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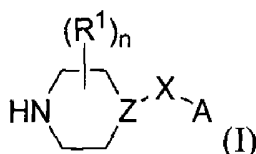
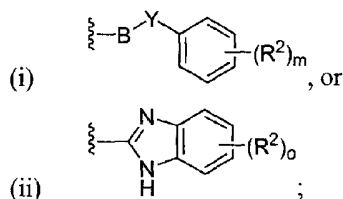
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(54) Title: SUBSTITUTED HETEROCYCLIC DERIVATIVES FOR THE TREATMENT OF PAIN AND EPILEPSY



(57) Abstract: Compounds of formula (I) which are useful in ameliorating conditions characterized by unwanted sodium and/or calcium channel activity, particularly unwanted Na_v 1.7, Na_v 1.8, or Ca_v 3.2 channel activity are disclosed. Specifically, a series of compounds containing piperidine or piperazine linked through an amide, isoxazole or similar linker to an aryl ring are described and are shown to be useful for the treatment of pain or epilepsy. A is selected from Formulae (i) or (ii).

SUBSTITUTED HETEROCYCLIC DERIVATIVES FOR THE TREATMENT OF PAIN AND EPILEPSY

5 Cross-Reference to Related Applications

[0001] This application claims benefit of U.S. Provisional Application No. 61/240,013, filed September 4, 2009, which is hereby incorporated by reference.

Field of the Invention

10 **[0002]** The invention relates to compounds useful in treating conditions associated with calcium channel function, and particularly conditions associated with sodium channel and T-type calcium channel activity. More specifically, the invention concerns compounds containing piperazine-N-arylacetamide and piperazine-aryl-isoxazole derivatives that are useful in treatment of conditions such as epilepsy, 15 cancer, pain, migraine, Parkinson's Disease, depression, schizophrenia, psychosis, and tinnitus.

Background of the Invention

[0003] Voltage-gated sodium (Na_V) channels are present in neurons and excitable
20 tissues where they contribute to processes such as membrane excitability and muscle
contraction (Ogata et al., *Jpn. J. Pharmacol.* (2002) 88(4) 365-77). Nine different
transmembrane α -subunits ($\text{Na}_\text{V}1.1$ -1.9) from a single $\text{Na}_\text{V}1$ family combine with
auxiliary β -subunits that modify channel function to form functional Na_V channels.
Of the nine $\text{Na}_\text{V}1$ α -subunit isoforms, five are expressed in the dorsal root ganglion
25 where they are involved in setting the resting membrane potential and the threshold
for generating action potentials, and also contribute to the upstroke as well as firing of
action potentials during sustained depolarization. In particular, the tetrodotoxin (TTX)
sensitive $\text{Na}_\text{V}1.7$ and TTX- insensitive $\text{Na}_\text{V}1.8$ channel subtypes act as major
30 contributors to both inflammatory and neuropathic pain (Momin et al., *Curr Opin*
Neurobiol. 18(4):383-8, 2008; Rush et al., *J Physiol.* 579(Pt 1):1-14, 2007).

[0004] Calcium channels mediate a variety of normal physiological functions and are also implicated in a number of human disorders. Examples of calcium-mediated human disorders include but are not limited to congenital migraine, cerebellar ataxia,

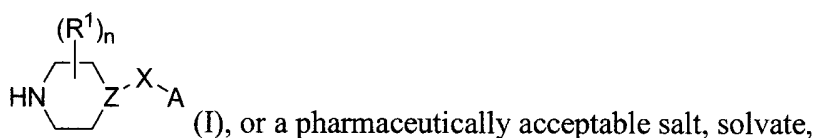
angina, epilepsy, hypertension, ischemia, and some arrhythmias (see, e.g., Janis et al., *Ion Calcium Channels: Their Properties, Functions, Regulation and Clinical Relevance* (1991) CRC Press, London). T-type, or low voltage-activated, channels describe a broad class of molecules that transiently activate at negative potentials and are highly sensitive to changes in resting potential and are involved in various medical conditions. For example, in mice lacking the gene expressing the 3.1 subunit, resistance to absence seizures was observed (Kim et al., *Mol Cell Neurosci* 18(2): 235-245, 2001). Other studies have also implicated the 3.2 subunit in the development of epilepsy (Su et al., *J Neurosci* 22: 3645-3655, 2002).

[0005] Novel allosteric modulators of the slow-inactivation sodium or the slow-inactivation calcium channel are thus desired. Modulators may affect the kinetics and/or the voltage potentials of the slow-inactivation of one or any combination of $\text{Na}_v1.7$, $\text{Na}_v1.8$ or $\text{Ca}_v3.2$ channels.

Summary of the Invention

[0006] The invention relates to compounds useful in conditions modulated by sodium and/or calcium channels. The compounds of the invention include substituted piperidine/piperazine-N-arylacetamide, piperidine/piperazine-N-aryl-isoxazole derivatives, and piperidine/piperazine-benzimidazole derivatives.

[0007] In a first aspect, the invention relates to a compound having a structure according to the following formula,

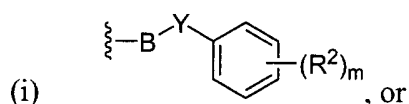
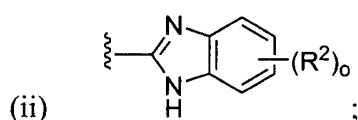


prodrug, or stereoisomer thereof, where

X is an optionally substituted alkylene (1-3C);

Z is N or CR^4 ;

A is selected from



B is N-R^3 or an optionally substituted isoxazolyl;

Y is a bond or an optionally substituted alkylene (1-3C);

m is an integer between 0-5;

n is an integer between 0-6;

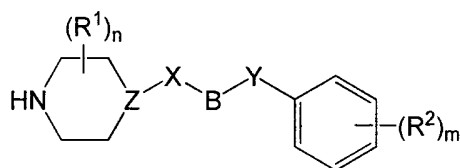
o is an integer between 0-4;

- 5 each R^1 and R^2 is, independently, selected from halo, CN, NO_2 , $COOR'$, $CONR'_2$, OR' , SR' , SOR' , SO_2R' , NR'_2 , $NR'(CO)R'$, and $NR'SO_2R'$, wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6), and heteroalkynyl (2-6C); or R^1 and R^2 may independently be one or more optionally substituted groups selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), or heteroalkynyl (2-6C); and wherein each R^1 may further be selected from =O and =NOR';

R^3 is H or an optionally substituted alkyl (1-3C); and

R^4 is H, methyl, fluoro, hydroxyl or cyano.

- 15 **[0008]** In some embodiments, the compound has a structure according to:



(II). In some embodiments, R^1 or R^2 is

CF_3 or OCF_3 .

[0009] In some embodiments, B is $N-R^3$.

- [0010]** In other embodiments, X is substituted by =O. In further embodiments, X is $-CH_2C(=O)-$ or $-C(=O)CH_2-$. In further embodiments, X is $-CH_2C(=O)-$.

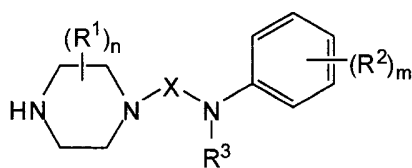
[0011] In certain embodiments, n is an integer between 0-3. In some embodiments, n is 0.

[0012] In some embodiments, Y is a bond.

[0013] In certain embodiments, R^1 is independently halo, methyl, CF_3 , or =O.

- 25 **[0014]** In other embodiments, m is 0-3. In further embodiments, m is 2 or 3. In some embodiments, R^2 is independently halo, methyl or CF_3 .

[0015] In certain embodiments, the compound has a structure according to the following formula,

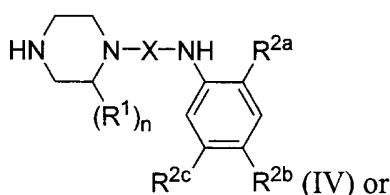
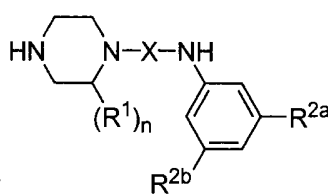


(III). In some embodiments, X is -

CH₂C(=O)- or -C(=O)CH₂-. In further embodiments, X is -CH₂C(=O)-. In certain

5 embodiments, R³ is H. In other embodiments, independently, n is 0 or 1, and m is 2 or 3. In still other embodiments, n is 1 and R¹ is =O.

