -OC(O)N(R^o)2; -OC(O)R^o; -C(O)N(OR^o) R^o; -C(NOR^o) R^o; -S(O)2R^o; -S(O)R^o; -SO2N(R^o)2; -S(O)R^o; -NR^oSO2R^o; -NR^oSO2R^o; -N(OR^o)R^o; -C(=NH)-N(R^o)2; -P(O)2R^o; -PO(R^o)2; -OPO(R^o)2; -(CH2)2NHC(O)R^o; phenyl (Ph) optionally substituted with R^o; -O(Ph) optionally substituted with R^o; -(CH2)1-2(Ph), optionally substituted with R^o; or -CH=CH(Ph), optionally substituted with R^o; wherein each independent occurrence of R^o is selected from hydrogen, optionally substituted C1-6 aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or -CH2(Ph), or, notwithstanding the definition above, two independent occurrences of R^o, on the same substituent or different substituents, taken together with the atom(s) to which each R^o group is bound, to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Unless otherwise specified herein, optional substituents on the aliphatic group of R^o are selected from NH2, NH(C1-4aliphatic), N(C1-4aliphatic)2, halogen, C1-4aliphatic, OH, O(C1-4aliphatic), NO2, CN, CO2H, CO2(C1-4aliphatic), O(haloC1-4 aliphatic), or haloC1-4aliphatic, wherein each of the foregoing C1-4aliphatic groups of R^o is unsubstituted.

An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents and thus may be “optionally substituted”. Unless otherwise specified herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, =NNHR^a, =NN(R^a)2, =NNHC(O)R^a, =NNHCO2(alkyl), =NNH2SO2(alkyl), or =NR^a, where each R^a is independently selected from hydrogen or an optionally substituted C1-6 aliphatic group.

Unless otherwise specified herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring are generally selected from -R^a, -N(R^a)2, -C(O)R^a, -CO2R^a, -C(O)C(O)R^a, -C(O)CH2C(O)R^a, -SO2R^a, -SO2N(R^a)2, -C(=S)N(R^a)2, -C(=NH)-N(R^a)2, or -NR^aSO2R^a; wherein R^a is hydrogen, an optionally substituted C1-6 aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted -CH2(Ph), optionally substituted -(CH2)1-2(Ph); optionally substituted -CH=CH(Ph); or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently
selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two
independent occurrences of R⁺, on the same substituent or different substituents, taken
together with the atom(s) to which each R⁺ group is bound, form an optionally substituted 3-
12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic
ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00041] Unless otherwise specified herein, optional substituents on the aliphatic group
or the phenyl ring of R⁺ are selected from -NH₂, -NH(C₁₋₄ aliphatic), -N(C₁₋₄ aliphatic)₂,
halogen, C₁₋₄ aliphatic, -OH, -O(C₁₋₄ aliphatic), -NO₂, -CN, -CO₂H, -CO₂(C₁₋₄ aliphatic), -
O(halo C₁₋₄ aliphatic), or halo(C₁₋₄ aliphatic), wherein each of the foregoing C₁₋₄ aliphatic
groups of R⁺ is unsubstituted.

[00042] The term “alkylidene chain” refers to a straight or branched carbon chain that
may be fully saturated or have one or more units of unsaturation and has two points of
attachment to the rest of the molecule.

[00043] As detailed above, in some embodiments, two independent occurrences of R⁰
(or R⁺, R, R’ or any other variable similarly defined herein), are taken together with the
atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated,
partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms
independently selected from nitrogen, oxygen, or sulfur.

[00044] Exemplary rings that are formed when two independent occurrences of R⁰ (or
R⁺, R, R’ or any other variable similarly defined herein), are taken together with the atom(s)
to which each variable is bound include, but are not limited to the following: a) two
independent occurrences of R⁰ (or R⁺, R, R’ or any other variable similarly defined herein)
that are bound to the same atom and are taken together with that atom to form a ring, for
example, N(R⁰)₂, where both occurrences of R⁰ are taken together with the nitrogen atom to
form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent
occurrences of R⁰ (or R⁺, R, R’ or any other variable similarly defined herein) that are bound
to different atoms and are taken together with both of those atoms to form a ring, for example

\[
\begin{array}{c}
\text{OR}^c \\
\text{OR}^c \\
\end{array}
\]

where a phenyl group is substituted with two occurrences of OR⁰, these two
occurrences of R⁰ are taken together with the oxygen atoms to which they are bound to form
a fused 6-membered oxygen containing ring: \( \text{\includegraphics[width=1cm]{diagram}} \). It will be appreciated that a variety of other rings can be formed when two independent occurrences of \( R^2 \) (or \( R^2, R, R' \) or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[00045] Unless otherwise specified herein, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a \( ^{13}\text{C} \)- or \( ^{14}\text{C} \)-enriched carbon or a nitrogen by a \( ^{15}\text{N} \) nitrogen are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[00046] 3. Description of Exemplary Compounds:

[00047] In one embodiment of the present invention, \( R^1 \) and \( R^2 \) taken together form an azetidinyl ring:

\( \text{\includegraphics[width=1cm]{diagram}} \)

In another embodiment of the present invention, \( R^1 \) and \( R^2 \) taken together form a pyrrolidinyl ring:
bb.

[00049] In another embodiment of the present invention, $R^1$ and $R^2$ taken together form a piperidinyl ring:

![Piperidinyl Ring](image)

c.

[00050] In another embodiment of the present invention, $R^1$ and $R^2$ taken together form a piperazinyl ring:

![Piperazinyl Ring](image)

d.

[00051] In another embodiment of the present invention, $R^1$ and $R^2$ taken together form a morpholinyl ring:

![Morpholinyl Ring](image)

e.

[00052] In another embodiment of the present invention, $R^1$ and $R^2$ taken together form a thiomorpholinyl ring:

![Thiomorpholinyl Ring](image)

f.

[00053] In another embodiment of the present invention, $R^1$ and $R^2$ taken together form an azepanyl ring:

![Azepanyl Ring](image)
In another embodiment of the present invention, $R^1$ and $R^2$ taken together form an azocanyl ring:

\[
\begin{array}{c}
\text{N} \\
\text{-(R^2)}_z \\
\end{array}
\]

In one embodiment, $R^1$ and $R^2$ together form a ring (ii) or (jj) as shown below:

\[
\begin{array}{c}
\text{(ii)} \\
\end{array}
\quad
\begin{array}{c}
\text{(jj)} \\
\end{array}
\]

wherein:
\[
\begin{align*}
G_1 & \text{ is } -\text{N}, -\text{CH}-, \text{ or } -\text{CH}_2\text{-NH}-; \\
\text{each of } m_1 \text{ and } n_1 & \text{ is independently } 0-3, \text{ provided that } m_1+n_1 \text{ is } 2-6; \\
p_1 & \text{ is } 0-2; \\
z & \text{ is } 0-4; \\
\text{each } R^{xx} & \text{ is hydrogen, } C_1\text{--6 aliphatic group, a } 3\text{-}8\text{-membered saturated, partially unsaturated,} \\
& \text{or fully unsaturated monocular ring having } 0\text{-}3 \text{ heteroatoms independently selected from} \\
& \text{nitrogen, oxygen, or sulfur, or an } 8\text{-}12 \text{ membered saturated, partially unsaturated, or fully} \\
& \text{unsaturated bicyclic ring system having } 0\text{-}5 \text{ heteroatoms independently selected from} \\
& \text{nitrogen, oxygen, or sulfur; wherein } R^{xx} \text{ is optionally substituted with } w_1 \text{ independent} \\
& \text{occurrences of } -\text{R}^{11}, \text{ wherein } w_1 \text{ is } 0-3; \\
\text{provided that both } R^{xx} & \text{ are not simultaneously hydrogen;}
\end{align*}
\]
R

\textsuperscript{VY} is hydrogen, -COR', -CO_2R', -CON(R')_2, -SOR', -SO_2R', -SO_2N(R')_2, -COCOR', -COCH_2COR', -P(O)(OR')_2, -P(O)_2OR', or -PO(R');

each occurrence of R\textsuperscript{11} is independently Q-R\textsuperscript{X}, wherein Q is a bond or is a C\textsubscript{1}-C\textsubscript{6} alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by -NR-, -S-, -O-, -CS-, -CO_2-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO_2-, -SO_2NR-, -NRSO_2NR-, -NRCONR-, -OCONR-, -NRN-, -NRSO_2NR-, -SO-, -SO_2-, -PO-, -PO_2-, -OP(O)(OR)-, or -POR-; and each occurrence of R\textsuperscript{X} is independently selected from -R', halogen, =O, =N=NR', =NO_2, -CN, -OR', -SR', -N(R')_2, -NR'COR', -NR'CON(R')_2, -NR'CO_2R', -COR', -CO_2R', -OCOR', -CON(R')_2, -OCON(R')_2, -SOR', -SO_2R', -SO_2N(R')_2, -NR'SO_2R', -NR'SO_2N(R')_2, -COCOR', -COCH_2COR', -OP(O)(OR')_2, -P(O)(OR')_2, -P(O)_2OR', -PO(O)(OR')_2, or -OPO(R')_2; and

each occurrence of R is independently hydrogen or C\textsubscript{1}-C\textsubscript{6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C\textsubscript{1}-C\textsubscript{6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00056] In one embodiment of the present invention, one R\textsuperscript{XX} is hydrogen and the other R\textsuperscript{XX} is not hydrogen.

[00057] In another embodiment of the present invention, both R\textsuperscript{XX} are not hydrogen.

[00058] In one embodiment of the present invention, p\textsubscript{1} is 0. Or, p\textsubscript{1} is 1. Or, p\textsubscript{1} is 2.

[00059] In one embodiment of the present invention, m\textsubscript{1} and n\textsubscript{1} each is 1. Or, m\textsubscript{1} and n\textsubscript{1} each is 2. Or, m\textsubscript{1} and n\textsubscript{1} each is 3.

[00060] In one embodiment of the present invention, R\textsuperscript{XX} is C\textsubscript{1}-C\textsubscript{6} aliphatic group, wherein R\textsuperscript{XX} is optionally substituted with w independent occurrences of -R\textsuperscript{11}, wherein w\textsubscript{1} is
0-3. Or, \( R^{xx} \) is C1-C6 alkyl group optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.

[00061] In one embodiment of the present invention, \( R^{xx} \) is C1-C6 alkyl group.

[00062] In another embodiment of the present invention, \( R^{xx} \) is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein \( R^{xx} \) is optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.

[00063] In another embodiment, \( R^{xx} \) is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein \( R^{xx} \) is optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.

[00064] In another embodiment, \( R^{xx} \) is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein \( R^{xx} \) is optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.

[00065] In another embodiment, \( R^{yy} \) is hydrogen, \(-COR', -CO_{2}R', -CON(R')_{2}, -SOR', -SO_{2}R', -SO_{2}N(R')_{2}, -COCOR', -COCH_{2}COR', -P(O)(OR')_{2}, -P(O)_{2}OR', or -PO(R')\).

[00066] Or, \( R^{yy} \) is hydrogen.

[00067] In another embodiment, \( R^{yy} \) is \(-COR', -CO_{2}R', -CON(R')_{2}, -SOR', -SO_{2}R', -SO_{2}N(R')_{2}, -COCOR', -COCH_{2}COR', -P(O)(OR')_{2}, -P(O)_{2}OR', or -PO(R').\)

[00068] In one embodiment, \( R \) is hydrogen. Or, \( R \) is C1-C6 alkyl. Preferred \( R \) include methyl, ethyl, propyl, or butyl.

[00069] In another embodiment, \( R^{yy} \) is hydrogen, one \( R^{xx} \) is hydrogen, and the other \( R^{xx} \) is C1-C6 alkyl.

[00070] In yet another embodiment, \( p_1 \) is 0, \( R^{yy} \) is hydrogen, one \( R^{xx} \) is hydrogen, and the other \( R^{xx} \) is C1-C6 alkyl.

[00071] In another embodiment, \( R^{yy} \) is hydrogen, one \( R^{xx} \) is hydrogen, and the other \( R^{xx} \) is C1-C6 alkyl.
In yet another embodiment, \( p_1 \) is 0, \( R^{\text{XY}} \) is hydrogen, one \( R^{\text{XX}} \) is hydrogen, and the other \( R^{\text{XX}} \) is C1-C6 alkyl.

In one embodiment of the present invention, \( R^1 \) and \( R^2 \) together form a ring as shown below:

![Diagram of a ring structure]

In one embodiment, \( R^{\text{XX}} \) is C1-C6 alkyl.

In one embodiment, \( R^{\text{XX}} \) is methyl, \( n \)-propyl, isopropyl, \( n \)-butyl, isobutyl, or \( t \)-butyl.

In one embodiment, \( R^1 \) and \( R^2 \) taken together form ring (kk) as shown below:

![Diagram of ring structure (kk)]

\( G_3 \) is \(-N-\), or \( \text{CH} \);
each of \( m_2 \) and \( n_2 \) is independently \( 0-3 \), provided that \( m_2 + n_2 \) is \( 2-6 \);
\( p_2 \) is \( 0-2 \); provided that when \( G_3 \) is \( \text{N} \), then \( p_2 \) is not \( 0 \);
\( q_2 \) is \( 0 \) or \( 1 \);
\( z \) is \( 0-4 \);
\( \text{Sp} \) is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by \(-\text{O}-, -\text{S}-, -\text{CO}-, -\text{CS}-, -\text{COCO}-, -\text{CONR}'-, -\text{CONR}'\text{NR}'-, -\text{CO}_2-, -\text{OCO}-, -\text{NR'}CO_2-, -\text{NR'CONR}'-, -\text{OCONR}'-, -\text{NR'NR'}, -\text{NR'NR'}CO-, -\text{NR'CO}-, -\text{SO}-, -\text{OSO}_2-, -\text{NR'}-, -\text{SO}_2\text{NR'}-, \text{NR'SO}_2-, \text{or -NR'SO}_2\text{NR'}-\);
ring B is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with \( w \) independent occurrences of \(-R^1\), wherein \( w_2 = 0-4\); each occurrence of \( R^2 \) is independently \( Q\)-R\(^X\); wherein \( Q\) is a bond or is a \( C_1-C_6 \) alkylidene chain wherein up to two non-adjacent methylene units of \( Q\) are optionally and independently replaced by \(-NR^-, -S^-, -O^-, -CS^-, -CO_2^-, -OCO^-, -CO^-, -COCONR^-, -NRCO^-, -NRCO_2^-, -SO_2NR^-, -NRSO_2^-, -CONNR^-, -NCONR^-, -NCOOR^-, -NRNR^-, -NRSO_2NR^-, -SO_-, -SO_2^-, -PO_-, -PO_2^-, -OP(O)(OR)^-, or \(-POR^-, and each occurrence of \( R^X \) is independently selected from \(-R^-, \) halogen, \(-O^-, \) \(-NO_2^-, \) \(-CN^-, \) \(-OR^-, \) \(-SR^-, \) \(-N(R')^-, \) \(-NR'COR^-, \) \(-NR'CON(R')^2-, \) \(-NR'CO_2R^-, \) \(-COR^-, \) \(-CO_2R^-, \) \(-OCOR^-, \) \(-CON(R')^2-, \) \(-OCO(N')(R')\), \(-SO_2R^-, \) \(-SO_2N(R')^-, \) \(-NR'SO_2R^-, \) \(-NR'SO_2N(R')^-, \) \(-COCH_2COR^-, \) \(-OP(O)(OR')^-, \) \(-P(O)(OR')^2-, \) \(-P(O)O_2OR^-, \) \(-P(O)O_2OR^-, \) \(-P(O)R^-, or \(-OPO(R')^2-, and each occurrence of \( R^\) is independently hydrogen or \( C_1-C_6 \) aliphatic group having up to three substituents; and each occurrence of \( R^{'}\) is independently hydrogen or \( C_1-C_6 \) aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein \( R^{'}\) has up to four substituents; or \( R\) and \( R^{'}\), two occurrences of \( R\), or two occurrences of \( R^{'}\), are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00077] In one embodiment, \( G_3 \) is N. Or, \( G_3 \) is CH.

[00078] In one embodiment, \( p_2 \) is 0. Or, \( p_2 \) is 1. Or, \( p_2 \) is 2.

[00079] In another embodiment, \( q_2 \) is 0. Or, \( q_2 \) is 1.

[00080] In one embodiment, \( p_2 \) is 1, and \( q_2 \) is 1.

[00081] In another embodiment, \( G_3 \) is CH, \( p_2 \) is 0, and \( q_2 \) is 1.

[00082] In one embodiment, \( m_2 \) and \( n_2 \) each is 1. Or, \( m_2 \) and \( n_2 \) each is 2.

[00083] In another embodiment, \( S_p \) is selected from \(-O^-, \) \(-S^-, \) or \(-NR^1-, \) In one embodiment, \( S_p \) is \(-O^-, \) Or, \( S_p \) is \(-NR^1-, \) Or, \( S_p \) is \(-NH^-).
[00084] In one embodiment, ring B is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with \( w \) independent occurrences of \(-R^{12}\), wherein \( w_2 \) is 0-4.

[00085] In another embodiment, ring B is a 4-8 membered, saturated, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with \( w \) independent occurrences of \(-R^{12}\), wherein \( w_2 \) is 0-4.

[00086] In yet another embodiment, ring B is a 5-6 membered, saturated, monocyclic heterocyclic ring having 1-2 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with \( w \) independent occurrences of \(-R^{12}\), wherein \( w_2 \) is 0-4.

[00087] In one embodiment, \( w_2 \) is 0.

[00088] In another embodiment, ring B is tetrahydrofuranyl.

[00089] In yet another embodiment,

i) Sp is a bond, O, or \(-O-CH_2\)-;

ii) \( p_2 \) is 1;

iii) \( R \) is hydrogen; and

iv) \( n_2 \) and \( m_2 \) are both simultaneously 1 or 2.

[00090] In one embodiment, \( R \) is hydrogen. Or, \( R \) is C1-C6 alkyl. Preferred \( R \) include methyl, ethyl, propyl, or butyl.

[00091] In one embodiment, \( R^1 \) and \( R^2 \) taken together form a ring of formula (kk-i) or formula (kk-ii):

```
\[ kk-i \]
```

```
\[ kk-ii \]
```
According to one embodiment, ring B is a 5-6 membered, saturated, monocyclic heterocyclic ring having 1-2 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of \(-R^{12}\), wherein \(w_2\) is 0-4.

According to another embodiment, \(R\) is hydrogen. Or, \(R\) is hydrogen and ring B is tetrahydrofurfuryl.

According to yet another embodiment, \(Sp\) is a bond, -O-, or -O-CH2-.

In one embodiment, \(R^1\) and \(R^2\) taken together form a ring (II):

\[
\begin{align*}
&\text{B}^3 \\
&\text{O} \\
&(\text{Sp}^3) \text{N}_3 \\
&(\text{R}^4) \text{N}_3 \\
&(\text{m}_3) \\
\end{align*}
\]

each of \(m_3\) and \(n_3\) is independently 0-3, provided that \(m_3 + n_3\) is 2-6;

\(z\) is 0-4;

\(Sp^3\) is \(-O-, -S-, -NR^1-,\) or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by \(-O-, -S-, -CO-, -CS-, -COCO-, -CONR^-,\)

\(-\text{CONR}^'\text{NR}^1-, -\text{CO}_2-, -\text{OOCO}-, -\text{NR}^'\text{CO}_2-, -\text{NR}^'\text{CONR}^'-, -\text{OCONR}^'-, -\text{NR}^'\text{NR}^-, -\text{NR}^'\text{NR}^'\text{CO}_2-, -\text{NR}^'\text{CO}_2-, -\text{SO}_2\), -\text{SO}_2, -\text{NR}^-, -\text{SO}_2\text{NR}^-, \text{NR}^'\text{SO}_2, or \text{NR}^'\text{SO}_2\text{NR}^'-,\) provided that \(Sp^3\) is attached to the carbonyl group through an atom other than carbon;

ring \(B^3\) is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring \(B^3\) is optionally substituted with \(w\) independent occurrences of \(-R^{13}\), wherein \(w_3\) is 0-4;

each occurrence of \(R^{13}\) is independently \(Q-R^X\), wherein \(Q\) is a bond or is a C1-C6 alkylidene chain wherein up to two non-adjacent methylene units of \(Q\) are optionally and independently replaced by \(-\text{NR}^-, -\text{S}-, -\text{O}-, -\text{CS}-, -\text{CO}_2-, -\text{OOCO}-, -\text{CO}-, -\text{COCO}-, -\text{CONR}^-, -\text{NRCO}-, -\text{NRCO}_2-, -\text{SO}_2\text{NR}^-, -\text{NRSO}_2, -\text{CONRNR}^-, -\text{NRCONR}^-, -\text{OCONR}^-, -\text{NRNR}^-, -\text{NRSO}_2\text{NR}^-, -\text{SO}_-, -\text{SO}_2-, -\text{PO}-, -\text{PO}_2-, -\text{OP}(O)(\text{OR})-\), or \(-\text{POR}-\); and each occurrence of \(R^X\) is
independently selected from -R', halogen, =O, =NR', -NO₂, -CN, -OR', -SR', -N(R')₂, -NR'COR', -NR'CON(R')₂, -NR'CO₂R', -COR', -CO₂R', -OCOR', -CON(R')₂, -OCON(R')₂, -SOR', -SO₂R', -SO₂N(R')₂, -NR'SO₂R', -NR'SO₂N(R')₂, -COCOR', -COC₂COR', -OP(O)(OR')₂, -P(O)(OR')₂, -OP(O₂OR'), -P(O₂OR'), -PO(R')₂, or -OPO(R')₂; and

each occurrence of R is independently hydrogen or C₁₋₆ aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C₁₋₆ aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00096] In one embodiment, Sp³ is selected from -O-, -S-, or -NR'. Or, Sp is -O-. Or, Sp³ is -O-CH₂-. In another embodiment, Sp³ is -NR'. Or, Sp³ is -NH-. Or, Sp³ is -NH-CH₂-.

[00097] In one embodiment, each of m₃ and n₃ is 1. In another embodiment, each of m₃ and n₃ is 2.

[00098] In one embodiment, ring B₃ is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B₃ is optionally substituted with w independent occurrences of -R¹₃, wherein w is 0-4.

[00099] In another embodiment, ring B₃ is a 4-8 membered, saturated, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B₃ is optionally substituted with w independent occurrences of -R¹₃, wherein w is 0-4.

[00100] In yet another embodiment, ring B₃ is a 5-6 membered, saturated, monocyclic heterocyclic ring having 1-2 heteroatoms selected from O, S, or N, wherein ring B₃ is optionally substituted with w independent occurrences of -R¹₂, wherein w is 0-4.

[00101] In one embodiment, w is 0.
[000102] In another embodiment, ring B₃ is tetrahydrofuranyl.

[000103] In yet another embodiment, Sp³ is a bond, O, or -O-CH₂--; R is hydrogen; and n₃ and m₃ are both simultaneously 1 or 2.

[000104] In one embodiment, R is hydrogen. Or, R is C₁-C₆ alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[000105] In another embodiment, z is 0.

[000106] According to one embodiment, ring B₃ is a 5-6 membered, saturated, monocyclic heterocyclic ring having 1-2 heteroatoms selected from O, S, or N, wherein ring B₃ is optionally substituted with w₃ independent occurrences of -R¹³, wherein w is 0-4.

[000107] According to another embodiment, R is hydrogen. Or, R is hydrogen and ring B₃ is tetrahydrofuranyl.

[000108] According to yet another embodiment, Sp₃ is a bond, -O-, -O-CH₂-, or -NH-CH₂.

[000109] In one embodiment, R¹ and R² taken together form a ring (mm):

```
O
O
N-R
(R⁴)ₙ₄
p₄

m₄

```
each of m₄ and n₄ is independently 0-3, provided that m₄ + n₄ is 2-6;

p₄ is 1-2;

R⁴ is C₁-C₆ aliphatic group, optionally substituted with w₄ independent occurrences of -R¹⁴, wherein w₄ is 0-3;

each occurrence of R¹⁴ is independently Q-Rₓ, wherein Q is a bond or is a C₁-C₆ alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by -NR-, -S-, -O-, -CS-, -CO₂-, -OCO₂-, -CO-, -COCO₂-, -CONR-, -NRCO₂-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONNR-, -NRCONR-, -OCONR-, -NRNR-, -
NRSO₂NR⁻, -SO₂⁻, -PO₂⁻, -OP(O)(OR)⁻, or -POR⁻; and each occurrence of R⁻ is independently selected from -R', halogen, =O, =NR', -NO₂, -CN, -OR', -SR', -N(R')₂, -NR'COR', -NR'CON(R')₂, -NR'CO₂R', -COR', -CO₂R', -OCOR', -CON(R')₂, -OCON(R')₂, -SOR', -SO₂R', -SO₂N(R')₂, -NR'SO₂R', -NR'SO₂N(R')₂, -COCH₂COR', -OP(O)(OR')₂, -P(O)(OR')₂, -OP(OR)₂OR', -P(O)₂OR', -PO(R')₂, or -OPO(R')₂; and

each occurrence of R is independently hydrogen or C₁₋₆ aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C₁₋₆ aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[000110] In one embodiment, p₄ is 1. Or, p₄ is 2.

[000111] In one embodiment, m₄ and n₄ each is 1. Or, m₄ and n₄ each is 2. Or, m₄ and n₄ each is 3.

[000112] In one embodiment, R⁻¹² is C₁₋₆ alkyl, optionally substituted with w₄ independent occurrences of -R¹⁴, wherein w₄ is 0-3. In another embodiment, R⁻¹² is C₁₋₄ alkyl group optionally substituted with w₄ independent occurrences of -R¹⁴, wherein w₄ is 0-3. Or, R⁻¹ is C₁₋₆ alkyl group.

[000113] In one embodiment, R is hydrogen. Or, R is C₁₋₆ alkyl. Preferred R include methyl, ethyl, propyl, or butyl.

[000114] In another embodiment, R¹ and R₂ taken together form a ring (mm-1):
each of $m_4$ and $n_4$ is independently 0-3, provided that $m_4 + n_4$ is 2-6; $p_4$ is 0-2; $R^{YZ}$ is C$_1$-C$_6$ aliphatic group, optionally substituted with $w_4$ independent occurrences of $-R^{14}$, wherein $w_4$ is 0-3; wherein up to two methylene units in $R^{YZ}$ are optionally replaced with $-NR_2$, $-O_2$, $-CO_2$, $-OCO_2$, $-NRCO_2$, $-CONR_2$, $-CO_2$, $-SO_2NR_2$, or $-NSO_2$; each occurrence of $R^{14}$ is independently Q-$R^X$; wherein Q is a bond or is a C$_1$-C$_6$ alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by $-NR_2$, $-S_2$, $-O_2$, $-CS_2$, $-CO_2$, $-OCO_2$, $-CO_2$, $-COCO_2$, $-CONR_2$, $-NRCO_2$, $-NRCONR_2$, $-SO_2NR_2$, $-NRCONR_2$, $-NRCONR_2$, $-NRCONR_2$, $-NSO_2NR_2$, $-SO_2$, $-SO_2$, $-PO_2$, $-PO_2$, $-OP(O)(OR)$, or $-POR$; and each occurrence of $R^X$ is independently selected from $-R'$, halogen, $=O$, $=NR'$, $=NO_2$, $=CN$, $=OR'$, $=SR'$, $=N(R')_2$, $=NR'COR'$, $=NR'CON(R')_2$, $=NR'CO_2R'$, $=COR'$, $=CO_2R'$, $=OCOR'$, $=CON(R')_2$, $=OCON(R')_2$, $=SOR'$, $=SO_2R'$, $=SO_2N(R')_2$, $=NR'SO_2R'$, $=NR'SO_2N(R')_2$, $=COCOR'$, $=COCH_2COR'$, $=OP(O)(OR')_2$, $=OP(O)(OR')_2$, $=P(O)(OR')_2$, $=P(O)(OR')_2$, or $=PO(R')_2$; and each occurrence of R is independently hydrogen or C$_1$-$C_6$ aliphatic group having up to three substituents; and each occurrence of $R'$ is independently hydrogen or C$_1$-$C_6$ aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein $R'$ has up to
four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[000115] In another embodiment, the present invention provides a compound of formula mm-2 or mm-3:

![Chemical Structures](image)

**mm-2**  **mm-3**

[000116] In one embodiment of formula mm-2 and mm-3, R^{YZ} is an unsubstituted C_{1-6} aliphatic group.

[000117] In one embodiment of formula mm-2, R^{YZ} is -CH_{3}, -CH_{2}CH_{3}, -CH(CH_{3})_{2}, -CH_{2}CH_{2}CH_{3}, -CH(CH_{3})_{3}, -CH_{2}CH(CH_{3})_{2}, or -CH_{2}C(CH_{3})_{3}.

[000118] In one embodiment of formula mm-3, R^{YZ} is -CH_{3}, -CH_{2}CH_{3}, -CH(CH_{3})_{2}, -CH_{2}CH_{2}CH_{3}, -CH_{2}CH(CH_{3})_{2}, or -CH_{2}C(CH_{3})_{3}.

[000119] In one embodiment, R^1 and R^2 are taken together to form a ring (nn):

![Chemical Structure](image)

**nn.**

[000120] In one embodiment, G_1 is -N-. Or, G_1 is -CH-NH-. Or, G_1 is -CH-CH_{2}-NH-.

[000121] In another embodiment, R^{YY} is hydrogen, one R^{XX} is hydrogen, and the other R^{XX} is C_{1-6} alkyl.
In yet another embodiment, \( p_4 \) is 0, \( R^{YY} \) is hydrogen, one \( R^{XX} \) is hydrogen, and the other \( R^{XX} \) is C1-C6 alkyl.

In one embodiment, \( R^1 \) and \( R^2 \) are taken together to form a ring (pp):

\[
\begin{align*}
\text{pp}.
\end{align*}
\]

In another embodiment, \( R^{YY} \) is hydrogen, one \( R^{XX} \) is hydrogen, and the other \( R^{XX} \) is C1-C6 alkyl.

In yet another embodiment, \( p_4 \) is 0, \( R^{YY} \) is hydrogen, one \( R^{XX} \) is hydrogen, and the other \( R^{XX} \) is C1-C6 alkyl.

In one embodiment of the present invention, \( W \) is OR'. In another embodiment, \( W \) is OH.

In one embodiment of the present invention, \( W \) is SR'. In another embodiment, \( W \) is SH.