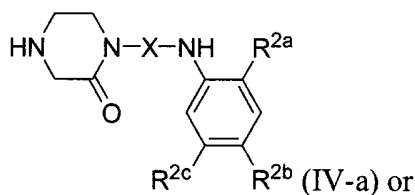
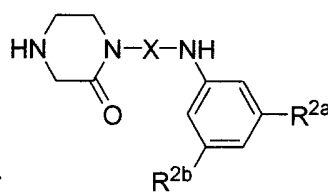
[0016] In some embodiments, the compound has a structure according to



(V), where

R¹ is =O; n is 0 or 1; and each of R^{2a}, R^{2b}, and R^{2c} is selected, independently,

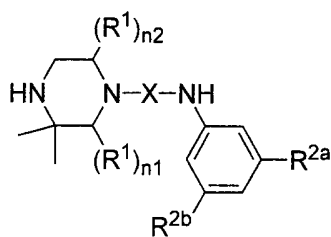
10 from halogen and substituted 1C alkyl. In still other embodiments, the compound has a structure according to



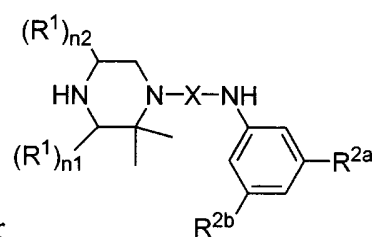
(V-a). In certain

embodiments, X is -CH₂C(=O)-.

[0017] In still other embodiments, the compound has a structure according to



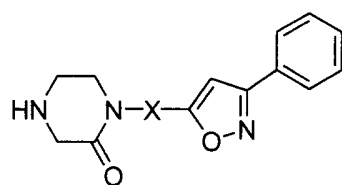
(VI) or



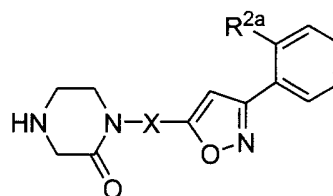
(VII),

15 where R¹ is =O; n₁ is 0 or 1; n₂ is 0 or 1; each R^{2a}, R^{2b}, and R^{2c} is selected, independently, from halogen and substituted 1C alkyl; and wherein at least one of n₁ and n₂ is 0. In some embodiments, both n₁ and n₂ are 0.

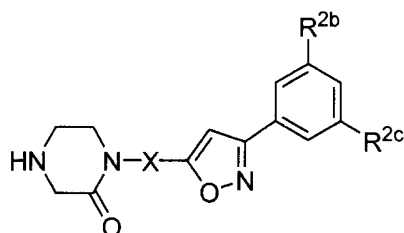
[0018] In certain embodiments, the compound has a structure selected from the group consisting of:



(VIII),



(IX), and



(X), where each R^{2a} , R^{2b} , and R^{2c} is selected,

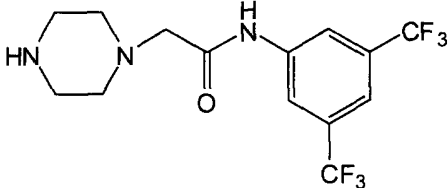
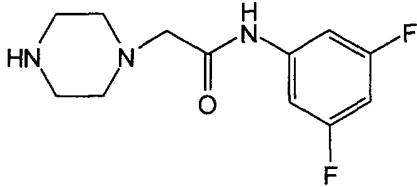
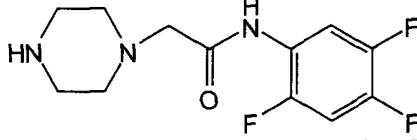
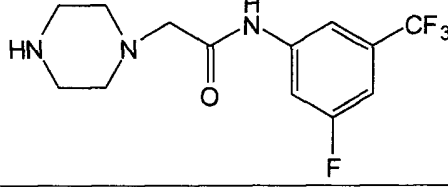
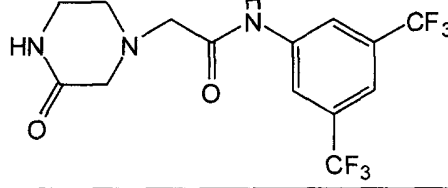
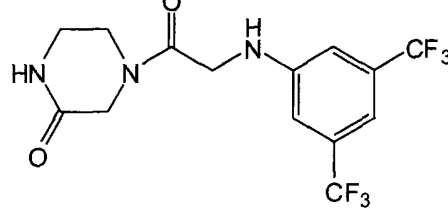
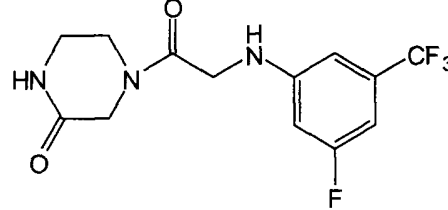
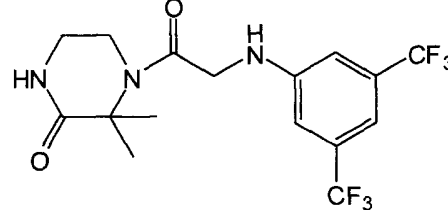
- 5 independently, from halogen and substituted 1C alkyl. In some embodiments, X is -CH₂-. In other embodiments, the halogen is fluoro and the substituted 1C alkyl is CF₃.

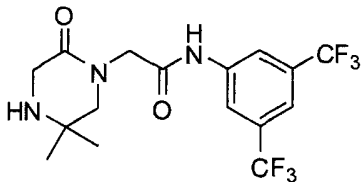
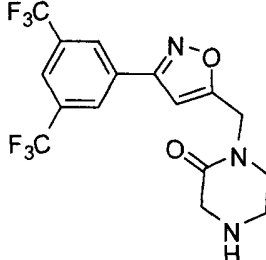
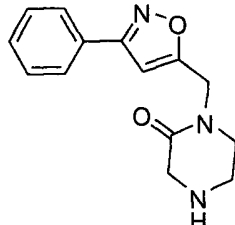
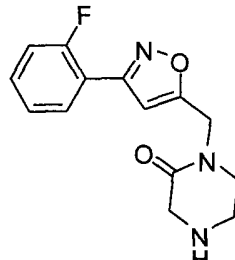
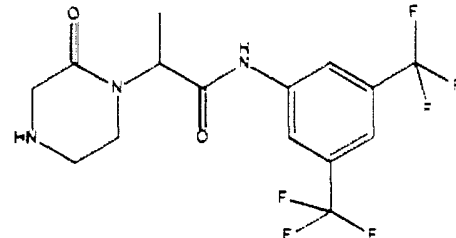
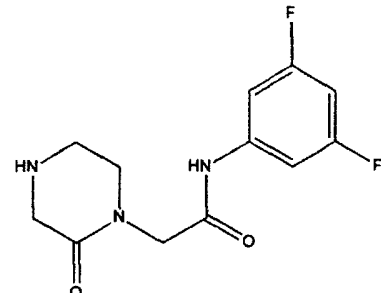
[0019] In some embodiments, the compound is selected from any of the compounds of Table 1.

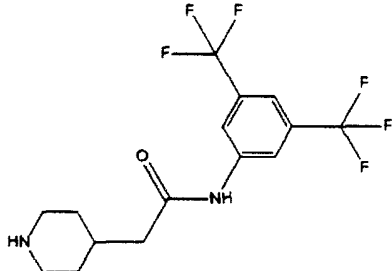
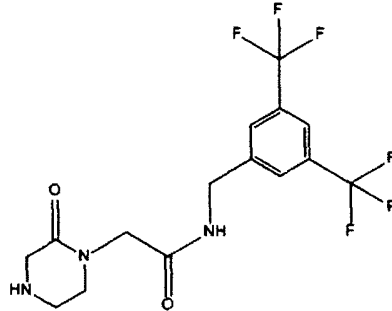
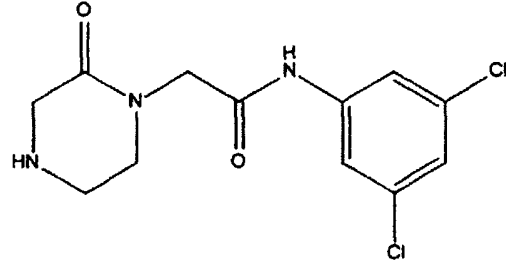
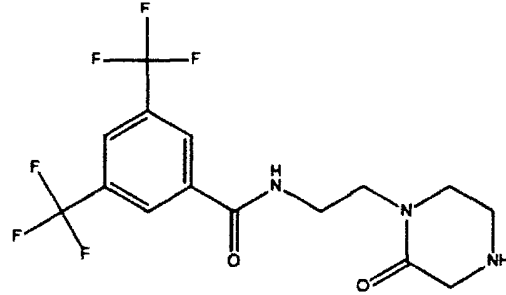
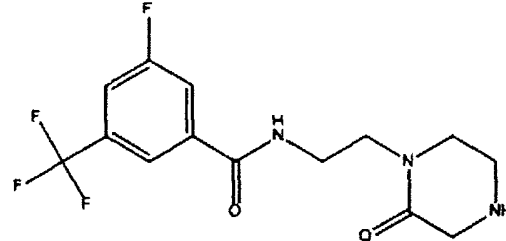
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Table 1

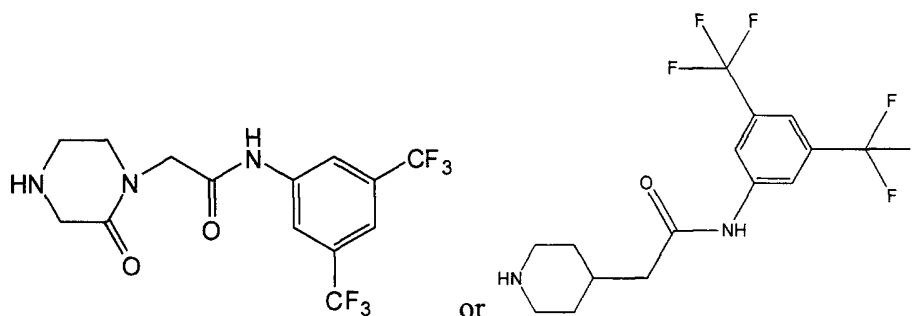
Compound No.	Name	Structure
1	N-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxopiperazin-1-yl)acetamide	
2	2-(2-oxopiperazin-1-yl)-N-(2,4,5-trifluorophenyl)acetamide;	
3	1-(2-(3,5-difluorophenylamino)acetyl)piperazin-2-one	
4	N-(3,5-bis(trifluoromethyl)phenyl)-2-(3,3-dimethyl-2-oxopiperazin-1-yl)acetamide	

Compound No.	Name	Structure
5	N-(3,5-bis(trifluoromethyl)phenyl)-2-(piperazin-1-yl)acetamide	
6	N-(3,5-difluorophenyl)-2-(piperazin-1-yl)acetamide	
7	2-(piperazin-1-yl)-N-(2,4,5-trifluorophenyl)acetamide	
8	N-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(piperazin-1-yl)acetamide	
9	N-(3,5-bis(trifluoromethyl)phenyl)-2-(3-oxopiperazin-1-yl)acetamide	
10	4-(2-(3,5-bis(trifluoromethyl)phenylamino)acetyl)piperazin-2-one	
11	4-(2-(3-fluoro-5-(trifluoromethyl)phenylamino)acetyl)piperazin-2-one	
12	4-(2-(3,5-bis(trifluoromethyl)phenylamino)acetyl)-3,3-dimethylpiperazin-2-one	

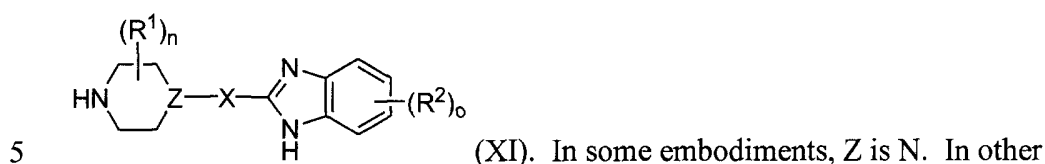
Compound No.	Name	Structure
13	N-(3,5-bis(trifluoromethyl)phenyl)-2-(5,5-dimethyl-2-oxopiperazin-1-yl)acetamide	
14	1-((3-(3,5-bis(trifluoromethyl)phenyl)isoxazol-5-yl)methyl)piperazin-2-one	
15	1-((3-phenylisoxazol-5-yl)methyl)piperazin-2-one	
16	1-((3-(2-fluorophenyl)isoxazol-5-yl)methyl)piperazin-2-one	
17	N-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxopiperazin-1-yl)propanamide	
18	N-(3,5-difluorophenyl)-2-(2-oxopiperazin-1-yl)acetamide	

Compound No.	Name	Structure
19	N-(3,5-bis(trifluoromethyl)phenyl)-2-(piperidin-4-yl)acetamide	
20	N-(3,5-bis(trifluoromethyl)benzyl)-2-(2-oxopiperazin-1-yl)acetamide	
21	N-(3,5-dichlorophenyl)-2-(2-oxopiperazin-1-yl)acetamide	
22	N-(2-(2-oxopiperazin-1-yl)ethyl)-3,5-bis(trifluoromethyl)benzamide	
23	3-fluoro-N-(2-(2-oxopiperazin-1-yl)ethyl)-5-(trifluoromethyl)benzamide	

[0020] In some embodiments, the compound is



[0021] In still other embodiments, the compound has a structure according to the following formula,



embodiments, n is 0-3. In further embodiments, n is 0. In some embodiments, n is 1 and R₁ is =O. In other embodiments, X is -CH₂C(=O)- or -C(=O)CH₂-. In further embodiments, X is -CH₂C(=O)-.

[0022] In a second aspect, the invention relates to a pharmaceutical composition
10 that includes any of the compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of compounds 1-23) and a pharmaceutically acceptable carrier or excipient.

[0023] In some embodiments, the pharmaceutical composition is formulated in unit dosage form. In other embodiments, the unit dosage form is a tablet, caplet,
15 capsule, lozenge, film, strip, gelcap, or syrup.

[0024] In a third aspect, the invention relates to a method to treat a condition (e.g., pain or epilepsy), where the method includes administering to a subject in need of such treatment an amount (e.g., an effective amount) of any of the compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of
20 compounds 1-23), or any of the pharmaceutical compositions described herein. In some embodiments, the condition requires modulation of sodium and/or calcium channel activity (e.g., Na_v 1.7, Na_v1.8, or Ca_v 3.2 channel activity, or any combination thereof of sodium and calcium channels).

[0025] In some embodiments, the pain is inflammatory pain or neuropathic pain.

[0026] In other embodiments, the pain is chronic pain. In further embodiments,
25 the chronic pain is peripheral neuropathic pain (e.g., post-herpetic neuralgia, diabetic

neuropathic pain, neuropathic cancer pain, failed back-surgery syndrome, trigeminal neuralgia, or phantom limb pain), central neuropathic pain (e.g., multiple sclerosis related pain, Parkinson disease related pain, post-stroke pain, post-traumatic spinal cord injury pain, or pain in dementia), musculoskeletal pain (e.g., osteoarthritic pain and fibromyalgia syndrome; inflammatory pain such as rheumatoid arthritis, or
5 endometriosis), headache (e.g., migraine, cluster headache, tension headache syndrome, facial pain, or headache caused by other diseases), visceral pain (e.g., interstitial cystitis, irritable bowel syndrome, or chronic pelvic pain syndrome), or mixed pain (e.g., lower back pain, neck and shoulder pain, burning mouth syndrome,
10 or complex regional pain syndrome).

[0027] In some embodiments, the pain is acute pain (e.g. nociceptive pain or post-operative pain).

[0028] Exemplary, non-limiting conditions modulated by sodium and/or calcium channel activity include pain, epilepsy, migraine, Parkinson's disease, depression,
15 schizophrenia, psychosis, or tinnitus.

[0029] In a fourth aspect, the invention relates to a method of modulating a voltage-gated sodium channel or a calcium channel, where the method includes contacting a cell with any of the compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of compounds 1-23), or any of the
20 pharmaceutical compositions described herein.

[0030] In another aspect, the invention relates to the use of any of the compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of compounds 1-23) for the preparation of medicaments for the treatment of any of the conditions described herein (e.g., a condition requiring modulation of sodium and/or
25 calcium channel activity (e.g., Nav 1.7, Nav1.8, or Cav 3.2 channel activity, or any combination thereof of sodium and calcium channels)).

[0031] In some embodiments, two or more of the particularly described groups are combined into one compound: it is often suitable to combine one of the specified embodiments of one feature as described above with a specified embodiment or
30 embodiments of one or more other features as described above.