In one embodiment of the present invention, \( W \) is N(R')2. In another embodiment, \( W \) is NHR'. Or, \( W \) is NH2.

In one embodiment of the present invention, \( W \) is CHF2, or CH2F. In one embodiment, \( W \) is CHF2. In another embodiment, \( W \) is CH2F.

In one embodiment of the present invention, \( z \) is 0-5. In another embodiment, \( z \) is 1-3. In yet another embodiment, \( z \) is 1-2. In yet another embodiment, \( z \) is 1.

In one embodiment of the present invention, \( R^4 \) is independently halogen, CN, NO2, -N(R')2, -CH2N(R')2, -OR', -CH2OR', -SR', -CH2SR', -COOR', -NRCOR', -CON(R')2, -OCON(R')2, COR', -NHCOR', -SO2R', -SO2N(R')2, or an optionally
substituted group selected from C1-C6 aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC1-C6 alkyl, heteroarylC1-C6 alkyl, cycloaliphaticC1-C6 alkyl, or heterocycloaliphaticC1-C6 alkyl.

[000132] In another embodiment of the present invention, R4 is independently Cl, Br, F, CF3, CH3, -CH2CH3, CN, -COOH, -N(CH3)2, -N(Et)2, -N(iPr)2, -O(CH2)2OCH3, -CONH2, -COOCH3, -OH, -CH2OH, -NHCOC2H5, -SO2NH2, -SO2C2H5, -SO2CH3, -SO2N(CH3)2, -SO2CH2CH3, -C(O)OCH2CH(CH3)2, -C(O)NHCH2CH2CH3, -NHCOOCH3, -C(O)C(CH3)3, -COO(CH2)2CH3, -C(O)NHCH(CH3)2, -C(O)CH2CH3, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, C1-C6 alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, -CH2cyclohexyl, pyridyl, -CH2pyridyl, or -CH2thiazolyl.

[000133] In one embodiment of the present invention, R1 and R2, taken together is optionally substituted azetidin-1-yl (aa), wherein z is 1 or 2 and at least one occurrence of R4 is -NRSO2R’, -NRCOC2H5’, or -NRCOR’. In another embodiment, R1 and R2, taken together is optionally substituted azetidin-1-yl (aa), wherein z is 1 and R4 is -NRSO2R’. In another embodiment, R1 and R2, taken together is optionally substituted azetidin-1-yl (aa), wherein z is 1 and R4 is -NRCOR’. In another embodiment, R1 and R2, taken together is optionally substituted azetidin-1-yl (aa), wherein z is 1 and R4 is -NRCOC2H5’.

[000134] In yet another embodiment, R1 and R2, taken together is optionally substituted pyrrolidin-1-yl (bb), wherein z is 1 or 2 and R4 is Cl, Br, F, CF3, CH3, -CH2CH3, -OR’, or -CH2OR’.

[000135] In another embodiment, R1 and R2, taken together is optionally substituted piperidin-1-yl (cc), wherein z is 1 or 2 and at least one occurrence of R4 is Cl, Br, F, CF3, CH3, -CH2CH3, -OR’, or -CH2OR’, -NRSO2R’, -NRCOC2H5’, or -CON(R’). In another embodiment, R1 and R2, taken together is optionally substituted piperidin-1-yl (cc), wherein z is 1 and R4 is F, CF3, CH3, -CH2CH3, -OR’, or -CH2OR’. In another embodiment, R1 and R2, taken together is optionally substituted piperidin-1-yl (cc), wherein z is 1 and R4 is -NRSO2R’. In another embodiment, R1 and R2, taken together is optionally substituted piperidin-1-yl (cc), wherein z is 1 and R4 is -NRCOC2H5’.

[000136] In yet another embodiment, R1 and R2, taken together is optionally substituted piperazin-1-yl (dd), wherein z is 1 or 2 and at least one occurrence of R4 is -SOR’, -CON(R’), -SO2N(R’), -COR’, or -COOR’. In another embodiment, R1 and R2, taken
together is optionally substituted piperazin-1-yl (dd), wherein z is 1 and R¹ is -SOR¹. In another embodiment, R¹ and R², taken together is optionally substituted piperazin-1-yl (dd), wherein z is 1 and R⁴ is -COOR¹. In another embodiment, R¹ and R², taken together is optionally substituted piperazin-1-yl (dd), wherein z is 1 and R⁴ is -CON(R¹)₂. In another embodiment, R¹ and R², taken together is optionally substituted piperazin-1-yl (dd), wherein z is 1 and R⁴ is -SO₂N(R¹)₂. In another embodiment, R¹ and R², taken together is optionally substituted piperazin-1-yl (dd), wherein z is 1 and R⁴ is -COR¹.

[000137] In yet another embodiment, R¹ and R², taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein z is 1 or 2 and at least one occurrence of R⁴ is -SOR¹, -CON(R¹)₂, -SO₂N(R¹)₂, -COR¹, or -COOR¹. In another embodiment, R¹ and R², taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein z is 1 and R⁴ is -SOR¹. In another embodiment, R¹ and R², taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein z is 1 and R⁴ is -CON(R¹)₂. In another embodiment, R¹ and R², taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein z is 1 and R⁴ is -SO₂N(R¹)₂. In another embodiment, R¹ and R², taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein z is 1 and R⁴ is -COR¹.

[000138] In yet another embodiment, R¹ and R², taken together is optionally substituted azepan-1-yl (gg), wherein z is 1 or 2 and at least one occurrence of R⁴ is -SOR¹, -CON(R¹)₂, -SO₂N(R¹)₂, -COR¹, or -COOR¹. In another embodiment, R¹ and R², taken together is optionally substituted azepan-1-yl (gg), wherein z is 1 and R⁴ is -SOR¹. In another embodiment, R¹ and R², taken together is optionally substituted azepan-1-yl (gg), wherein z is 1 and R⁴ is -COOR¹. In another embodiment, R¹ and R², taken together is optionally substituted azepan-1-yl (gg), wherein z is 1 and R⁴ is -CON(R¹)₂. In another embodiment, R¹ and R², taken together is optionally substituted azepan-1-yl (gg), wherein z is 1 and R⁴ is -SO₂N(R¹)₂. In another embodiment, R¹ and R², taken together is optionally substituted azepan-1-yl (gg), wherein z is 1 and R⁴ is -COR¹.

[000139] In yet another embodiment, R¹ and R², taken together is optionally substituted azocan-1-yl (hh), wherein z is 1 or 2 and at least one occurrence of R⁴ is -SOR¹, -CON(R¹)₂,
-SO₂N(R’₂), -COR’, or -COOR’. In another embodiment, R¹ and R², taken together is optionally substituted azocan-1-yl (hh), wherein z is 1 and R⁴ is -SOR’. In another embodiment, R¹ and R², taken together is optionally substituted azocan-1-yl (hh), wherein z is 1 and R⁴ is -COOR’. In another embodiment, R¹ and R², taken together is optionally substituted azocan-1-yl (hh), wherein z is 1 and R⁴ is -CON(R’₂). In another embodiment, R¹ and R², taken together is optionally substituted azocan-1-yl (hh), wherein z is 1 and R⁴ is -SO₂N(R’₂). In another embodiment, R¹ and R², taken together is optionally substituted azocan-1-yl (hh), wherein z is 1 and R⁴ is -COR’.

[000140] In one embodiment, y is 0-5. In another embodiment, y is 0. Or, y is 1-3. In another embodiment, y is 1-2. Or, y is 1.

[000141] In one embodiment, R⁵ is independently halogen, CN, NO₂, -N(R’₂), -CH₂N(R’₂), -OR’, -CH₂OR’, -SR’, -CH₂SR’, -NRCOR’, -CON(R’₂), -S(O)₂N(R’₂), -OCOR’, -COR’, -CO₂R’, -OCON(R’₂), -NR’₂SO₂R’, -OP(O)(OR’₂), -P(O)(OR’₂), -OP(O)₂OR’, -PO(R’₂), -OPO(R’₂), or an optionally substituted group selected from C₁₋₆aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC₁₋₆alkyl, heteroarylC₁₋₆alkyl, cycloaliphaticC₁₋₆alkyl, or heterocycloaliphaticC₁₋₆alkyl.

[000142] In another embodiment, R⁵ is independently Cl, Br, F, CF₃, Me, Et, CN, -COOH, -NH₂, -N(CH₃)₂, -N(Et)₂, -N(iPr)₂, -O(CH₂)₂OCH₃, -CONH₂, -COOCH₃, -OH, -OCH₃, -OCH₂CH₃, -CH₂OH, -NHOCH₃, -SO₂NH₂, -SO₂NH(CH₃)₂, -OCOC(CH₃)₃, -OCOCH₂C(CH₃)₃, -O(CH₂)₂N(CH₃)₂, 4-CH₃-piperazin-1-yl, OOC(CH₃)₂, OCO(cyclopentyl), -COCH₃, optionally substituted phenoxy, or optionally substituted benzyloxy.

[000143] In another embodiment, R⁵ is F. Or, R⁵ is OR’. In one embodiment, R⁵ is OH.

[000144] In one embodiment, the present invention provides a compound of formula I-A-i, formula I-B-i, formula I-C-i, or formula I-D-i:
or a pharmaceutically acceptable salt thereof;
wherein R\(^1\), R\(^2\), R\(^3\)\(^a\), R\(^3\)\(^b\), and R\(^3\)\(^c\) are as defined above for formula I-A, formula I-B, formula I-C, and formula I-D.

[000145] In one embodiment, R\(^3\)\(^a\) is hydrogen. In another embodiment, R\(^3\)\(^a\) is X-R\(^Q\).

[000146] In one embodiment, X is a C1-C6 alkylidene. In another embodiment, X is a C1-C4 alkylidene. Or, X is –CH\(_2\)-.

[000147] In one embodiment, R\(^Q\) is independently selected from -R\(^-\), -OR\(^-\), -SR\(^-\), -N(R\(^{R'}\))\(_2\), -NR\(^{R'}\)COR\(^-\), -NR\(^{R'}\)CON(R\(^{R'}\))\(_2\), -NR\(^{R'}\)CO\(_2\)R\(^-\), -COR\(^-\), -CO\(_2\)R\(^-\), -OCOR\(^-\), -CON(R\(^{R'}\))\(_2\), -OCON(R\(^{R'}\))\(_2\), -SOR\(^-\), -SO\(_2\)R\(^-\), -SO\(_2\)N(R\(^{R'}\))\(_2\), -NR\(^{R'}\)SO\(_2\)R\(^-\), -NR\(^{R'}\)SO\(_2\)N(R\(^{R'}\))\(_2\), -COCOR\(^-\), -COCH\(_2\)COR\(^-\), -OP(O)(OR\(^{R'}\))\(_2\), -P(O)(OR\(^{R'}\))\(_2\), -OP(O)OR\(^{R'}\), -P(O)OR\(^{R'}\), -PO(R\(^{R'}\))\(_2\), or -OPO(R\(^{R'}\))\(_2\).

[000148] In another embodiment R\(^Q\) is R\(^-\).

[000149] In one embodiment, R\(^3\)\(^b\) is hydrogen. In another embodiment, R\(^3\)\(^c\) is hydrogen. Or, R\(^3\)\(^b\) and R\(^3\)\(^c\), both are simultaneously hydrogen.

[000150] In one embodiment, R\(^3\)\(^b\) and R\(^3\)\(^c\) each is independently halogen, CN, NO\(_2\), -N(R\(^{R'}\))\(_2\), -CH\(_2\)N(R\(^{R'}\))\(_2\), -OR\(^-\), -CH\(_2\)OR\(^-\), -SR\(^-\), -CH\(_2\)SR\(^-\), -COOR\(^-\), -NRCOR\(^-\), -CON(R\(^{R'}\))\(_2\), -OCON(R\(^{R'}\))\(_2\), COR\(^-\), -NHCOOR\(^-\), -SO\(_2\)R\(^-\), -SO\(_2\)N(R\(^{R'}\))\(_2\), or an optionally substituted group selected from C\(_1\)-C\(_6\) aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, aryl(C\(_1\)-C\(_6\) alkyl, heteroaryl(C\(_1\)-C\(_6\) alkyl, cycloaliphatic(C\(_1\)-C\(_6\) alkyl, or heterocycloaliphatic(C\(_1\)-C\(_6\) alkyl.

[000151] In yet another embodiment, each occurrence of R\(^3\)\(^b\) and R\(^3\)\(^c\) is independently Cl, Br, F, CF\(_3\), -OCF\(_3\), Me, Et, CN, -COOH, -NH\(_2\), -N(CH\(_3\))\(_2\), -N(Et)\(_2\), -N(iPr)\(_2\), -O(CH\(_2\))\(_2\)OCH\(_3\), -CONH\(_2\), -COOCH\(_3\), -OH, -OCH\(_3\), -OCH\(_2\)CH\(_3\), -CH\(_2\)OH, -NHCOCH\(_3\), -NHCOCH(CH\(_3\))\(_2\), -SO\(_2\)NH\(_2\), -CONH(cyclopropyl), -CONHCH\(_3\), -CONHCH\(_2\)CH\(_3\), or an
optionally substituted group selected from -piperidinyl, piperazinyl, morpholino, phenyl, phenoxy, benzyl, or benzyloxy.

[000152] In another embodiment, each occurrence of R\textsuperscript{3b} and R\textsuperscript{3c} is independently halogen, CN, optionally substituted C\textsubscript{1}-C\textsubscript{6}alkyl, OR', N(R')\textsubscript{2}, CON(R')\textsubscript{2}, or NRCOR'.

[000153] In yet another embodiment, each R\textsuperscript{3b} and R\textsuperscript{3c} is independently -Cl, -CH\textsubscript{3}, -CH\textsubscript{2}CH\textsubscript{3}, -F, -CF\textsubscript{3}, -OCF\textsubscript{3}, -CONHCH\textsubscript{3}, -CONHCH\textsubscript{2}CH\textsubscript{3}, -CONH(cyclopropyl), -OCH\textsubscript{3}, -NH\textsubscript{2}, -OCH\textsubscript{2}CH\textsubscript{3}, or -CN.

[000154] In yet another embodiment, each R\textsuperscript{3b} and R\textsuperscript{3c} is independently -Cl, -CH\textsubscript{3}, -CH\textsubscript{2}CH\textsubscript{3}, -F, -CF\textsubscript{3}, -OCF\textsubscript{3}, -CONHCH\textsubscript{3}, -CONHCH\textsubscript{2}CH\textsubscript{3}, -CONH(cyclopropyl), -OCH\textsubscript{3}, -NH\textsubscript{2}, -OCH\textsubscript{2}CH\textsubscript{3}, or -CN.

[000155] In yet another embodiment, R\textsuperscript{3b} and R\textsuperscript{3c} is independently selected -Cl, -CH\textsubscript{3}, -CH\textsubscript{2}CH\textsubscript{3}, -F, -CF\textsubscript{3}, -OCF\textsubscript{3}, -CONHCH\textsubscript{3}, -CONHCH\textsubscript{2}CH\textsubscript{3}, -CONH(cyclopropyl), -OCH\textsubscript{3}, -NH\textsubscript{2}, -OCH\textsubscript{2}CH\textsubscript{3}, or -CN.