[0032] As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight-chain, branched-chain and cyclic monovalent substituents, as well as combinations of these, containing only C and H when unsubstituted. Examples include methyl, ethyl,

isobutyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butenyl, and the like. Typically, the alkyl, alkenyl and alkynyl groups contain 1-8C (alkyl) or 2-8C (alkenyl or alkynyl). In some embodiments, they contain 1-6C, 1-4C, 1-3C or 1-2C (alkyl); or 2-6C, 2-4C or 2-3C (alkenyl or alkynyl). Further, any hydrogen atom on one of these groups can be replaced with a halogen atom, and in particular a fluoro or chloro, and still be within the scope of the definition of alkyl, alkenyl and alkynyl. For example, CF₃ is a 1C alkyl. These groups may be also be substituted by other substituents.

[0033] Heteroalkyl, heteroalkenyl and heteroalkynyl are similarly defined and contain at least one carbon atom but also contain one or more O, S or N heteroatoms or combinations thereof within the backbone residue whereby each heteroatom in the heteroalkyl, heteroalkenyl or heteroalkynyl group replaces one carbon atom of the alkyl, alkenyl or alkynyl group to which the heteroform corresponds. In preferred embodiments, the heteroalkyl, heteroalkenyl and heteroalkynyl groups have C at each terminus to which the group is attached to other groups, and the heteroatom(s) present are not located at a terminal position. As is understood in the art, these heteroforms do not contain more than three contiguous heteroatoms. In preferred embodiments, the heteroatom is O and/or N.

[0034] To the extent that alkyl is defined as 1-6C, then the corresponding heteroalkyl contains for example 1-5C, and at least one N, O, or S atom such that the heteroalkyl contains at least one C atom and at least one heteroatom. Similarly, when alkyl is defined as 1-6C or 1-4C, the heteroform would be 1-5C or 1-3C respectively, wherein at least one C is replaced by O, N or S. Accordingly, when alkenyl or alkynyl is defined as 2-6C (or 2-4C), then the corresponding heteroform would also contain 2-6 C, N, O, or S atoms (or 2-4) since the heteroalkenyl or heteroalkynyl contains at least one carbon atom and at least one heteroatom. Further, heteroalkyl, heteroalkenyl or heteroalkynyl substituents may also contain one or more carbonyl groups. Examples of heteroalkyl, heteroalkenyl and heteroalkynyl groups are CH₂OCH₃, CH₂N(CH₃)₂, CH₂OH, (CH₂)_nNR₂, OR, COOR, CONR₂, (CH₂)_nOR, (CH₂)_nCOR, (CH₂)_nCOOR, (CH₂)_nSR, (CH₂)_nSOR, (CH₂)_nSO₂R, (CH₂)_nCONR₂, NRCOR, NR₂COOR, OCONR₂, OCOR and the like wherein R is H or alkyl wherein the group contains at least one C and the size of the substituent is consistent with the definition of alkyl, alkenyl and alkynyl.

[0035] As used herein, the terms “alkylene,” “alkenylene” and “alkynylene” refers to divalent or trivalent groups having a specified size, typically 1-2C, 1-3C, 1-4C, 1-6C or 1-8C for the saturated groups and 2-3C, 2-4C, 2-6C or 2-8C for the unsaturated groups. They include straight-chain, branched-chain and cyclic forms as well as combinations of these, containing only C and H when unsubstituted. Because they are divalent, they can link together two parts of a molecule, as exemplified by X in the compounds described herein. Examples are methylene, ethylene, propylene, cyclopropan-1,1-diyl, ethylidene, 2-butene-1,4-diyl, and the like. These groups can be substituted by the groups typically suitable as substituents for alkyl, alkenyl and alkynyl groups as set forth herein. Thus C=O is a C1 alkylene that is substituted by =O, for example.

[0036] Heteroalkylene, heteroalkenylene and heteroalkynylene are similarly defined as divalent groups having a specified size, typically 1-3C, 1-4C, 1-6C or 1-8C for the saturated groups and 2-3C, 2-4C, 2-6C or 2-8C for the unsaturated groups. They include straight chain, branched chain and cyclic groups as well as combinations of these, and they further contain at least one carbon atom but also contain one or more O, S or N heteroatoms or combinations thereof within the backbone residue, whereby each heteroatom in the heteroalkylene, heteroalkenylene or heteroalkynylene group replaces one carbon atom of the alkylene, alkenylene or alkynylene group to which the heteroform corresponds. As is understood in the art, these heteroforms do not contain more than three contiguous heteroatoms.

[0037] “Aromatic” moiety or “aryl” moiety refers to any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system and includes a monocyclic or fused bicyclic moiety such as phenyl or naphthyl; “heteroaromatic” or “heteroaryl” also refers to such monocyclic or fused bicyclic ring systems containing one or more heteroatoms selected from O, S and N. The inclusion of a heteroatom permits inclusion of 5-membered rings to be considered aromatic as well as 6-membered rings. Thus, typical aromatic/heteroaromatic systems include pyridyl, pyrimidyl, indolyl, benzimidazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl and the like. Because tautomers are theoretically possible, phthalimido is also considered aromatic. Typically, the ring systems contain 5-12 ring member atoms or 6-10 ring member

atoms. In some embodiments, the aromatic or heteroaromatic moiety is a 6-membered aromatic rings system optionally containing 1-2 nitrogen atoms. More particularly, the moiety is an optionally substituted phenyl, 2-, 3- or 4-pyridyl, indolyl, 2- or 4- pyrimidyl, pyridazinyl, benzothiazolyl or benzimidazolyl. Even more particularly, such moiety is phenyl, pyridyl, or pyrimidyl and even more particularly, it is phenyl.

[0038] Halo may be any halogen atom, especially F, Cl, Br, or I, and more particularly it is fluoro or chloro.

[0039] In general, a substituent group (e.g., alkyl, alkenyl, alkynyl, or aryl (including all heteroforms defined above) may itself optionally be substituted by additional substituents. The nature of these substituents is similar to those recited with regard to the substituents on the basic structures above. Thus, where an embodiment of a substituent is alkyl, this alkyl may optionally be substituted by the remaining substituents listed as substituents where this makes chemical sense, and where this does not undermine the size limit of alkyl per se; e.g., alkyl substituted by alkyl or by alkenyl would simply extend the upper limit of carbon atoms for these embodiments, and is not included. However, alkyl substituted by aryl, amino, halo and the like would be included. For example, where a group is substituted, the group may be substituted with 1, 2, 3, 4, 5, or 6 substituents. Optional substituents include, but are not limited to: 1C-6C alkyl or heteroaryl, 2C-6C alkenyl or heteroalkenyl, 2C-6C alkynyl or heteroalkynyl, halogen; aryl, heteroaryl, azido(-N₃), nitro (-NO₂), cyano (-CN), acyloxy(-OC(=O)R'), acyl (-C(=O)R'), alkoxy (-OR'), amido (-NR'C(=O)R'' or -C(=O)NRR'), amino (-NRR'), carboxylic acid (-CO₂H), carboxylic ester (-CO₂R'), carbamoyl (-OC(=O)NR'R'' or -NRC(=O)OR'), hydroxy (-OH), isocyano (-NC), sulfonate (-S(=O)₂OR), sulfonamide (-S(=O)₂NRR' or -NRS(=O)₂R'), or sulfonyl (-S(=O)₂R), where each R or R' is selected, independently, from H, 1C-6C alkyl or heteroaryl, 2C-6C alkenyl or heteroalkenyl, 2C-6C alkynyl or heteroalkynyl, aryl, or heteroaryl. A substituted group may have, for example, 1, 2, 3, 4, 5, 6, 7, 8, or 9 substituents.

[0040] The term an "effective amount" of an agent (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23), as used herein, is that amount sufficient to effect beneficial or desired results, such as clinical results, and, as such, an "effective amount" depends upon the context in which it is being applied. For

example, in the context of administering an agent that is a modulator of sodium or calcium channels, an effective amount of an agent is, for example, an amount sufficient to achieve a change in sodium or calcium channel activity as compared to the response obtained without administration of the agent.

5 [0041] The term “pharmaceutical composition,” as used herein, represents a composition containing a compound described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) formulated with a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is manufactured or sold with the approval of a governmental regulatory
10 agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent
15 system suitable for intravenous use); or in any other formulation described herein.

 [0042] A “pharmaceutically acceptable excipient,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. Excipients may include, for example:
20 antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene
25 (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone,
30 povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[0043] The term “pharmaceutically acceptable prodrugs” as used herein, represents those prodrugs of the compounds of the present invention that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

[0044] The term “pharmaceutically acceptable salt,” as use herein, represents those salts of the compounds described here (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

[0045] The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulphuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines, and the like for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art.

[0046] Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate,

dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, 5 oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium, and amine 10 cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like.

[0047] The term “pharmaceutically acceptable solvate” as used herein means a compound as described herein (e.g., a compound according to any of Formulas (I)- 15 (XI) or any of Compounds 1-23) where molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, 20 mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the 25 molecule is referred to as a “hydrate.”

[0048] The term “prevent,” as used herein, refers to prophylactic treatment or treatment that prevents one or more symptoms or conditions of a disease, disorder, or conditions described herein (for example, pain (e.g., chronic or acute pain), epilepsy, Alzheimer’s disease, Parkinson’s disease, cardiovascular disease, diabetes, cancer, 30 sleep disorders, obesity, psychosis such as schizophrenia, overactive bladder, renal disease, neuroprotection, addiction, and male birth control). Preventative treatment can be initiated, for example, prior to (“pre-exposure prophylaxis”) or following (“post-exposure prophylaxis”) an event that precedes the onset of the disease,

disorder, or conditions. Preventive treatment that includes administration of a compound described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23), or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof, can be acute, short-term, or chronic. The doses administered may be varied during the course of preventative treatment.

[0049] The term “prodrug,” as used herein, represents compounds that are rapidly transformed in vivo to the parent compound of the above formula, for example, by hydrolysis in blood. Prodrugs of the compounds described herein may be conventional esters. Some common esters that have been utilized as prodrugs are phenyl esters, aliphatic (C1-C8 or C8-C24) esters, cholesterol esters, acyloxymethyl esters, carbamates, and amino acid esters. For example, a compound that contains an OH group may be acylated at this position in its prodrug form. A thorough discussion is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, and Judkins et al., *Synthetic Communications* 26(23):4351-4367, 1996, each of which is incorporated herein by reference. Preferably, prodrugs of the compounds of the present invention are suitable for use in contact with the tissues of humans and animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use.

[0050] In addition, the compounds of the invention may be coupled through conjugation to substances designed to alter the pharmacokinetics, for targeting, or for other reasons. Thus, the invention further includes conjugates of these compounds. For example, polyethylene glycol is often coupled to substances to enhance half-life; the compounds may be coupled to liposomes covalently or noncovalently or to other particulate carriers. They may also be coupled to targeting agents such as antibodies or peptidomimetics, often through linker moieties. Thus, the invention is also directed to compounds (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) when modified so as to be included in a conjugate of this type.

[0051] As used herein, and as well understood in the art, “to treat” a condition or “treatment” of the condition (e.g., the conditions described herein such as pain (e.g., chronic or acute pain), epilepsy, Alzheimer’s disease, Parkinson’s disease,

cardiovascular disease, diabetes, cancer, sleep disorders, obesity, psychosis such as schizophrenia, overactive bladder, renal disease, neuroprotection, addiction, and male birth control) is an approach for obtaining beneficial or desired results, such as clinical results. Beneficial or desired results can include, but are not limited to, 5 alleviation or amelioration of one or more symptoms or conditions; diminishment of extent of disease, disorder, or condition; stabilized (i.e., not worsening) state of disease, disorder, or condition; preventing spread of disease, disorder, or condition; delay or slowing the progress of the disease, disorder, or condition; amelioration or palliation of the disease, disorder, or condition; and remission (whether partial or 10 total), whether detectable or undetectable. "Palliating" a disease, disorder, or condition means that the extent and/or undesirable clinical manifestations of the disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to the extent or time course in the absence of treatment.

15 [0052] The term "unit dosage form" refers to a physically discrete unit suitable as a unitary dosage for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with any suitable pharmaceutical excipient or excipients. Exemplary, non-limiting unit dosage forms include a tablet (e.g., a 20 chewable tablet), caplet, capsule (e.g., a hard capsule or a soft capsule), lozenge, film, strip, gelcap, and syrup.

[0053] Because some of the compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) readily form acid addition salts and such salts may be advantageous for handling or stability, in some 25 embodiments the compound is preferably a pharmaceutically acceptable salt.

[0054] In some cases, the compounds of the invention contain one or more chiral centers. The invention includes each of the isolated stereoisomeric forms as well as mixtures of stereoisomers in varying degrees of chiral purity, including racemic mixtures. It also encompasses the various diastereomers and tautomers that can be 30 formed.

[0055] The compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) are also useful for the manufacture of a medicament useful to treat conditions requiring modulation of sodium and/or calcium

channel activity, and in particular Na_v 1.7, Na_v 1.8, and Ca_v 3.2 channel activity, or any combination thereof of sodium and calcium channels.

[0056] Other features and advantages of the invention will be apparent from the following detailed description, the drawings, and the claims.

5

Brief Description of the Drawing

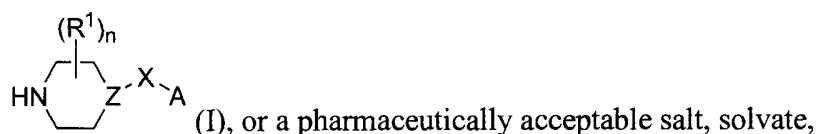
[0057] Figure 1 shows the antiallodynic effects of Compounds 1 and 9 compared to baseline and post-SNL as measured in the Von Frey assessment of tactile allodynia.

10

Detailed Description of the Invention

Compounds

[0058] The invention features compounds that have a structure according to the following formula,

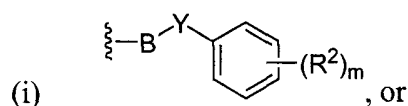
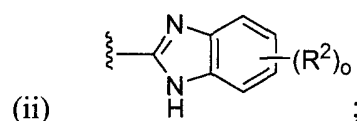
15

prodrug, or stereoisomer thereof, where

X is an optionally substituted alkylene (1-3C);

Z is N or CR^4 ;

A is selected from



20

B is N-R^3 or an optionally substituted isoxazolyl;

Y is a bond or an optionally substituted alkylene (1-3C);

m is an integer between 0-5;

n is an integer between 0-6;

25

o is an integer between 0-4;

each R^1 and R^2 is, independently, selected from halo, CN, NO_2 , COOR' , CONR'_2 , OR' , SR' , SOR' , $\text{SO}_2\text{R}'$, NR'_2 , $\text{NR}'(\text{CO})\text{R}'$, and $\text{NR}'\text{SO}_2\text{R}'$, wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6), and

heteroalkynyl (2-6C); or R^1 and R^2 may independently be one or more optionally substituted groups selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), or heteroalkynyl (2-6C); and wherein each R^1 may further be selected from =O and =NOR';

5 R^3 is H or an optionally substituted alkyl (1-3C); and

R^4 is H, methyl, fluoro, hydroxyl or cyano.

Other embodiments (e.g., Formulas (II)-(XI) and Compounds 1-23), exemplary methods for the synthesis of these compounds are described herein.

10 Utility and Administration

[0059] The compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to modulate the activity of sodium and/or calcium channels, particularly the activity of $Na_v1.7$, $Na_v1.8$ or $Ca_v3.2$ channels. This makes them
15 useful for treatment of certain conditions where modulation of sodium or T-type calcium channels is desired including pain, epilepsy, migraine, Parkinson's disease, depression, schizophrenia, psychosis, and tinnitus.

20 Modulation of Sodium Channels

[0060] The nine Na_v1 α -subunit isoforms $Na_v1.7$ and $Na_v1.8$ channel subtypes act as major contributors to both inflammatory and neuropathic pain (*vide infra*). Recently, mutations have been identified in the $Na_v1.7$ channel that lead either to a gain of channel function (Dib-Hajj et al., *Brain* 128:1847-1854, 2005) or more
25 commonly to a loss of channel function (Chatelier et al., *J. Neurophysiol.* 99:2241-50, 2008). These mutations underlie human heritable disorders such as erythralgia (Yang et al., *J Med Genet.* 41(3) 171-4, 2004), paroxysmal extreme pain disorder (Fertleman et al., *Neuron.* 52(5) 767-74, 2006), and congenital indifference to pain (Cox et al., *Nature* 444(7121):894-8, 2006). Behavioral studies have shown in mice
30 that inflammatory and acute mechanosensory pain is reduced when $Na_v1.7$ is knocked out in $Na_v1.8$ -positive neurons (Nassar et al., *Proc Natl Acad Sci U S A.* 101(34):12706-11, 2004). In addition, siRNA of $Na_v1.7$ attenuates inflammatory hyperalgesia (Yeomans et al., *Hum Gene Ther.* 16(2) 271-7, 2005). The role of

Nav1.8 in inflammatory (Khasar et al., *Neurosci Lett.* 256(1):17-20, 1998), neuropathic and mechanical hyperalgesia (Joshi et al., *Pain* 123(1-2):75-82, 2006) has also emerged using molecular techniques to knockdown Nav 1.8, which has been shown to reduce the maintenance of these different pain states.