[000156] In another embodiment, R\textsuperscript{3b} and R\textsuperscript{3c} is independently selected -Cl, -CH\textsubscript{3}, -CH\textsubscript{2}CH\textsubscript{3}, -F, -CF\textsubscript{3}, -OCF\textsubscript{3}, -OCH\textsubscript{3}, or -OCH\textsubscript{2}CH\textsubscript{3}.

[000157] In another embodiment, R\textsuperscript{3b} and R\textsuperscript{3c} is independently selected from -Cl, -CH\textsubscript{3}, -CH\textsubscript{2}CH\textsubscript{3}, -F, -CF\textsubscript{3}, -OCF\textsubscript{3}, -OCH\textsubscript{3}, or -OCH\textsubscript{2}CH\textsubscript{3}.

[000158] In another embodiment, each R\textsuperscript{3b} and R\textsuperscript{3c} is -CON(R')\textsubscript{2}, or -NRCOR'.

[000159] In another embodiment, R\textsuperscript{3b} and R\textsuperscript{3c} is independently selected from -Cl, -CH\textsubscript{3}, -CH\textsubscript{2}CH\textsubscript{3}, -F, -CF\textsubscript{3}, -OCF\textsubscript{3}, -OCH\textsubscript{3}, or -OCH\textsubscript{2}CH\textsubscript{3}.

[000160] In one embodiment, the present invention provides compounds of formula IA-ii, formula IB-ii, formula IC-ii, and formula ID-ii:

![Chemical Structures](image_url)
wherein $R^1$, $R^2$, $R^{3b}$, and $R^{3c}$ are as defined above.

[000161] In one embodiment of formula IA-ii, formula IB-ii, formula IC-ii, and formula ID-ii, one of $R^{3b}$ and $R^{3c}$ is hydrogen. In another embodiment, both of $R^{3b}$ and $R^{3c}$ are simultaneously hydrogen.

[000162] In one embodiment or formula IA-ii, both of $R^{3b}$ and $R^{3c}$ are simultaneously hydrogen, $R^1$ and $R^2$, taken together is optionally substituted piperazin-1-yl (dd), wherein $z$ is 1, $R^4$ is -COOR’, and $R’$ is C$_{1-6}$ aliphatic group. In another embodiment, $R’$ is methyl, n-propyl, isopropyl, n-butyl, isobutyl, or t-butyl. In yet another embodiment, $R’$ is isobutyl.

[000163] In another embodiment of formula IA-ii, both of $R^{3b}$ and $R^{3c}$ are simultaneously hydrogen, $R^1$ and $R^2$, taken together is optionally substituted piperazin-1-yl (dd), wherein $z$ is 1, $R^4$ is -COR’, and $R’$ is C$_{1-6}$ aliphatic group. In another embodiment, $R’$ is methyl, n-propyl, isopropyl, n-butyl, isobutyl, or t-butyl. In yet another embodiment, $R’$ is isobutyl.

[000164] In another embodiment of formula IA-ii, both of $R^{3b}$ and $R^{3c}$ are simultaneously hydrogen, $R^1$ and $R^2$ together form a ring as shown below:

[000165] wherein $R^{XX}$ is C1-C6 alkyl. In another embodiment, $R^{XX}$ is methyl, n-propyl, isopropyl, n-butyl, isobutyl, or t-butyl. In yet another embodiment, $R^{XX}$ is isobutyl.

[000166] In another embodiment, the present invention provides compounds recited below in Table 2.

[000167] Table 2
In another embodiment, the present invention provides a compound selected from:

![Chemical Structures](image)

4. General Synthetic Methodology:

The compounds of this invention may be prepared in general by methods known to those skilled in the art. Exemplary synthetic routes are illustrated below for the preparation of the compounds of the present invention.

Compounds of formula IA may be prepared as illustrated in Scheme 1 and Scheme 1A below.

Scheme 1:
Conditions: a) dioxane, reflux, o/n; b) Pd(PPh₃)₄, K₂CO₃, CH₃CN, H₂O, microwave, 120 °C
Compounds of formula IB may be prepared as illustrated in Scheme 2 and Scheme 2A below.

Scheme 2:

**Conditions:**

- a) Pd(OAc)$_2$, PPh$_3$, PrOH, reflux;
- b) CH$_3$ReO$_3$, H$_2$O$_2$, DCM, RT, o/n;
- c) POCl$_3$, 100 °C;
- d) DMSO, 140 °C, o/n

Scheme 2A:
Compounds of formula IC may be prepared as illustrated in Scheme 3 and Scheme 3A below.

**Scheme 3:**

Conditions: a) Pd(OAc)$_2$, PPh$_3$, PrOH, reflux; b) CH$_3$ReO$_2$, H$_2$O$_2$, DCM, 25 °C; c) POCl$_3$, 100 °C; d) DMSO, 140 °C

**Scheme 3A:**

Conditions: a) Pd(PPh$_3$)$_4$, Ag$_2$CO$_3$, benzene, 80 °C; b) i-PrMgCl, aq. quench; c) R$^1$R$^2$NLi, R$^1$R$^2$NH, THF, reflux
Compounds of formula **ID** may be prepared as illustrated in Scheme 4 and Scheme 4A below.

**Scheme 4:**

**Conditions:**
- a) Pd(PPh₃)₄, Xantphos, NaOBut, toluene, microwave, 150 °C
- b) Pd(PPh₃)₄, K₂CO₃, CH₃CN, H₂O, microwave, 120 °C
5. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

As discussed above, the present invention provides compounds that are inhibitors of voltage-gated sodium ion channels and/or calcium channels, and thus the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, and incontinence. Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable
derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[000187] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a voltage-gated sodium ion channel or calcium channel.

[000188] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences, 1977*, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate; butyrate, camphorate; camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxyethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate
salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N\(^+\)(C\(_{1-4}\)alkyl)\(_4\) salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypolyethylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt;
gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[000190] Uses of Compounds and Pharmaceutically Acceptable Compositions

[000191] In yet another aspect, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments, a method for the treatment or lessening the severity of acute, chronic, neuropathic, or inflammatory pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In certain other embodiments, a method for the treatment or lessening the severity of radicular pain, sciatica, back pain, head pain, or neck pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof. In still other embodiments, a method for the treatment or lessening the severity of severe or intractable pain, acute pain, postsurgical pain, back pain, tinnitus or cancer pain is provided comprising administering an effective amount of a compound or a pharmaceutically acceptable composition to a subject in need thereof.
In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, tinnitus or cancer pain.

The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, tinnitus or cancer pain. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and
diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term “patient”, as used herein, means an animal, preferably a mammal, and most preferably a human.

The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylen glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or
suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[000197] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[000198] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[000199] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[000200] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates,
gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar–agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[000201] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[000202] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally,
in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[000203] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[000204] As described generally above, the compounds of the invention are useful as inhibitors of voltage-gated sodium ion channels or calcium channels, preferably N-type calcium channels. In one embodiment, the compounds and compositions of the invention are inhibitors of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2, and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 is implicated in the disease, condition, or disorder. When activation or hyperactivity of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2, is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as a “NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8 or NaV1.9-mediated disease, condition or disorder” or a “CaV2.2-mediated condition or disorder”. Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 is implicated in the disease state.
The activity of a compound utilized in this invention as an inhibitor of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 may be assayed according to methods described generally in the Examples herein, or according to methods available to one of ordinary skill in the art.

In certain exemplary embodiments, compounds of the invention are useful as inhibitors of NaV1.8. In other embodiments, compounds of the invention are useful as inhibitors of NaV1.8 and CaV2.2. In still other embodiments, compounds of the invention are useful as inhibitors of CaV2.2. In yet other embodiments, compounds of the invention are useful as dual inhibitors of NaV1.8 and a TTX-sensitive ion channel such as NaV1.3 or NaV1.7.

It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated". For example, exemplary additional therapeutic agents include, but are not limited to: nonopiod analgesics (indoles such as Etodolac, Indomethacin, Sulindac, Tolmetin; naphthylalkanones such as Nabumetone; oxicams such as Piroxicam; para-aminophenol derivatives, such as Acetaminophen; propionic acids such as Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Naproksen sodium, Oxaprozin; salicylates such as Aspirin, Choline magnesium trisalicylate, Diflunisal; fenamates such as meclofenamic acid, Mefenamic acid; and pyrazoles such as Phenylbutazone); or opioid (narcotic) agonists (such as Codeine, Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Propoxyphene, Buprenorphine,
Butorphanol, Dezocine, Nalbuphine, and Pentazocine). Additionally, non-drug analgesic approaches may be utilized in conjunction with administration of one or more compounds of the invention. For example, anesthesiologic (intraspinal infusion, neural blockade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Seventeenth Edition, Ed. Mark H. Beers and Robert Berkow, Merck Research Laboratories, 1999, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[000208] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[000209] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable
topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

Another aspect of the invention relates to inhibiting one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said said compound. The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Inhibition of one or more of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, NaV1.9, or CaV2.2 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium ion channels in biological and pathological phenomena; and the comparative evaluation of new sodium ion channel inhibitors.

In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

Example

(R)-1-(4-(6-bromopyridin-2-yl)piperazin-1-yl)-2-hydroxy-4-methylpentan-1-one (1a).

\[
\begin{align*}
\text{F} & \quad + \quad \text{OH} \\
\text{Br} & \quad + \quad \text{N} \\
\text{N} & \quad + \quad \text{OH}
\end{align*}
\]

- 58 -
[000215] 2-Bromo-6-fluoropyridine (0.44 g, 2.5 mmol) and (R)-2-hydroxy-4-methyl-1-(piperazin-1-yl)pentan-1-one (0.47 g, 2.5 mmol) in 25 mL dioxane under N₂ were heated to reflux for 16 hours. The solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography (SiO₂, MeOH/CH₂Cl₂) to afford 1a as a colorless oil (0.38 g, 44% yield). LCMS: m/z 356.1 (M+H)⁺ at 3.02 minutes (10% – 99% CH₃CN/H₂O), (10%–99% CH₃CN (0.035% TFA)/H₂O (0.05% TFA).

[000216] (R)-2-hydroxy-1-(4-(6-(2-hydroxyphenyl)pyridin-2-yl)piperazin-1-yl)-4-methylpentan-1-one (4).

[000217] 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol (25 µL, 120 µmol), 1a (36 mg, 100 µmol), Pd(Ph₃P)₄ (12 mg, 10 µmol), K₂CO₃ (28 mg, 200 µmol), CH₃CN (900 µL), and H₂O (100 µL) were sealed in a microwave vessel and heated by microwave irradiation at 120 °C for 15 minutes. The reaction was filtered and purified by reverse phase HPLC to give 4. (10% – 99% CH₃CN/H₂O), (10%–99% CH₃CN (0.035% TFA)/H₂O (0.05% TFA). LCMS: m/z 370.1 (M+H)⁺ at 2.89 minutes (10% – 99% CH₃CN/H₂O), (10%–99% CH₃CN (0.035% TFA)/H₂O (0.05% TFA).

[000218] Isobutyl 4-(2-chloropyridin-4-yl)piperazine-1-carboxylate (3a).
4-Bromo-2-chloropyridine (125 mg, 0.65 mmol), isobutyl piperazine-1-carboxylate (93 mg, 0.5 mmol), Pd$_2$(dba)$_3$ (10 mg, 10 μmol), t-BuONa (72 mg, 0.75 mmol), and Xantphos (17 mg, 30 μmol) in dry toluene (5 mL) were sealed in a microwave vessel and heated by microwave irradiation at 150 °C for 15 minutes. The reaction was diluted with EtOAc, washed with water, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. Purification by flash chromatography (SiO$_2$, MeOH/CH$_2$Cl$_2$) afforded 3a as a tan oil (94 mg, 63% yield). LCMS: m/z 298.5 (M+H)$^+$ at 1.93 minutes (10% – 99% CH$_3$CN/H$_2$O), (10%–99% CH$_3$CN (0.035% TFA)/H$_2$O (0.05% TFA).

Isobutyl 4-(2-(2-hydroxyphenyl)pyridin-4-yl)piperazine-1-carboxylate (1).

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-phenol (25 μL, 120 μmol), 3a (30 mg, 100 μmol), Pd(Ph$_3$P)$_4$ (12 mg, 10 μmol), K$_2$CO$_3$ (28 mg, 200μmol), CH$_3$CN (900 μL), and H$_2$O (100 μL) were sealed in a microwave vessel and heated by microwave irradiation at 120 °C for 15 minutes. The reaction was filtered and purified by reverse phase HPLC to give compound 1. (10% – 99% CH$_3$CN/H$_2$O), (10%–99% CH$_3$CN (0.035% TFA)/H$_2$O (0.05% TFA). LCMS: m/z 356.1 (M+H)$^+$ at 2.24 minutes (10% – 99% CH$_3$CN/H$_2$O), (10%–99% CH$_3$CN (0.035% TFA)/H$_2$O (0.05% TFA).
2-(2-Chloro-pyridin-4-yl)-phenol (5a).

4-Bromo-2-chloropyridine (310 mg, 1.6 mmol), 531 mg (2.4 mmol) of 2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol, 10.8 mg (0.016 mmol) of Pd(OAc)$_2$, 710 mg (3.3 mmol) of K$_3$PO$_4$ and Xantphos[9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene] (18.6 mg, 0.032 mmol) in toluene: water (5:0.5 mL) were sealed in a microwave vessel and heated by microwave irradiation at 100 °C for 2 minutes. The reaction mixture was cooled and diluted with 10 mL of CH$_2$Cl$_2$, washed with water (5 mL), dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The residue was dissolved in DMSO and purified by reverse phase HPLC (10%–99% CH$_3$CN (0.035% TFA)/H$_2$O (0.05% TFA) to give 5a. LC/MS: m/z 206.1 ([M+H]$^+$), r.t (retention time) = 2.86 min (10%–99% CH$_3$CN (0.035% TFA)/H$_2$O (0.05% TFA) to give 5.

Isobutyl-4-[(4′-(2-hydroxyphenyl)-pyridin-2′-yl]-piperazine-1-carboxylate (5)

Isobutyl piperazine-1-carboxylate (153 mg, 0.82 mmol), 2-(2-chloro-pyridin-4-yl)-phenol (130 mg, 0.63 mmol), Pd$_2$(dba)$_3$ (12 mg, 13 μmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (22 mg, 38 μmol), K$_2$CO$_3$ (174 mg, 1.26 mmol), and toluene (2.1 mL) were sealed in a microwave vessel and heated by microwave irradiation at 140 °C for 3 minutes. The reaction was filtered, and the solvent was evaporated under
reduced pressure. The residue was dissolved in DMSO and purified by reverse phase HPLC (10%–99% CH₃CN (0.035% TFA)/H₂O (0.05% TFA)) to give 5. LC/MS: m/z 356.2 (M+H)⁺ at 2.49 min (10%–99% CH₃CN (0.035% TFA)/H₂O (0.05% TFA)).

[000225] The analytical data for representative compounds of the present invention are shown below in Table 3.

<table>
<thead>
<tr>
<th>Cmpd No.</th>
<th>LC-MS M+1</th>
<th>LC-RT min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>356.3</td>
<td>2.59</td>
</tr>
<tr>
<td>3</td>
<td>356.1</td>
<td>3.35</td>
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<tr>
<td>4</td>
<td>370.1</td>
<td>2.89</td>
</tr>
<tr>
<td>5</td>
<td>356.2</td>
<td>2.49</td>
</tr>
</tbody>
</table>

[000226] ASSAYS FOR DETECTING AND MEASURING NaV INHIBITION PROPERTIES OF COMPOUND

[000227] Optical methods for assaying NaV inhibition properties of compounds:

[000228] Compounds of the invention are useful as antagonists of voltage-gated sodium ion channels. Antagonist properties of test compounds were assessed as follows. Cells expressing the NaV of interest were placed into microtiter plates. After an incubation period, the cells were stained with fluorescent dyes sensitive to the transmembrane potential. The test compounds were added to the microtiter plate. The cells were stimulated with either a chemical or electrical means to evoke a NaV dependent membrane potential change from unblocked channels, which was detected and measured with trans-membrane potential-sensitive dyes. Antagonists were detected as a decreased membrane potential response to the stimulus. The optical membrane potential assay utilized voltage-sensitive FRET sensors described by Gonzalez and Tsien (See, Gonzalez, J. E. and R. Y. Tsien (1995) “Voltage sensing by fluorescence resonance energy transfer in single cells” Biophys J 69(4): 1272-80, and Gonzalez, J. E. and R. Y. Tsien (1997) “Improved indicators of cell membrane potential that use fluorescence resonance energy transfer” Chem Biol 4(4): 269-77) in combination with instrumentation for measuring fluorescence changes such as the Voltage/Ion Probe Reader (VIPR®) (See, Gonzalez, J. E., K. Oades, et al. (1999) “Cell-based assays and instrumentation for screening ion-channel targets” Drug Discov Today 4(9): 431-439).
B) VIPR® optical membrane potential assay method with chemical stimulation

Cell Handling and Dye Loading

24 hours before the assay on VIPR, CHO cells endogenously expressing a NaV1.2 type voltage-gated NaV are seeded in 96-well poly-lysine coated plates at 60,000 cells per well. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

1) On the day of the assay, medium is aspirated and cells are washed twice with 225 μL of Bath Solution #2 (BS#2).

2) A 15 μM CC2-DMPE solution is prepared by mixing 5 mM coumarin stock solution with 10% Pluronic 127 1:1 and then dissolving the mix in the appropriate volume of BS#2.

3) After bath solution is removed from the 96-well plates, the cells are loaded with 80 μL of the CC2-DMPE solution. Plates are incubated in the dark for 30 minutes at room temperature.

4) While the cells are being stained with coumarin, a 15 μL oxonol solution in BS#2 is prepared. In addition to DiSBAC2(3), this solution should contain 0.75 mM ABSC1 and 30 μL veratridine (prepared from 10 mM EtOH stock, Sigma #V-5754).

5) After 30 minutes, CC2-DMPE is removed and the cells are washed twice with 225 μL of BS#2. As before, the residual volume should be 40 μL.

6) Upon removing the bath, the cells are loaded with 80 μL of the DiSBAC2(3) solution, after which test compound, dissolved in DMSO, is added to achieve the desired test concentration to each well from the drug addition plate and mixed thoroughly. The volume in the well should be roughly 121 μL. The cells are then incubated for 20-30 minutes.

7) Once the incubation is complete, the cells are ready to be assayed on VIPR® with a sodium addback protocol. 120 μL of Bath solution #1 is added to stimulate the NaV dependent depolarization. 200 μL tetracaine was used as an antagonist positive control for block of the NaV channel.

Analysis of VIPR® Data:
[000231] Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

\[
R(t) = \frac{\text{intensity}_{460\,\text{nm}} - \text{background}_{460\,\text{nm}}}{\text{intensity}_{580\,\text{nm}} - \text{background}_{580\,\text{nm}}}
\]

[000232] The data is further reduced by calculating the initial (R_i) and final (R_f) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus \( R = R_f/R_i \) is then calculated. For the Na⁺ addback analysis time windows, baseline is 2-7 sec and final response is sampled at 15-24 sec.

[000233] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative (N) and positive (P) controls are calculated as above. The compound antagonist activity \( A \) is defined as:

\[
A = \frac{R - P}{N - P} \times 100
\]

where \( R \) is the ratio response of the test compound

Solutions [mM]

Bath Solution #1: NaCl 160, KCl 4.5, CaCl₂ 2, MgCl₂ 1, HEPES 10, pH 7.4 with NaOH

Bath Solution #2: TMA-Cl 160, CaCl₂ 0.1, MgCl₂ 1, HEPES 10, pH 7.4 with KOH (final K concentration ~ 5 mM)

CC2-DMPE: prepared as a 5 mM stock solution in DMSO and stored at -20°C
DiSBAC$_2$(3): prepared as a 12 mM stock in DMSO and stored at -20°C.
ABSC1: prepared as a 200 mM stock in distilled H$_2$O and stored at room temperature.

**Cell Culture**

[0220] CHO cells are grown in DMEM (Dulbecco’s Modified Eagle Medium; GibcoBRL #10569-010) supplemented with 10% FBS (Fetal Bovine Serum, qualified; GibcoBRL #16140-071) and 1% Pen-Strep (Penicillin-Streptomycin; GibcoBRL #15140-122). Cells are grown in vented cap flasks, in 90% humidity and 10% CO$_2$, to 100% confluence. They are usually split by trypsinization 1:10 or 1:20, depending on scheduling needs, and grown for 2-3 days before the next split.

**C) VIPR® optical membrane potential assay method with electrical stimulation**

[000234] The following is an example of how NaV1.3 inhibition activity is measured using the optical membrane potential method#2. Other subtypes are performed in an analogous mode in a cell line expressing the NaV of interest.

[000235] HEK293 cells stably expressing NaV1.3 are plated into 96-well microtiter plates. After an appropriate incubation period, the cells are stained with the voltage sensitive dyes CC2-DMPE/DiSBAC2(3) as follows.

**Reagents:**
- 100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO
- 10 mM DiSBAC$_2$(3) (Aurora #00-100-010) in dry DMSO
- 10 mM CC2-DMPE (Aurora #00-100-008) in dry DMSO
- 200 mM ABSC1 in H$_2$O
- Hank’s Balanced Salt Solution (Hyclone #SH30268.02) supplemented with 10 mM HEPES (Gibco #15630-080)

[000236] **Loading protocol:**
[000237] **2X CC2-DMPE = 20 μM CC2-DMPE:** 10 mM CC2-DMPE is vortexed with an equivalent volume of 10% pluronic, followed by vortexing in required amount of HBSS containing 10 mM HEPES. Each cell plate will require 5 mL of 2X CC2-DMPE. 50 μL of 2X CC2-DMPE is to wells containing washed cells, resulting in a 10 μM final staining concentration. The cells are stained for 30 minutes in the dark at RT.
2X DiSBAC\(_2\)(3) with ABSC1 = 6\(\mu\)M DiSBAC\(_2\)(3) and 1 mM ABSC1:
The required amount of 10 mM DiSBAC\(_2\)(3) is added to a 50 ml conical tube and mixed with
1 \(\mu\)L 10% pluronic for each mL of solution to be made and vortexed together. Then
HBSS/HEPES is added to make up 2X solution. Finally, the ABSC1 is added.

The 2X DiSBAC\(_2\)(3) solution can be used to solvate compound plates. Note
that compound plates are made at 2X drug concentration. Wash stained plate again, leaving
residual volume of 50 \(\mu\)L. Add 50 uL/well of the 2X DiSBAC\(_2\)(3) w/ ABSC1. Stain for 30
minutes in the dark at RT.

The electrical stimulation instrument and methods of use are described in ION
Channel Assay Methods PCT/US01/21652, herein incorporated by reference. The
instrument comprises a microtiter plate handler, an optical system for exciting the coumarin
dye while simultaneously recording the coumarin and oxonol emissions, a waveform
generator, a current- or voltage-controlled amplifier, and a device for inserting electrodes in
well. Under integrated computer control, this instrument passes user-programmed electrical
stimulus protocols to cells within the wells of the microtiter plate.

**Reagents**

Assay buffer #1
140 mM NaCl, 4.5 mM KCl, 2 mM CaCl\(_2\), 1 mM MgCl\(_2\), 10 mM HEPES, 10 mM glucose,
pH 7.40, 330 mOsm

Pluronic stock (1000X): 100 mg/mL pluronic 127 in dry DMSO
Oxonol stock (3333X): 10 mM DiSBAC\(_2\)(3) in dry DMSO
Coumarin stock (1000X): 10 mM CC2-DMPE in dry DMSO
ABSC1 stock (400X): 200 mM ABSC1 in water

**Assay Protocol**

1. Insert or use electrodes into each well to be assayed.
2. Use the current-controlled amplifier to deliver stimulation wave pulses for 3 s. Two
   seconds of pre-stimulus recording are performed to obtain the un-stimulated intensities. Five
   seconds of post-stimulation recording are performed to examine the relaxation to the resting
   state.
Data Analysis

[000241] Data are analyzed and reported as normalized ratios of background-subtracted emission intensities measured in the 460 nm and 580 nm channels. Background intensities are then subtracted from each assay channel. Background intensities are obtained by measuring the emission intensities during the same time periods from identically treated assay wells in which there are no cells. The response as a function of time is then reported as the ratios obtained using the following formula:

\[
R(t) = \frac{\text{intensity}_{460\text{ nm}} - \text{background}_{460\text{ nm}}}{\text{intensity}_{580\text{ nm}} - \text{background}_{580\text{ nm}}}
\]

[000242] The data is further reduced by calculating the initial (R_i) and final (R_f) ratios. These are the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus \( R = R_f/R_i \) is then calculated.

[000243] Control responses are obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative (N) and positive (P) controls are calculated as above. The compound antagonist activity (A) is defined as:

\[
A = \frac{R - P}{N - P} \times 100
\]

where R is the ratio response of the test compound.

ELECTROPHYSIOLOGY ASSAYS FOR NaV ACTIVITY AND INHIBITION OF TEST COMPOUNDS

[000244] Patch clamp electrophysiology was used to assess the efficacy and selectivity of sodium channel blockers in dorsal root ganglion neurons. Rat neurons were isolated from the dorsal root ganglia and maintained in culture for 2 to 10 days in the presence of NGF (50 ng/ml) (culture media consisted of NeurobasalA supplemented with B27, glutamine and antibiotics). Small diameter neurons (nociceptors, 8-12 μm in diameter) have been visually
identified and probed with fine tip glass electrodes connected to an amplifier (Axon Instruments). The "voltage clamp" mode has been used to assess the compound's IC50 holding the cells at −60 mV. In addition, the "current clamp" mode has been employed to test the efficacy of the compounds in blocking action potential generation in response to current injections. The results of these experiments have contributed to the definition of the efficacy profile of the compounds.

**VOLTAGE-CLAMP assay in DRG neurons**

[000245] TTX-resistant sodium currents were recorded from DRG somata using the whole-cell variation of the patch clamp technique. Recordings were made at room temperature (~220 C) with thick walled borosilicate glass electrodes (WPI; resistance 3-4 MΩ) using an Axopatch 200B amplifier (Axon Instruments). After establishing the whole-cell configuration, approximately 15 minutes were allowed for the pipette solution to equilibrate within the cell before beginning recording. Currents were lowpass filtered between 2-5 kHz and digitally sampled at 10 kHz. Series resistance was compensated 60-70% and was monitored continuously throughout the experiment. The liquid junction potential (~7 mV) between the intracellular pipette solution and the external recording solution was not accounted for in the data analysis. Test solutions were applied to the cells with a gravity driven fast perfusion system (SP-77; Warner Instruments).

[000246] Dose-response relationships were determined in voltage clamp mode by repeatedly depolarizing the cell from the experiment specific holding potential to a test potential of +10mV once every 60 seconds. Blocking effects were allowed to plateau before proceeding to the next test concentration.

**Solutions**

[000247] Intracellular solution (in mM): Cs-F (130), NaCl (10), MgCl2 (1), EGTA (1.5), CaCl2 (0.1), HEPES (10), glucose (2), pH = 7.42, 290 mOsm.

[000248] Extracellular solution (in mM): NaCl (138), CaCl2 (1.26), KCl (5.33), KH2PO4 (0.44), MgCl2 (0.5), MgSO4 (0.41), NaHCO3 (4), Na2HPO4 (0.3), glucose (5.6), HEPES (10), CdCl2 (0.4 ), NiCl2 (0.1), TTX (0.25 x 10^-3).

**CURRENT-CLAMP assay for NaV channel inhibition activity of compounds**
Cells were current-clamped in whole-cell configuration with a MultiClamp 700A amplifier (Axon Inst). Borosilicate pipettes (4-5 MOhm) were filled with (in mM): 150 K-gluconate, 10 NaCl, 0.1 EGTA, 10 Heps, 2 MgCl₂, (buffered to pH 7.34 with KOH). Cells were bathed in (in mM): 140 NaCl, 3 KCl, 1 MgCl₂, 1 CaCl₂, and 10 Heps). Pipette potential was zeroed before seal formation; liquid junction potentials were not corrected during acquisition. Recordings were made at room temperature.

The activity of selected compounds of the present invention against NaV 1.8 channel is shown below in Table 4. In Table 4, the symbols have the following meanings: “+++” means < 10 μM; “++” means between 10 μM and 15 μM; and “+” means > 15 μM.