- 5 **[0061]** Lacosamide is a functionalized amino acid that has shown effectiveness as an analgesic in several animal models of neuropathic pain and is currently in late stages of clinical development for epilepsy and diabetic neuropathic pain. One mode of action that has been validated for lacosamide is inhibition of voltage-gated sodium channel activity by selective inhibition with the slow-inactivated conformation of the
- 10 channel (Sheets et al., *Journal of Pharmacology and Experimental Therapeutics*, 326(1) 89-99 (2008)). Modulators of sodium channels, including clinically relevant compounds, can exhibit a pronounced state-dependent binding, where sodium channels that are rapidly and repeatedly activated and inactivated are more readily blocked. In a simplified scheme, voltage-gated sodium channels have four distinct
- 15 states: open, closed, fast-inactivated and slow-inactivated. Classic sodium channel modulators, such as lidocaine, are believed to exhibit the highest affinity for the fast-inactivated state. However, alteration of the slow inactivated state is also clinically relevant.

20 *Modulation of Calcium Channels*

- [0062]** The entry of calcium into cells through voltage-gated calcium channels mediates a wide variety of cellular and physiological responses, including excitation-contraction coupling, hormone secretion and gene expression (e.g., Miller et al., *Science* 235:46-52 (1987); Augustine et al., *Annu Rev Neurosci* 10: 633-693
- 25 (1987)). In neurons, calcium channels directly affect membrane potential and contribute to electrical properties such as excitability, repetitive firing patterns and pacemaker activity. Calcium entry further affects neuronal functions by directly regulating calcium-dependent ion channels and modulating the activity of calcium-dependent enzymes such as protein kinase C and calmodulin-dependent
- 30 protein kinase II. An increase in calcium concentration at the presynaptic nerve terminal triggers the release of neurotransmitter, which also affects neurite outgrowth and growth cone migration in developing neurons.

[0063] Calcium channels mediate a variety of normal physiological functions, and are also implicated in a number of human disorders as described herein. For example, calcium channels also have been shown to mediate the development and maintenance of the neuronal sensitization and hyperexcitability processes associated with

5 neuropathic pain, and provide attractive targets for the development of analgesic drugs (reviewed in Vanegas et al., *Pain* 85: 9-18 (2000)). Native calcium channels have been classified by their electrophysiological and pharmacological properties into T-, L-, N-, P/Q- and R- types (reviewed in Catterall, *Annu Rev Cell Dev Biol* 16: 521-555, 2000; Huguenard, *Annu Rev Physiol* 58: 329-348, 1996). The L-, N- and

10 P/Q-type channels activate at more positive potentials (high voltage-activated) and display diverse kinetics and voltage-dependent properties (*Id.*). T-type channels can be distinguished by having a more negative range of activation and inactivation, rapid inactivation, slow deactivation, and smaller single-channel conductances. There are three subtypes of T-type calcium channels that have been molecularly,

15 pharmacologically, and electrophysiologically identified: these subtypes have been termed α_{1G} , α_{1H} , and α_{1I} (alternately called Cav 3.1, Cav 3.2 and Cav 3.3 respectively).

[0064] T-type calcium channels are involved in various medical conditions. In mice lacking the gene expressing the 3.1 subunit, resistance to absence seizures was

20 observed (Kim et al., *Mol. Cell Neurosci.* 18(2): 235-245 (2001)). Other studies have also implicated the 3.2 subunit in the development of epilepsy (Su et al., *J. Neurosci.* 22: 3645-3655 (2002)). There is also evidence that some existing anticonvulsant drugs, such as ethosuximide, function through the blockade of T-type channels (Gomora et al., *Mol. Pharmacol.* 60: 1121-1132 (2001)).

25 [0065] Low voltage-activated calcium channels are highly expressed in tissues of the cardiovascular system. There is also a growing body of evidence that suggests that T-type calcium channels are abnormally expressed in cancerous cells and that blockade of these channels may reduce cell proliferation in addition to inducing apoptosis. Recent studies also show that the expression of T-type calcium channels in

30 breast cancer cells is proliferation state dependent, i.e. the channels are expressed at higher levels during the fast-replication period, and once the cells are in a non-proliferation state, expression of this channel is minimal. Therefore, selectively blocking calcium channel entry into cancerous cells may be a valuable approach for

preventing tumor growth (e.g., PCT Patent Application Nos. WO 05/086971 and WO 05/77082; Taylor et al., *World J. Gastroenterol.* 14(32): 4984-4991 (2008); Heo et al., *Biorganic & Medicinal Chemistry Letters* 18:3899-3901 (2008)).

[0066] T-type calcium channels may also be involved in still other conditions. A recent study also has shown that T-type calcium channel antagonists inhibit high-fat diet-induced weight gain in mice. In addition, administration of a selective T-type channel antagonist reduced body weight and fat mass while concurrently increasing lean muscle mass (e.g., Uebele et al., *The Journal of Clinical Investigation*, 119(6):1659–1667 (2009)). T-type calcium channels may also be involved in pain (see for example: US Patent Publication No. 2003/0086980; PCT Publication Nos. WO 03/007953 and WO 04/000311). In addition to cardiovascular disease, epilepsy (see also US Patent Application No. 2006/0025397), cancer, and chronic or acute pain, T-type calcium channels have been implicated in diabetes (US Patent Publication No. 2003/0125269), sleep disorders (US Patent Publication No. 2006/0003985), Parkinson's disease and psychosis such as schizophrenia (US Patent Publication No. 2003/0087799); overactive bladder (Sui et al., *British Journal of Urology International* 99(2): 436-441 (2007); US Patent Publication No. 2004/0197825), renal disease (Hayashi et al., *Journal of Pharmacological Sciences* 99: 221-227 (2005)), anxiety and alcoholism (US Patent Publication No. 2009/0126031), neuroprotection, and male birth control.

[0067] The modulation of ion channels by the compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) can be measured according to methods known in the art (e.g., in the references provided herein). Modulators of ion channels, e.g., voltage gated sodium and calcium ion channels, and the medicinal chemistry or methods by which such compounds can be identified, are also described in, for example: Birch et al., *Drug Discovery Today*, 9(9):410-418 (2004); Audesirk, "Chapter 6-Electrophysiological Analysis of Ion Channel Function," *Neurotoxicology: Approaches and Methods*, 137-156 (1995); Camerino et al., "Chapter 4: Therapeutic Approaches to Ion Channel Diseases," *Advances in Genetics*, 64:81-145 (2008); Petkov, "Chapter 16-Ion Channels," *Pharmacology: Principles and Practice*, 387-427 (2009); Standen et al., "Chapter 15-Patch Clamping Methods and Analysis of Ion Channels," *Principles of Medical Biology*, Vol. 7, Part 2, 355-375 (1997); Xu et al., *Drug Discovery Today*, 6(24):1278-

1287 (2001); and Sullivan et al., *Methods Mol. Biol.* 114:125-133 (1999). Exemplary experimental methods are also provided in the Examples.

Diseases and Conditions

5 **[0068]** Exemplary conditions that can be treated using the compounds described herein include pain (e.g., chronic or acute pain), epilepsy, Alzheimer's disease, Parkinson's disease, diabetes; cancer; sleep disorders; obesity; psychosis such as schizophrenia; overactive bladder; renal disease, neuroprotection, and addiction. For example, the condition can be pain (e.g., neuropathic pain or post-surgery pain),
10 epilepsy, migraine, Parkinson's disease, depression, schizophrenia, psychosis, or tinnitus.

[0069] Epilepsy as used herein includes but is not limited to partial seizures such as temporal lobe epilepsy, absence seizures, generalized seizures, and tonic/clonic seizures.