<table>
<thead>
<tr>
<th>Cmpd #</th>
<th>IC50 μM</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>+++</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
</tr>
</tbody>
</table>
What is claimed is:

1. A compound of formula **IA**, formula **IB** formula **IC**, or formula **ID**:

   \[ \text{or a pharmaceutically acceptable salt thereof,} \]

   \[ \text{wherein:} \]

   \[ W = \text{OR'}, \text{SR'}, \text{N(R')}_2, \text{CHF}_2, \text{or CH}_2\text{F}; \]

   \[ R^1 \text{ and } R^2, \text{ taken together with the nitrogen atom to which they are bound, form an optionally substituted 3-8-membered, monocyclic saturated or partially unsaturated ring having 0-3 additional heteroatoms independently selected from nitrogen, sulfur, or oxygen; wherein the ring formed by } R^1 \text{ and } R^2 \text{ taken together, are each optionally and independently substituted at one or more substitutable carbon, nitrogen, or sulfur atoms with } z \text{ independent occurrences of } \sim R^4, \text{ wherein } z \text{ is 0-5;} \]

   \[ y = 0-5; \]

   \[ R^{3a} \{is hydrogen or X-R^Q, wherein X is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of X other than the carbon atom directly attached to the pyridinyl ring are optionally and independently replaced by } \text{-NR}, \text{-S}, \text{-O}, \text{-CS, -CO}_2, \text{-OCO, -CO,} \text{-COCO, -CONR, -NRCO}_2, \text{-SO}_2\text{NR, -NRSO}_2_2, \text{-CONRNR, -NRCONR, -OCONR, -NRNR, -NRSO}_2\text{NR, -SO}_2, \text{-SO, -PO}, \text{-PO}_2, \text{-OP(O)(OR), or -POR;}} \]
R<sup>0</sup> is independently selected from -R', =O, =NR', halogen, -NO<sub>2</sub>, -CN, -OR', -SR', -N(R')<sub>2</sub>, -NR'COR', -NR'CON(R')<sub>2</sub>, -NR'CO<sub>2</sub>R', -COR', -CO<sub>2</sub>R', -OCOR', -CON(R')<sub>2</sub>, -OCON(R')<sub>2</sub>, -SOR', -SO<sub>2</sub>R', -SO<sub>2</sub>N(R')<sub>2</sub>, -NR'SO<sub>2</sub>R', -NR'SO<sub>2</sub>N(R')<sub>2</sub>, -COCOR', -COCH<sub>3</sub>COR', -OP(O)(OR')<sub>2</sub>, -P(O)(OR')<sub>2</sub>, -OP(O)OR', -P(O)OR', -PO(R')<sub>2</sub>, or -OP(O)(R')<sub>2</sub>;

each occurrence of R<sup>3b</sup>, R<sup>3c</sup>, R<sup>4</sup>, and R<sup>5</sup> is independently Q-R<sup>x</sup>; wherein Q is a bond or is a C<sub>1</sub>-C<sub>6</sub> alkyldiene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by -NR-, -S-, -O-, -CS-, -CO<sub>2</sub>-, -OCO-, -CO-, -COCO-, -CONR-, -NRCON-,-NRCON-, -CONNR-, -NRCO-, -NR<sub>2</sub>C<sub>2</sub>-,-SO<sub>2</sub>NR-, -NRSO<sub>2</sub>-,-CONNR-, -NRCO-, -NRCON-, -NRCO-, -NRSO<sub>2</sub>NR-, -SO<sub>2</sub>-,-PO-, -PO<sub>2</sub>-,-OP(O)(OR)-, or -POR-; and each occurrence of R<sup>x</sup> is independently selected from -R', halogen, -NO<sub>2</sub>, -CN, -OR', -SR', -N(R')<sub>2</sub>, -NR'COR', -NR'CON(R')<sub>2</sub>, -NR'CO<sub>2</sub>R', -COR', -CO<sub>2</sub>R', -OCOR', -CON(R')<sub>2</sub>, -OCON(R')<sub>2</sub>, -SOR', -SO<sub>2</sub>R', -SO<sub>2</sub>N(R')<sub>2</sub>, -NR'SO<sub>2</sub>R', -NR'SO<sub>2</sub>N(R')<sub>2</sub>, -COCOR', -COCH<sub>3</sub>COR', -OP(O)(OR')<sub>2</sub>, -P(O)(OR')<sub>2</sub>, -PO(O)OR', -PO(R')<sub>2</sub>, or -OP(O)(R')<sub>2</sub>;

each occurrence of R is independently hydrogen or an optionally substituted C<sub>1</sub>-C<sub>6</sub> aliphatic group;

each occurrence of R' is independently hydrogen or an optionally substituted C<sub>1</sub>-C<sub>6</sub> aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

provided that:

iii) in formula I-D, when R<sup>3a</sup>, R<sup>3b</sup>, and R<sup>3c</sup> are hydrogen, and R<sup>1</sup> and R<sup>2</sup>,

together with the nitrogen atom form a 4-morpholinyl ring, then W is not SR' wherein R' is methyl or 1H-benzimidazol-2-yl;

iv) in formula I-A, when R<sup>3a</sup>, R<sup>3b</sup>, and R<sup>3c</sup> are hydrogen, and R<sup>1</sup> and R<sup>2</sup>,

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together with the nitrogen atom form a 4-morpholinyl ring, then W, together with R^5 and the phenyl ring, is not:

\[
\begin{array}{c}
\text{OMe} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{H}
\end{array}
\]

iii) in formula I-B, when y is 0, R3a and R3b are both hydrogen, R1 and R2 taken together form 4-hydroxy-2-hydroxymethyl-pyrrolidin-1-yl, then R^3c is not –NRCO–R^X or –NRCOR’.

2. A compound according to claim 1, wherein R^1 and R^2 taken together form an azetidinyl ring:

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{(R^4)_2}
\end{array}
\]

aa.

3. A compound according to claim 1, wherein R^1 and R^2 taken together form a pyrrolidiny1 ring:

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{(R^4)_2}
\end{array}
\]

bb.

4. A compound according to claim 1, wherein R^1 and R^2 taken together form a piperidinyl ring:

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{H} \\
\text{H} \\
\text{(R^4)_2}
\end{array}
\]

cc.
5. A compound according to claim 1, wherein \(R^1\) and \(R^2\) taken together form a piperazinyl ring:

\[
\begin{align*}
\text{dd}.
\end{align*}
\]

6. A compound according to claim 1, wherein \(R^1\) and \(R^2\) taken together form a morpholinoyl ring:

\[
\begin{align*}
\text{ee}.
\end{align*}
\]

7. A compound according to claim 1, wherein \(R^1\) and \(R^2\) taken together form a thiomorpholinoyl ring:

\[
\begin{align*}
\text{ff}.
\end{align*}
\]

8. A compound according to claim 1, wherein \(R^1\) and \(R^2\) taken together form an azepanyl ring:

\[
\begin{align*}
\text{gg}.
\end{align*}
\]

9. A compound according to claim 1, wherein \(R^1\) and \(R^2\) taken together form an azocanonyl ring:
10. A compound according to claim 1, wherein R\(^1\) and R\(^2\) taken together form a ring (ii) or (jj) as shown below:

![Chemical Structures](image)

wherein:
G\(_1\) is -N-, -CH-NH-, or -CH-CH\(_2\)-NH-;
each of m\(_1\) and n\(_1\) is independently 0-3, provided that m\(_1\)+n\(_1\) is 2-6;
p\(_1\) is 0-2;
z is 0-4;
each R\(^{xx}\) is hydrogen, C\(_{1-6}\) aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein R\(^{xx}\) is optionally substituted with w\(_1\) independent occurrences of -R\(^{11}\), wherein w\(_1\) is 0-3;
provided that both R\(^{xx}\) are not simultaneously hydrogen;
R\(^{yy}\) is hydrogen, -COR', -CO\(_2\)R', -CON(R')\(_2\), -SOR', -SO\(_2\)R', -SO\(_2\)N(R')\(_2\), -COCOR', -COCH\(_2\)COR', -P(O)(OR')\(_2\), -P(O)\(_2\)OR', or -PO(R');
each occurrence of $R^{11}$ is independently $Q$-$R^X$, wherein $Q$ is a bond or is a C$_1$-C$_6$ alkylidene chain wherein up to two non-adjacent methylene units of $Q$ are optionally and independently replaced by $-NR_2, -S_2, -O_2, -CS_2, -CO_2, -OCO_2, -COC_2, -CONR_2, -NRCO_2, -NRCO_2, -SO_2NR_2, -NRSO_2NR_2, -CONNR_2, -NRCO_2NR_2, -OCONR_2, -NRNR_2, -NRSO_2NR_2, -SO_2, -SO_2, -PO_2, -PO_2, -OP(O)(OR)' or -POR'; and each occurrence of $R^X$ is independently selected from $-R'$, halogen, $=O$, $=NR'$, $-NO_2$, $-CN$, $-OR'$, $-SR'$, $-N(R')_2$, $-NR'COR'$, $-NR'CONR'_{2}$, $-NR'CO_2R'$, $-COR'$, $-CO_2R'$, $-OCOR'$, $-CON(R')_2$, $-OCON(R')_2$, $-SOR'$, $-SO_2R'$, $-SO_2N(R')_2$, $-NR'SO_2R'$, $-NR'SO_2N(R')_2$, $-COCOR'$, $-COCH_2COR'$, $-OP(O)(OR')_2$, $-P(O)(OR')_2$, $-OP(O)_{2}OR'$, $-P(O)_{2}OR'$, $-PO(R')_2$, or $-OPO(R')_2$; and

each occurrence of $R$ is independently hydrogen or C$_1$-C$_6$ aliphatic group having up to three substituents; and each occurrence of $R'$ is independently hydrogen or C$_1$-C$_6$ aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein $R'$ has up to four substituents; or $R$ and $R'$, two occurrences of $R$, or two occurrences of $R'$, are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

11. The compound according to claim 10, wherein one $R'^X$ is hydrogen and the other $R'^X$ is not hydrogen.

12. The compound according to claim 10, wherein both $R'^X$ are not hydrogen.

13. The compound according to claim 10, wherein $p_1$ is 0.

14. The compound according to claim 10, wherein $p_1$ is 1.

15. The compound according to claim 10, wherein $p_1$ is 2.
16. The compound according to claim 10, wherein \( m_1 \) and \( n_1 \) each is 1.

17. The compound according to claim 10, wherein \( m_1 \) and \( n_1 \) each is 2.

18. The compound according to claim 10, wherein \( m_1 \) and \( n_1 \) each is 3.

19. The compound according to any one of claims 10-18, wherein \( R^{XX} \) is \( C_{1-6} \) aliphatic group, wherein \( R^{XX} \) is optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.

20. The compound according to any one of claims 10-19, wherein \( R^{XX} \) is \( C1-C6 \) alkyl group optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.

21. The compound according to any one of claims 10-20, \( R^{XX} \) is \( C1-C6 \) alkyl group.

22. The compound according to claim 10, wherein \( R^{XX} \) is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein \( R^{XX} \) is optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.

23. The compound according to claim 10, wherein \( R^{XX} \) is a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein \( R^{XX} \) is optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.

24. The compound according to claim 10, wherein \( R^{XX} \) is an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein \( R^{XX} \) is optionally substituted with \( w_1 \) independent occurrences of \(-R^{11}\), wherein \( w_1 \) is 0-3.
25. The compound according to any one of claims 10-24, wherein $R^{YY}$ is hydrogen, -
COR', -CO$_2$R', -CON(R')$_2$, -SOR', -SO$_2$R', -SO$_2$N(R')$_2$, -COCOR', -COCH$_2$COR', -

P(O)(OR')$_2$, -P(O)$_2$OR', or -PO(R').

26. The compound according to claim 25, wherein $R^{YY}$ is hydrogen.

27. The compound according to claim 25, wherein $R^{YY}$ is -COR', -CO$_2$R', -
CON(R')$_2$, -SOR', -SO$_2$R', -SO$_2$N(R')$_2$, -COCOR', -COCH$_2$COR', -P(O)(OR')$_2$, -P(O)$_2$OR',

or -PO(R').

28. The compound according to any one of claims 10-27, wherein R is hydrogen.

29. The compound according to any one of claims 10-27, wherein R is C1-C6 alkyl.

30. The compound according to any one of claims 10-27, wherein R is methyl, ethyl,
propyl, or butyl.

31. The compound according to claim 10, wherein $R^{YY}$ is hydrogen, one $R^{XX}$ is
hydrogen, and the other $R^{XX}$ is C1-C6 alkyl.

32. The compound according to claim 10, wherein $p_1$ is 0, $R^{YY}$ is hydrogen, one $R^{XX}$
is hydrogen, and the other $R^{XX}$ is C1-C6 alkyl.

33. The compound according to claim 10, wherein $R^{YY}$ is hydrogen, one $R^{XX}$ is
hydrogen, and the other $R^{XX}$ is C1-C6 alkyl.

34. The compound according to claim 10, wherein $p_1$ is 0, $R^{YY}$ is hydrogen, one $R^{XX}$
is hydrogen, and the other $R^{XX}$ is C1-C6 alkyl.

35. The compound according to claim 1, wherein $R^1$ and $R^2$ together form a ring as
shown below:
36. The compound according to claim 35, wherein R'* is C1-C6 alkyl.

37. The compound according to claim 35, wherein R'* is methyl, n-propyl, isopropyl, n-butyl, isobutyl, or t-butyl.

38. The compound according to claim 1, wherein R¹ and R² taken together form ring (kk) as shown below:

```
B

R

={(Sp)q}

(R¹)z

G₃

p₂

N

n₂

m₂

kk
```

G₃ is -N-, or CH;
each of m₂ and n₂ is independently 0-3, provided that m₂ + n₂ is 2-6;
p₂ is 0-2; provided that when G₃ is N, then p₂ is not 0;
q₂ is 0 or 1;
z is 0-4;
Sp is a bond or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by -O-, -S-, -CO-, -CS-, -COCO-, -CONR'-, -CONR'NR'-, -CO₂-, -OCO-, -NR'CO₂-, -NR'CONR'-, -OCONR'-, -NR'NR', -NR'NR'CO-, -NR'CO-, -SO-, -SO₂-, -NR', -SO₂NR', NR'SO₂, or -NR'SO₂NR';
ring B is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of \(-R^{12}\), wherein \(w_2\) is 0-4; each occurrence of \(R^{12}\) is independently \(Q-R^X\); wherein Q is a bond or is a C\(_1\)-C\(_6\) alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally and independently replaced by \(-\text{NR}_2\), \(-\text{S}_2\), \(-\text{O}_2\), \(-\text{CS}_2\), \(-\text{CO}_2\), \(-\text{O}_2\text{C}_2\), \(-\text{CO}_2\text{C}_2\), \(-\text{CONR}_2\), \(-\text{NR}_2\text{CO}_2\), \(-\text{SO}_2\text{NR}_2\), \(-\text{NRSO}_2\), \(-\text{CONRN}_2\), \(-\text{COCO}_2\), \(-\text{NRCON}_2\), \(-\text{OCON}_2\), \(-\text{RNOR}_2\), \(-\text{NRSO}_2\text{NR}_2\), \(-\text{SO}_2\), \(-\text{PO}_2\), \(-\text{PO}_2\), \(-\text{OP(O)}(OR)\), or \(-\text{POR}\); and each occurrence of \(R^X\) is independently selected from \(-R'\), halogen, \(=\text{O}\), \(=\text{NR}'\), \(-\text{NO}_2\), \(-\text{CN}\), \(-\text{OR}'\), \(-\text{SR}'\), \(-\text{N(R')}_2\), \(-\text{NR'COR}'\), \(-\text{NR'CON(R')}_2\), \(-\text{NR'CO}_2\text{R}'\), \(-\text{COR}'\), \(-\text{CO}_2\text{R}'\), \(-\text{OCOR}'\), \(-\text{CON(R')}_2\), \(-\text{OCON(R')}_2\), \(-\text{SOR}'\), \(-\text{SO}_2\text{R}'\), \(-\text{SO}_2\text{N(R')}_2\), \(-\text{NR'SO}_2\text{R}'\), \(-\text{NR'SO}_2\text{N(R')}_2\), \(-\text{COCOR}'\), \(-\text{COCH}_2\text{COR}'\), \(-\text{OP(O)(OR')}_2\), \(-\text{P(O)(OR')}_2\), \(-\text{PO}(\text{OR})_2\), \(-\text{PO}(\text{OR})_2\), or \(-\text{PO}(\text{OR})_2\); and

each occurrence of R is independently hydrogen or C\(_1\)-C\(_6\) aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C\(_1\)-C\(_6\) aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

39. The compound according to claim 38, wherein G\(_3\) is N.

40. The compound according to claim 38, wherein G\(_3\) is CH.

41. The compound according to any one of claims 38-40, wherein p\(_2\) is 0.
42. The compound according to any one of claims 38-40, wherein p is 1.

43. The compound according to any one of claims 38-40, wherein p is 2.

44. The compound according to any one of claims 38-43, wherein q is 0.

45. The compound according to any one of claims 38-43, wherein q is 1.

46. The compound according to claim 38, wherein p is 1, and q is 1.

47. The compound according to claim 38, wherein G is CH, p is 0, and q is 1.

48. The compound according to claim 38, wherein m and n each is 1.

49. The compound according to any one of claims 38-48, wherein m and n each is 2.

50. The compound according to any one of claims 38-49, wherein S is selected from -O-, -S-, or -NR'.

51. The compound according to any one of claims 38-50, wherein S is -O-.

52. The compound according to any one of claims 38-50, wherein S is -NR'.

53. The compound according to any one of claims 38-50, wherein S is -NH-

54. The compound according to any one of claims 38-53 wherein ring B is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of -R', wherein w is 0-4.
55. The compound according to any one of claims 38-54, wherein ring B is a 4-8 membered, saturated, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with \( w_2 \) independent occurrences of \(-R_{12}^1\), wherein \( w_2 \) is 0-4.