15 **[0070]** Cancer as used herein includes but is not limited to breast carcinoma, neuroblastoma, retinoblastoma, glioma, prostate carcinoma, esophageal carcinoma, fibrosarcoma, colorectal carcinoma, pheochromocytoma, adrenocarcinoma, insulinoma, lung carcinoma, melanoma, and ovarian cancer.

[0071] Acute pain as used herein includes but is not limited to nociceptive pain
20 and post-operative pain. Chronic pain includes but is not limited by: peripheral neuropathic pain such as post-herpetic neuralgia, diabetic neuropathic pain, neuropathic cancer pain, failed back-surgery syndrome, trigeminal neuralgia, and phantom limb pain; central neuropathic pain such as multiple sclerosis related pain, Parkinson disease related pain, post-stroke pain, post-traumatic spinal cord injury
25 pain, and pain in dementia; musculoskeletal pain such as osteoarthritic pain and fibromyalgia syndrome; inflammatory pain such as rheumatoid arthritis and endometriosis; headache such as migraine, cluster headache, tension headache syndrome, facial pain, headache caused by other diseases; visceral pain such as interstitial cystitis, irritable bowel syndrome and chronic pelvic pain syndrome; and
30 mixed pain such as lower back pain, neck and shoulder pain, burning mouth syndrome and complex regional pain syndrome.

[0072] In treating osteoarthritic pain, joint mobility can also improve as the underlying chronic pain is reduced. Thus, use of compounds of the present invention

to treat osteoarthritic pain inherently includes use of such compounds to improve joint mobility in patients suffering from osteoarthritis.

[0073] The compounds described herein can be tested for efficacy in any standard animal model of pain. Various models test the sensitivity of normal animals to
5 intense or noxious stimuli (physiological or nociceptive pain). These tests include responses to thermal, mechanical, or chemical stimuli. Thermal stimuli usually involve the application of hot stimuli (typically varying between 42 -55 °C) including, for example: radiant heat to the tail (the tail flick test), radiant heat to the plantar surface of the hindpaw (the Hargreaves test), the hotplate test, and immersion of the
10 hindpaw or tail into hot water. Immersion in cold water, acetone evaporation, or cold plate tests may also be used to test cold pain responsiveness. Tests involving mechanical stimuli typically measure the threshold for eliciting a withdrawal reflex of the hindpaw to graded strength monofilament von Frey hairs or to a sustained pressure stimulus to a paw (e.g., the Ugo Basile analgesimeter). The duration of a
15 response to a standard pinprick may also be measured. When using a chemical stimulus, the response to the application or injection of a chemical irritant (e.g., capsaicin, mustard oil, bradykinin, ATP, formalin, acetic acid) to the skin, muscle joints or internal organs (e.g., bladder or peritoneum) is measured.

[0074] In addition, various tests assess pain sensitization by measuring changes in
20 the excitability of the peripheral or central components of the pain neural pathway. In this regard, peripheral sensitization (i.e., changes in the threshold and responsiveness of high threshold nociceptors) can be induced by repeated heat stimuli as well as the application or injection of sensitizing chemicals (e.g., prostaglandins, bradykinin, histamine, serotonin, capsaicin, or mustard oil). Central sensitization (i.e., changes in
25 the excitability of neurons in the central nervous system induced by activity in peripheral pain fibers) can be induced by noxious stimuli (e.g., heat), chemical stimuli (e.g., injection or application of chemical irritants), or electrical activation of sensory fibers.

[0075] Various pain tests developed to measure the effect of peripheral
30 inflammation on pain sensitivity can also be used to study the efficacy of the compounds (Stein et al., *Pharmacol. Biochem. Behav.* (1988) 31: 445-451; Woolf et al., *Neurosci.* (1994) 62: 327-331). Additionally, various tests assess peripheral neuropathic pain using lesions of the peripheral nervous system. One such example is

the “axotomy pain model” (Watson, *J. Physiol.* (1973) 231:41). Other similar tests include the SNL test which involves the ligation of a spinal segmental nerve (Kim and Chung *Pain* (1992) 50: 355), the Seltzer model involving partial nerve injury (Seltzer, *Pain* (1990) 43: 205-18), the spared nerve injury (SNI) model (Decosterd and Woolf, *Pain* (2000) 87:149), chronic constriction injury (CCI) model (Bennett (1993) *Muscle Nerve* 16: 1040), tests involving toxic neuropathies such as diabetes (streptozocin model), pyridoxine neuropathy, taxol, vincristine, and other antineoplastic agent-induced neuropathies, tests involving ischaemia to a nerve, peripheral neuritis models (e.g., CFA applied peri-neurally), models of post-herpetic neuralgia using HSV infection, and compression models.

[0076] In all of the above tests, outcome measures may be assessed, for example, according to behavior, electrophysiology, neurochemistry, or imaging techniques to detect changes in neural activity.

[0077] Exemplary models of pain are also described in the Examples provided herein.

[0078] In addition to being able to modulate a particular sodium or calcium channel, it may be desirable that the compound has very low activity with respect to the hERG K⁺ channel, which is expressed in the heart: compounds that block this channel with high potency may cause reactions which are fatal. See, e.g., Bowlby et al., “hERG (KCNH2 or K_v11.1 K⁺ Channels: Screening for Cardiac Arrhythmia Risk,” *Curr. Drug Metab.* 9(9):965-70 (2008)). Thus, for a compound that modulates the sodium or calcium channel, it may also be shown that the hERG K⁺ channel is not inhibited or only minimally inhibited as compared to the inhibition of the primary channel targeted. Similarly, it may be desirable that the compound does not inhibit cytochrome p450, an enzyme that is required for drug detoxification. Such compounds may be particularly useful in the methods described herein.

Pharmaceutical Compositions

[0079] For use as treatment of human and animal subjects, the compounds of the invention can be formulated as pharmaceutical or veterinary compositions.

Depending on the subject to be treated, the mode of administration, and the type of treatment desired-- e.g., prevention, prophylaxis, or therapy--the compounds are formulated in ways consonant with these parameters. A summary of such techniques

is found in *Remington: The Science and Practice of Pharmacy*, 21st Edition, Lippincott Williams & Wilkins, (2005); and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, each of which is incorporated herein by reference.

5 **[0080]** The compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) may be present in amounts totaling 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for intraarticular, oral, parenteral (e.g., intravenous, intramuscular), rectal, cutaneous, subcutaneous, topical, transdermal, 10 sublingual, nasal, vaginal, intravesicular, intraurethral, intrathecal, epidural, aural, or ocular administration, or by injection, inhalation, or direct contact with the nasal, genitourinary, gastrointestinal, reproductive or oral mucosa. Thus, the pharmaceutical composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, 15 creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, preparations suitable for iontophoretic delivery, or aerosols. The compositions may be formulated according to conventional pharmaceutical practice.

[0081] In general, for use in treatment, the compounds described herein (e.g., a 20 compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) may be used alone, as mixtures of two or more compounds or in combination with other pharmaceuticals. An example of other pharmaceuticals to combine with the compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) would include pharmaceuticals for the treatment of the 25 same indication. For example, in the treatment of pain, a compound may be combined with another pain relief treatment such as an NSAID, or a compound which selectively inhibits COX-2, or an opioid, or an adjuvant analgesic such as an antidepressant. Another example of a potential pharmaceutical to combine with the compounds described herein (e.g., a compound according to any of Formulas (I)-(XI) 30 or any of Compounds 1-23) would include pharmaceuticals for the treatment of different yet associated or related symptoms or indications. Depending on the mode of administration, the compounds will be formulated into suitable compositions to permit facile delivery. Each compound of a combination therapy may be formulated

in a variety of ways that are known in the art. For example, the first and second agents of the combination therapy may be formulated together or separately. Desirably, the first and second agents are formulated together for the simultaneous or near simultaneous administration of the agents.

5 **[0082]** The compounds of the invention may be prepared and used as pharmaceutical compositions comprising an effective amount of a compound described herein (e.g., a compound according to any of Formulas (I)-(XI) or any of Compounds 1-23) and a pharmaceutically acceptable carrier or excipient, as is well known in the art. In some embodiments, the composition includes at least two
10 different pharmaceutically acceptable excipients or carriers.