56. The compound according to any one of claims 38-55, wherein ring B is a 5-6 membered, saturated, monocyclic heterocyclic ring having 1-2 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with \( w_2 \) independent occurrences of \(-R_{12}^1\), wherein \( w_2 \) is 0-4.

57. The compound according to any one of claims 38-56, wherein \( w_2 \) is 0.

58. The compound according to any one of claims 38-57, wherein ring B is tetrahydrofuranyl.

59. The compound according to claim 38, wherein Sp is a bond, O, or \(-O-CH_2-\); \( p_2 \) is 1; R is hydrogen; and \( n_2 \) and \( m_2 \) are both simultaneously 1 or 2.

60. The compound according to any one of claims 38-59, wherein R is hydrogen.

61. The compound according to claim 60, wherein R is C1-C6 alkyl.

62. The compound according to claim 60, wherein R is methyl, ethyl, propyl, or butyl.

63. The compound according to claim 1, wherein \( R^1 \) and \( R^2 \) taken together form a ring of formula (kk-i) or formula (kk-ii):
64. The compound according to claim 63, wherein ring B is a 5-6 membered, saturated, monocyclic heterocyclic ring having 1-2 heteroatoms selected from O, S, or N, wherein ring B is optionally substituted with w independent occurrences of \(-R^{12}\), wherein \(w_2\) is 0-4.

65. The compound according to any one of claims 63-64, wherein R is hydrogen.

66. The compound according to claim 65, wherein R is hydrogen and ring B is tetrahydrofuranyl.

67. The compound according to any one of claims 63-66, wherein Sp is a bond, \(-O-,\) or \(-O-CH_2-\).

68. The compound according to claim 1, wherein \(R^1\) and \(R^2\) taken together form a ring (II):
wherein:

each of \( m_3 \) and \( n_3 \) is independently 0-3, provided that \( m_3+n_3 \) is 2-6;

\( z \) is 0-4;

\( \text{Sp}^3 \) is \(-\text{O}_, -\text{S}_, -\text{NR}^-, \) or a C1-C6 alkylidene linker, wherein up to two methylene units are optionally and independently replaced by \(-\text{O}_, -\text{S}_, -\text{CO}_-, -\text{CS}_-, -\text{COCO}_-, -\text{CONR}^-, -\text{CONR}^2\text{NR}^-, -\text{CO}_2-, -\text{OCO}_-, -\text{NR}^\prime\text{CO}_2-, -\text{NR}^\prime\text{CONR}^-, -\text{OCONR}^-, -\text{NR}^\prime\text{NR}^-, -\text{NR}^\prime\text{CO}_-, -\text{NR}^\prime\text{CO}_-, -\text{SO}_-, -\text{SO}_2-, -\text{NR}^-, -\text{SO}_2\text{NR}^-, \text{NR}^\prime\text{SO}_2-, \text{OR}^\prime\text{SO}_2\text{NR}^-, \) provided that \( \text{Sp}^3 \) is attached to the carbonyl group through an atom other than carbon;

ring \( \text{B}_3 \) is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring \( \text{B}_3 \) is optionally substituted with \( w \) independent occurrences of \(-\text{R}^{13} \), wherein \( w_3 \) is 0-4;

each occurrence of \( \text{R}^{13} \) is independently \( \text{Q}-\text{R}^X \); wherein \( \text{Q} \) is a bond or is a C1-C6 alkylidene chain wherein up to two non-adjacent methylene units of \( \text{Q} \) are optionally and independently replaced by \(-\text{NR}^-, -\text{S}-, -\text{O}-, -\text{CS}-, -\text{CO}_2-, -\text{OCO}_-, -\text{CO}_-, -\text{COCO}_-, -\text{CONR}^-, -\text{NR}^\prime\text{CO}_-, -\text{NR}^\prime\text{CO}_2-, -\text{SO}_2\text{NR}^-, -\text{NR}^\prime\text{SO}_2\text{NR}^-, -\text{NR}^\prime\text{CONR}^-, -\text{OCONR}^-, -\text{NR}^\prime\text{NR}^-, -\text{NR}^\prime\text{CO}_-, -\text{SO}_-, -\text{SO}_2-, -\text{PO}_-, -\text{PO}_2-, -\text{OP}(\text{O})(\text{OR})_-, \) or \(-\text{OR}^\prime\); and each occurrence of \( \text{R}^X \) is independently selected from \(-\text{R}^\prime \), halogen, =O, =NR^-, =NO_, =CN, =OR^-, =SR^-, =N(\text{R}^\prime)_2, -NR^\prime\text{COR}^-, -NR^\prime\text{CON}(\text{R}^\prime)_2, -NR^\prime\text{CO}_2\text{R}^\prime, -\text{COR}^-, -\text{CO}_2\text{R}^\prime, -\text{OCOR}^-, -\text{CON}(\text{R}^\prime)_2, -\text{OCON}(\text{R}^\prime)_2, -\text{SOR}^-, -\text{SO}_2\text{R}^\prime, -\text{SO}_2\text{N}(\text{R}^\prime)_2, -\text{NR}^\prime\text{SO}_2\text{R}^\prime, -\text{NR}^\prime\text{SO}_2\text{N}(\text{R}^\prime)_2, -\text{OCOR}^-, -\text{COCH}_2\text{COR}^-, -\text{OP}(\text{O})(\text{OR})^\prime)_2, -\text{P}(\text{O})(\text{OR})^\prime)_2, -\text{OP}(\text{O})\text{OR}^\prime, -\text{P}(\text{O})\text{OR}^\prime, -\text{PO}(\text{R}^\prime)_2, \) or \(-\text{OP}(\text{R}^\prime)_2; \) and
each occurrence of R is independently hydrogen or C_{1-6} aliphatic group having up to three substituents; and each occurrence of R' is independently hydrogen or C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R' has up to four substituents; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

69. The compound according to claim 68, wherein Sp^3 is selected from -O-, -S-, or -NR'.

70. The compound according to any one of claims 68-69, wherein Sp^3 is -O-.

71. The compound according to claim 68, wherein Sp^3 is -O-CH_2-.

72. The compound according to claim 69, wherein Sp^3 is -NR'.

73. The compound according to claim 69, wherein Sp^3 is -NH-.

74. The compound according to claim 68, wherein Sp^3 is -NH-CH_2-.

75. The compound according to any one of claims 68-74, wherein each of m_3 and n_3 is 1.

76. The compound according to claim 75, wherein each of m_3 and n_3 is 2.

77. The compound according to any one of claims 68-76, wherein ring B_3 is a 4-8 membered, saturated, partially unsaturated, or aromatic, monocyclic heterocyclic ring having
1-4 heteroatoms selected from O, S, or N, wherein ring B₃ is optionally substituted with w independent occurrences of -R¹³, wherein w₃ is 0-4.

78. The compound according to claim 77, wherein ring B₃ is a 4-8 membered, saturated, monocyclic heterocyclic ring having 1-4 heteroatoms selected from O, S, or N, wherein ring B₃ is optionally substituted with w independent occurrences of -R¹³, wherein w₃ is 0-4.

79. The compound according to anyone of claims 68-76, wherein ring B₃ is a 5-6 membered, saturated, monocyclic heterocyclic ring having 1-2 heteroatoms selected from O, S, or N, wherein ring B₃ is optionally substituted with w independent occurrences of -R¹³, wherein w₃ is 0-4.

80. The compound according to any one of claims 68-79, wherein w₃ is 0.

81. The compound according to any one of claims 68-80, wherein ring B₃ is tetrahydrofuranyl.

82. The compound according to claim 68, wherein, Sp³ is a bond, O, or -O-CH₂--; R is hydrogen; and n₃ and m₃ are both simultaneously 1 or 2.

83. The compound according to any one of claims 68-83, wherein R is hydrogen.

84. The compound according to any one of claims 68-83, wherein R is Cl-C₆ alkyl.

85. The compound according to claim 84, wherein R include methyl, ethyl, propyl, or butyl.

86. The compound according to any one of claims 68-85, wherein z is 0.
87. The compound according to any one of claims 68-76, wherein ring B₃ is a 5-6 membered, saturated, monocyclic heterocyclic ring having 1-2 heteroatoms selected from O, S, or N, wherein ring B₃ is optionally substituted with w₃ independent occurrences of -R¹³, wherein w is 0-4.

88. The compound according to claim 1, wherein R¹ and R² taken together form a ring (mm):

![Diagram]

wherein:
- each of m₄ and n₄ is independently 0-3, provided that m₄ + n₄ is 2-6;
- p₄ is 1-2;
- RYZ is C₁-C₆ aliphatic group, optionally substituted with w₄ independent occurrences of -R¹⁴, wherein w₄ is 0-3;
each occurrence of \( R \) is independently hydrogen or \( C_{1-6} \) aliphatic group having up to three substituents; and each occurrence of \( R' \) is independently hydrogen or \( C_{1-6} \) aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein \( R' \) has up to four substituents; or \( R \) and \( R' \), two occurrences of \( R \), or two occurrences of \( R' \), are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

89. The compound according to claim 88, wherein \( p_4 \) is 1.

90. The compound according to claim 88, wherein \( p_4 \) is 2.

91. The compound according to any one of claims 87-90, wherein \( m_4 \) and \( n_4 \) each is 1.

92. The compound according to any one of claims 87-90, wherein \( m_4 \) and \( n_4 \) each is 2.

93. The compound according to any one of claims 87-90, wherein \( m_4 \) and \( n_4 \) each is 3.

94. The compound according to any one of claims 88-93, wherein \( R^{YZ} \) is \( C_{1-6} \) alkyl, optionally substituted with \( w_4 \) independent occurrences of \( -R^{14} \), wherein \( w_4 \) is 0-3.

95. The compound according to claim 94, wherein \( R^{YZ} \) is \( C_{1-4} \) alkyl group optionally substituted with \( w_4 \) independent occurrences of \( -R^{14} \), wherein \( w_4 \) is 0-3.

96. The compound according to claim 94, wherein \( R^{YZ} \) is \( C_{1-6} \) alkyl group.
97. The compound according to any one of claims 87-96, wherein R is hydrogen.

98. The compound according to any one of claims 87-96, wherein R is C1-C6 alkyl.

99. The compound according to claim 98, wherein R is methyl, ethyl, propyl, or butyl.

100. The compound according to claim 1, wherein \( R^1 \) and \( R^2 \) are taken together to form a ring (nn):

\[
\begin{array}{c}
\text{nn.}
\end{array}
\]

101. The compound according to claim 100, wherein \( G_1 \) is -N-.

102. The compound according to claim 100, wherein \( G_1 \) is -CH-NH-.

103. The compound according to claim 100, wherein \( G_1 \) is -CH-CH2-NH-.

104. The compound according to any one of claims 100-103, wherein \( R^{YY} \) is hydrogen, one \( R^{XX} \) is hydrogen, and the other \( R^{XX} \) is C1-C6 alkyl.

105. The compound according to any one of claims 100-104, wherein \( p_4 \) is 0, \( R^{YY} \) is hydrogen, one \( R^{XX} \) is hydrogen, and the other \( R^{XX} \) is C1-C6 alkyl.
106. The compound according to claim 1, wherein R^1 and R^2 are taken together to form a ring (pp):

\[
\begin{array}{c}
\text{pp.}
\end{array}
\]

107. The compound according to claim 106, wherein R^{YY} is hydrogen, one R^{XX} is hydrogen, and the other R^{XX} is C1-C6 alkyl.

108. The compound according to any one of claims 100-107, wherein p_4 is 0, R^{YY} is hydrogen, one R^{XX} is hydrogen, and the other R^{XX} is C1-C6 alkyl.

109. The compound according to any one of claims 1-108, wherein W is OR'.

110. The compound according to claim 109, wherein W is OH.

111. The compound according to any one of claims 1-110, wherein W is SR'.

112. The compound according to claim 111, wherein W is SH.

113. The compound according to any one of claims 1-110, wherein W is N(R')2.

114. The compound according to claim 113, wherein W is NHR'.
115. The compound according to claim 114, wherein W is NH₂.

116. The compound according to any one of claims 1-110, wherein W is CHF₂, or CH₂F.

117. The compound according to claim 116, wherein W is CHF₂.

118. The compound according to claim 116, wherein W is CH₂F.

119. The compound according to any one of claims 1-118, wherein z is 0-5.

120. The compound according to claim 119, wherein z is 1-3.

121. The compound according to claim 120, wherein z is 1-2.

122. The compound according to claim 121, wherein z is 1.

123. The compound according to any one of claims 1-122, wherein R⁴ is independently halogen, CN, NO₂, -N(R’), -N(R’), -CH₂N(R’), -OR’, -CH₂OR’, -SR’, -CH₂SR’, -COOR’, -NRCOR’, -CON(R’), -OCO(NR’), -CON(R’), -COR’, -NHCOOR’, -SO₂R’, -SO₂N(R’), or an optionally substituted group selected from C₁₋₆alkyl, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC₁₋₆alkyl, heteroarylc₁₋₆alkyl, cycloaliphaticC₁₋₆alkyl, or heterocycloaliphaticC₁₋₆alkyl.

124. The compound according to claim 123, wherein R⁴ is independently Cl, Br, F, CF₃, CH₃, -CH₂CH₃, CN, -COOH, -N(CH₃)₂, -N(Et)₂, -N(iPr)₂, -O(CH₂)₃OCH₃, -CONH₂, -COOCH₃, -OH, -CH₂OH, -NHC(O)CH₃, -SO₂NH₂, -SO₂(CH₂)₃CH₃, -SO₂CH(CH₃)₂, -SO₂N(CH₃)₂, -SO₂CH₂CH₃, -C(O)OCH₂CH(CH₃)₂, -C(O)NHCH₂CH(CH₃)₂, -NHCOOCH₃, -C(O)C(CH₃)₃, -COO(CH₂)₂CH₃, -C(O)NHCH(CH₃)₂, -C(O)CH₂CH₃, or an optionally
substituted group selected from -piperidinyl, piperazinyl, morpholino, C14alkoxy, phenyl, phenyloxy, benzyl, benzyloxy, -CH2cyclohexyl, pyridyl, -CH2pyridyl, or -CH2thiazolyl.

125. The compound according to claim 1, wherein R1 and R2, taken together is optionally substituted azetidin-1-yl (aa), wherein z is 1 or 2 and at least one occurrence of R4 is -NRSO2R’, -NRCOOR’, or -NRCOR’.

126. The compound according to claim 125, wherein R1 and R2, taken together is optionally substituted azetidin-1-yl (aa), wherein z is 1 and R4 is -NRSO2R’.

127. The compound according to claim 125, wherein R1 and R2, taken together is optionally substituted azetidin-1-yl (aa), wherein z is 1 and R4 is -NRCOOR’.

128. The compound according to claim 125, wherein R1 and R2, taken together is optionally substituted azetidin-1-yl (aa), wherein z is 1 and R4 is -NRCOR’.

129. The compound according to claim 1, wherein R1 and R2, taken together is optionally substituted pyrrolidin-1-yl (bb), wherein z is 1 or 2 and R4 is Cl, Br, F, CF3, CH3, -CH2CH3, -OR’, or -CH2OR’.

130. The compound according to claim 1, wherein R1 and R2, taken together is optionally substituted piperidin-1-yl (cc), wherein z is 1 or 2 and at least one occurrence of R4 is Cl, Br, F, CF3, CH3, -CH2CH3, -OR’, or -CH2OR’, -NRSO2R’, -NRCOOR’, or -OCON(R’2).

131. The compound according to claim 130, wherein R1 and R2, taken together is optionally substituted piperidin-1-yl (cc), wherein z is 1 and R4 is F, CF3, CH3, -CH2CH3, -OR’, or -CH2OR’.

132. The compound according to claim 130, wherein R1 and R2, taken together is optionally substituted piperidin-1-yl (cc), wherein z is 1 and R4 is -NRSO2R’.
133. The compound according to claim 130, wherein $R^1$ and $R^2$, taken together is optionally substituted piperidin-1-y1 (ee), wherein $z$ is 1 and $R^4$ is -NRCOOR'.

134. The compound according to claim 1, wherein $R^1$ and $R^2$, taken together is optionally substituted piperazin-1-y1 (dd), wherein $z$ is 1 or 2 and at least one occurrence of $R^4$ is -SOR', -CON(R')$_2$, -SO$_2$N(R')$_2$, -COR', or -COOR'.

135. The compound according to claim 134, wherein $R^1$ and $R^2$, taken together is optionally substituted piperazin-1-y1 (dd), wherein $z$ is 1 and $R^4$ is -SOR'.

136. The compound according to claim 134, wherein $R^1$ and $R^2$, taken together is optionally substituted piperazin-1-y1 (dd), wherein $z$ is 1 and $R^4$ is -COOR'.

137. The compound according to claim 134, wherein $R^1$ and $R^2$, taken together is optionally substituted piperazin-1-y1 (dd), wherein $z$ is 1 and $R^4$ is -CON(R')$_2$.

138. The compound according to claim 134, wherein $R^1$ and $R^2$, taken together is optionally substituted piperazin-1-y1 (dd), wherein $z$ is 1 and $R^4$ is -SO$_2$N(R')$_2$.

139. The compound according to claim 134, wherein $R^1$ and $R^2$, taken together is optionally substituted piperazin-1-y1 (dd), wherein $z$ is 1 and $R^4$ is -COR'.

140. The compound according to claim 1, wherein $R^1$ and $R^2$, taken together is optionally substituted morpholin-1-y1 (ee) or thiomorpholin-1-y1 (ff), wherein $z$ is 1 or 2 and at least one occurrence of $R^4$ is -SOR', -CON(R')$_2$, -SO$_2$N(R')$_2$, -COR', or -COOR'.

141. The compound according to claim 140, wherein $R^1$ and $R^2$, taken together is optionally substituted morpholin-1-y1 (ee) or thiomorpholin-1-y1 (ff), wherein $z$ is 1 and $R^4$ is -SOR'.
142. The compound according to claim 140, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein \( z \) is 1 and \( R^4 \) is -COOR'.

143. The compound according to claim 140, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein \( z \) is 1 and \( R^4 \) is -CON(R')₂.

144. The compound according to claim 140, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein \( z \) is 1 and \( R^4 \) is -SO₂N(R')₂.

145. The compound according to claim 140, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted morpholin-1-yl (ee) or thiomorpholin-1-yl (ff), wherein \( z \) is 1 and \( R^4 \) is -COR'.

146. The compound according to claim 1, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted azepan-1-yl (gg), wherein \( z \) is 1 or 2 and at least one occurrence of \( R^4 \) is -SOR', -CON(R')₂, -SO₂N(R')₂, -COR', or -COOR'.

147. The compound according to claim 146, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted azepan-1-yl (gg), wherein \( z \) is 1 and \( R^4 \) is -SOR'.

148. The compound according to claim 146, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted azepan-1-yl (gg), wherein \( z \) is 1 and \( R^4 \) is -COOR'.

149. The compound according to claim 146, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted azepan-1-yl (gg), wherein \( z \) is 1 and \( R^4 \) is -CON(R')₂.

150. The compound according to claim 146, wherein \( R^1 \) and \( R^2 \), taken together is optionally substituted azepan-1-yl (gg), wherein \( z \) is 1 and \( R^4 \) is -SO₂N(R')₂.
151. The compound according to claim 146, wherein $R^1$ and $R^2$, taken together is optionally substituted azepan-1-yl (gg), wherein $z$ is 1 and $R^4$ is -COR'.

152. The compound according to claim 1, wherein $R^1$ and $R^2$, taken together is optionally substituted azocan-1-yl (hh), wherein $z$ is 1 or 2 and at least one occurrence of $R^4$ is -SOR', -CON($R'$)$_2$, -SO$_2$N($R'$)$_2$, -COR', or -COOR'.

153. The compound according to claim 152, wherein $R^1$ and $R^2$, taken together is optionally substituted azocan-1-yl (hh), wherein $z$ is 1 and $R^4$ is -SOR'.

154. The compound according to claim 152, wherein $R^1$ and $R^2$, taken together is optionally substituted azocan-1-yl (hh), wherein $z$ is 1 and $R^4$ is -COOR'.

155. The compound according to claim 152, wherein $R^1$ and $R^2$, taken together is optionally substituted azocan-1-yl (hh), wherein $z$ is 1 and $R^4$ is -CON($R'$)$_2$.

156. The compound according to claim 152, wherein $R^1$ and $R^2$, taken together is optionally substituted azocan-1-yl (hh), wherein $z$ is 1 and $R^4$ is -SO$_2$N($R'$)$_2$.

157. The compound according to claim 152, wherein $R^1$ and $R^2$, taken together is optionally substituted azocan-1-yl (hh), wherein $z$ is 1 and $R^4$ is -COR'.

158. The compound according to any one of claims 124-157, wherein $y$ is 0-5.

159. The compound according to claim 158, wherein $y$ is 0.

160. The compound according to claim 158, wherein $y$ is 1-3.

161. The compound according to claim 160, wherein $y$ is 1-2.
162. The compound according to claim 161, wherein \( y \) is 1.

163. The compound according to any one of claims 124-162, wherein \( R^5 \) is independently halogen, CN, NO\(_2\), -N(R')\(_2\), -CH\(_2\)N(R')\(_2\), -OR', -CH\(_2\)OR', -SR', -CH\(_2\)SR', -NRCOR', -CON(R')\(_2\), -S(O)\(_2\)N(R')\(_2\), -OCOR', -COR', -CO\(_2\)R', -OCON(R')\(_2\), -NR'SO\(_2\)R', -OP(O)(OR')\(_2\), -PO(O)OR', -P(O)\(_2\)OR', -PO(R')\(_2\), -OP(O)(R')\(_2\), or an optionally substituted group selected from C\(_1\)-C\(_6\)aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC\(_1\)-C\(_6\)alkyl, heteroarylC\(_1\)-C\(_6\)alkyl, cycloaliphaticC\(_1\)-C\(_6\)alkyl, or heterocycloaliphaticC\(_1\)-C\(_6\)alkyl.

164. The compound according to claim 163, wherein \( R^5 \) is independently Cl, Br, F, CF\(_3\), Me, Et, CN, -COOH, -NH\(_2\), -N(CH\(_3\))\(_2\), -N(Et)\(_2\), -N(iPr)\(_2\), -O(CH\(_2\))\(_2\)OCH\(_3\), -CONH\(_2\), -COOCH\(_3\), -OH, -OCH\(_3\), -OCH\(_2\)CH\(_3\), -CH\(_2\)OH, -NHC\(_3\), -SO\(_2\)NH\(_2\), -SO\(_2\)NHC(CH\(_3\))\(_2\), -OCOC(CH\(_3\))\(_3\), -OCOCH\(_2\)C(CH\(_3\))\(_3\), -O(CH\(_2\))\(_2\)N(CH\(_3\))\(_2\), 4-CH\(_3\)-piperazin-1-yl, OCOCH(CH\(_3\))\(_2\), OCO(cyclopentyl), -COCH\(_3\), optionally substituted phenoxy, or optionally substituted benzyloxy.

165. The compound according to claim 164, wherein \( R^5 \) is F.

166. The compound according to claim 163, wherein \( R^5 \) is OR'.

167. The compound according to claim 166, wherein \( R^5 \) is OH.

168. The compound according to claim 1, wherein said compound has formula I-A-i, formula I-B-i, formula I-C-i, or formula I-D-i:
or a pharmaceutically acceptable salt thereof;

wherein R¹, R², R₃ᵃ, R₃ᵇ, and R₃ᶜ are as defined in claim 1 for formula I-A, formula I-B, formula I-C, and formula I-D.

169. The compound according to claim 168, wherein R₃ᵃ is hydrogen.

170. The compound according to claim 168, wherein R₃ᵃ is X-R⁰.

171. The compound according to claim 170, wherein X is a C₁-C₆ alkylidene.

172. The compound according to claim 170, wherein X is a C₁-C₄ alkylidene.

173. The compound according to claim 170, wherein X is -CH₂-.


175. The compound according to claim 174, wherein R⁰ is R’.

176. The compound according to claim 168, wherein R₃ᵇ is hydrogen.

177. The compound according to claim 168, wherein R₃ᶜ is hydrogen.
178. The compound according to claim 168, wherein $R^{3b}$ and $R^{3c}$, both are simultaneously hydrogen.

179. The compound according to claim 168, wherein $R^{3b}$ and $R^{3c}$ each is independently halogen, CN, NO$_2$, -N(R')$_2$, -CH$_2$N(R')$_2$, -OR', -CH$_2$OR', -SR', -CH$_2$SR', -COOR', -NRCOR', -CON(R')$_2$, -OCON(R')$_2$, COR', -NHCOOR', -SO$_2$R', -SO$_2$N(R')$_2$, or an optionally substituted group selected from C$_1$-C$_6$ aliphatic, aryl, heteroaryl, cycloaliphatic, heterocycloaliphatic, arylC$_1$-C$_6$alkyl, heteroarylc$_1$-C$_6$alkyl, cycloaliphaticC$_1$-C$_6$alkyl, or heterocycloaliphaticC$_1$-C$_6$alkyl.

180. The compound according to claim 179, wherein each occurrence of $R^{3b}$ and $R^{3c}$ is independently Cl, Br, F, CF$_3$, -OCF$_3$, Me, Et, CN, -COOH, -NH$_2$, -N(CH$_3$)$_2$, -N(Et)$_2$, -N(iPr)$_2$, -O(CH$_2$)$_2$OCH$_3$, -CONH$_2$, -COOCH$_3$, -OH, -OCH$_3$, -OCH$_2$CH$_3$, -CH$_2$OH, -NHCOCH$_3$, -NHCOCH(CH$_3$)$_2$, -SO$_2$NH$_2$, -CONH(cyclopropyl), -CONHCH$_3$, -CONHCH$_2$CH$_3$, or an optionally substituted group selected from -piperidinyl, piperizinyl, morpholino, phenyl, phenyloxy, benzyl, or benzylxy.

181. The compound according to claim 179, wherein each occurrence of $R^{3b}$ and $R^{3c}$ is independently halogen, CN, optionally substituted C$_1$-C$_6$alkyl, OR', N(R')$_2$, CON(R')$_2$, or NRCOR'.

182. The compound according to claim 181, wherein, each $R^{3b}$ and $R^{3c}$ is independently -Cl, -CH$_3$, -CH$_2$CH$_3$, -F, -CF$_3$, -OCF$_3$, -CONHCH$_3$, -CONHCH$_2$CH$_3$, -CONH(cyclopropyl), -OCH$_3$, -NH$_2$, -OCH$_2$CH$_3$, or -CN.

183. The compound according to claim 182, wherein $R^{3b}$ and $R^{3c}$ is independently selected -Cl, -CH$_3$, -CH$_2$CH$_3$, -F, -CF$_3$, -OCF$_3$, -CONHCH$_3$, -CONHCH$_2$CH$_3$, -CONH(cyclopropyl), -OCH$_3$, -NH$_2$, -OCH$_2$CH$_3$, or -CN.
184. The compound according to claim 183, wherein \( R^{3b} \) and \( R^{3c} \) is independently selected -Cl, -CH\(_3\), -CH\(_2\)CH\(_3\), -F, -CF\(_3\), -OCF\(_3\), -OCH\(_3\), or -OCH\(_2\)CH\(_3\).

185. The compound according to claim 168, wherein each \( R^{3b} \) and \( R^{3c} \) is -CON(R')\(_2\), or -NRCOR'.

186. The compound according to claim 1, wherein said compound is selected from compound of formula IA-ii, formula IB-ii, formula IC-ii, and formula ID-ii:

\[
\begin{align*}
\text{IA-ii} & \quad \text{IB-ii} \\
\text{IC-ii} & \quad \text{ID-ii}
\end{align*}
\]

wherein \( R^1, R^2, R^{3b}, \) and \( R^{3c} \) are as defined in claim 1 for formula IA, formula IB, formula IC, and formula ID.

187. The compound according to claim 186, wherein one of \( R^{3b} \) and \( R^{3c} \) is hydrogen.

188. The compound according to claim 186, wherein both of \( R^{3b} \) and \( R^{3c} \) are simultaneously hydrogen.

189. A compound according to claim 1, wherein said compound is selected from:
190. A pharmaceutical composition comprising a compound according to any one of claims 1-189 and a pharmaceutically acceptable adjuvant or carrier.

191. A method for treating or lessening the severity of a disease, disorder, or condition selected from acute, chronic, neuropathic, or inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epilepsy conditions, neurodegenerative disorders, psychiatric disorders such as anxiety and depression, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, severe or intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, or cancer pain, said method comprising the step of administering to said patient an effective amount of a composition according to claim 190.

192. The method according to claim 191, wherein the disease, condition, or disorder is implicated in the activation or hyperactivity of voltage-gated sodium channels.

193. The method according to claim 192, wherein the disease, condition, or disorder is acute, chronic, neuropathic, or inflammatory pain.

194. The method according to claim 192, wherein the disease, condition, or disorder is radicular pain, sciatica, back pain, head pain, or neck pain.
The method according to claim 192, wherein the disease, condition, or disorder is severe or intractable pain, acute pain, postsurgical pain, back pain, or cancer pain.

The method according to claim 192, wherein said disease is selected from femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, including, abdominal; pancreatic; IBS pain; chronic headache pain; migraine; tension headache, including, cluster headaches; chronic neuropathic pain, including, post-herpetic neuralgia; diabetic neuropathy; HIV- associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phantom pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain, including, abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac Pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, including, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cystitis (IC); or prostatitis.
## INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

| INV. | C07D213/74 | A61K31/4439 | A61K31/496 | A61P29/00 |

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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

**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>

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier document but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document relating to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed

**Date of the actual completion of the international search**

4 September 2006

**Date of mailing of the international search report**

14/09/2006

**Name and mailing address of the ISA/ European Patent Office, P.B. 5816 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (31-70) 340-2040, Tx: 31 651 epo nl, Fax: (31-70) 340-3015**

**Authorized officer**

Allard, M
INTERNATIONAL SEARCH REPORT

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:
   Although claims 191-196 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.;
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.;
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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 an additional fee, this Authority did not invite payment of any additional fee.

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.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.
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