[0083] Formulations may be prepared in a manner suitable for systemic administration or topical or local administration. Systemic formulations include those designed for injection (e.g., intramuscular, intravenous or subcutaneous injection) or may be prepared for transdermal, transmucosal, or oral administration. The
15 formulation will generally include a diluent as well as, in some cases, adjuvants, buffers, preservatives and the like. The compounds can be administered also in liposomal compositions or as microemulsions.

[0084] For injection, formulations can be prepared in conventional forms as liquid solutions or suspensions or as solid forms suitable for solution or suspension in liquid
20 prior to injection or as emulsions. Suitable excipients include, for example, water, saline, dextrose, glycerol and the like. Such compositions may also contain amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as, for example, sodium acetate, sorbitan monolaurate, and so forth.

25 **[0085]** Various sustained release systems for drugs have also been devised. See, for example, U.S. patent No. 5,624,677, which is herein incorporated by reference.

[0086] Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal administration. Oral administration is also suitable for compounds of the
30 invention. Suitable forms include syrups, capsules, and tablets, as is understood in the art.

[0087] For administration to animal or human subjects, the dosage of the compounds of the invention may be, for example, 0.01-50 mg/kg (e.g., 0.01-15 mg/kg or 0.1-10 mg/kg). For example, the dosage can be 10-30 mg/kg.

[0088] Each compound of a combination therapy, as described herein, may be formulated in a variety of ways that are known in the art. For example, the first and second agents of the combination therapy may be formulated together or separately.

[0089] The individually or separately formulated agents can be packaged together as a kit. Non-limiting examples include, but are not limited to, kits that contain, e.g., two pills, a pill and a powder, a suppository and a liquid in a vial, two topical creams, etc. The kit can include optional components that aid in the administration of the unit dose to patients, such as vials for reconstituting powder forms, syringes for injection, customized IV delivery systems, inhalers, etc. Additionally, the unit dose kit can contain instructions for preparation and administration of the compositions. The kit may be manufactured as a single use unit dose for one patient, multiple uses for a particular patient (at a constant dose or in which the individual compounds may vary in potency as therapy progresses); or the kit may contain multiple doses suitable for administration to multiple patients ("bulk packaging"). The kit components may be assembled in cartons, blister packs, bottles, tubes, and the like.

[0090] Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients

can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

[0091] Two or more compounds may be mixed together in a tablet, capsule, or other vehicle, or may be partitioned. In one example, the first compound is contained
5 on the inside of the tablet, and the second compound is on the outside, such that a substantial portion of the second compound is released prior to the release of the first compound.

[0092] Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent
10 (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid
15 bed apparatus or a spray drying equipment.

[0093] Dissolution or diffusion controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above and/or, e.g.,
20 shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-poly(lactic acid), cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol
25 methacrylate, and/or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, and/or halogenated fluorocarbon.

[0094] The liquid forms in which the compounds and compositions of the present
30 invention can be incorporated for administration orally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with

edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

[0095] Generally, when administered to a human, the oral dosage of any of the compounds of the combination of the invention will depend on the nature of the compound, and can readily be determined by one skilled in the art. Typically, such dosage is normally about 0.001 mg to 2000 mg per day, desirably about 1 mg to 1000 mg per day, and more desirably about 5 mg to 500 mg per day. Dosages up to 200 mg per day may be necessary.

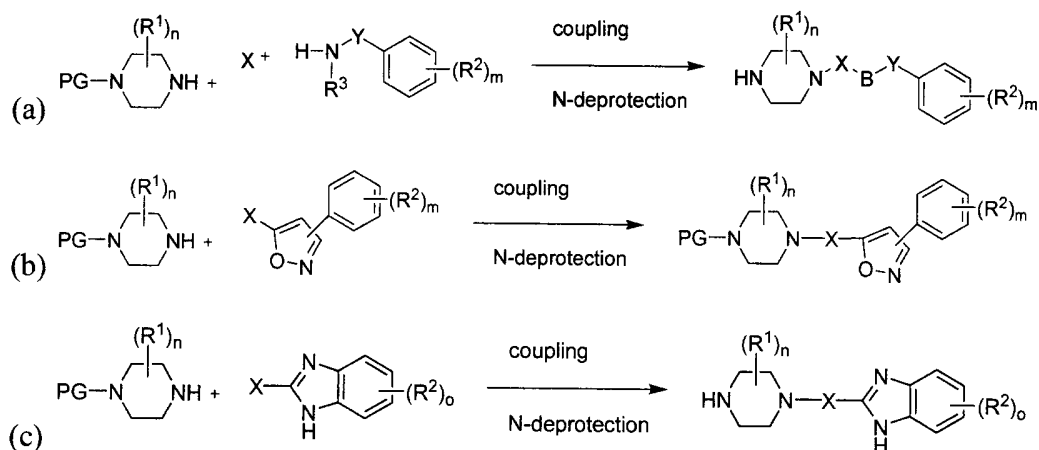
[0096] Administration of each drug in a combination therapy, as described herein, can, independently, be one to four times daily for one day to one year, and may even be for the life of the patient. Chronic, long-term administration may be indicated.

Synthesis

[0097] The reaction scheme and Examples are intended to illustrate the synthesis of a representative number of compounds. Accordingly, the Examples are intended to illustrate but not to limit the invention. Additional compounds not specifically exemplified may be synthesized using conventional methods in combination with the methods described herein.

[0098] The compounds described herein can be prepared according to methods known in the art, as shown in Scheme 1.

Scheme 1



In Scheme 1, PG may be H or an *N*-protecting group. The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting

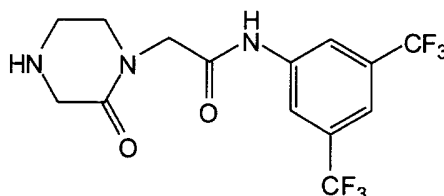
groups are disclosed in Greene, "Protective Groups In Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. *N*-protecting groups include acyl, aryloyl, or carbamyl groups; sulfonyl-containing groups; carbamate forming group; alkaryl groups such as benzyl; and silyl groups.

- 5 Exemplary *N*-protecting groups include formyl, acetyl, benzoyl, pivaloyl, *t*-butylacetyl, alanyl, phenylsulfonyl, benzyl, *t*-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

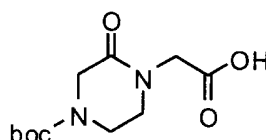
EXAMPLES

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Example 1: Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxopiperazin-1-yl)acetamide (Compound 1)



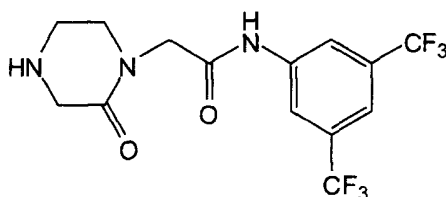
- 15 A. Synthesis of 2-(4-*tert*-butoxycarbonyl)-2-oxopiperazin-1-yl)acetic acid



- [0099] Under nitrogen and at room temperature, to a solution of 1-Boc-3-oxopiperazine (10.4 g, 51.9 mmol) in anhydrous DMF (100 mL) was added NaH (60% in mineral oil, 2.50 g, 62.3 mmol) portionwise. After addition, the mixture was stirred at room temperature for 30 min and then at 65 °C for 1 h. After the mixture was cooled to room temperature, ethyl chloroacetate (7.63 g, 62.3 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and at 65 °C for 2 h. Water (5 mL) was added, and the solution concentrated. Brine (100 mL) was added, and the reaction mixture was extracted with EtOAc (5 × 100 mL). The combined
20 extracts were washed with water (100 mL) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated by rotary evaporation, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes: 1/1 v/v) to give the
25 desired product as a white solid (13 g, 87%).

[00100] The solid was dissolved in methanol (50 mL) and treated with aqueous NaOH (2.5 N, 50 mL) for 2.5 h. The methanol was removed, and the residual aqueous solution was repeatedly acidified (carefully to pH = 2 each time) and then extracted with EtOAc (10 × 100 mL). The combined extracts were dried over anhydrous Na₂SO₄ and concentrated to afford the acid as a white solid (11.2 g, 85%).

B. *Synthesis of N-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxopiperazin-1-yl)acetamide*

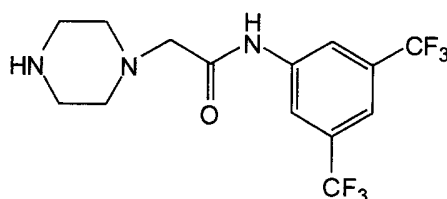


[00101] A 500 mL, single-necked, round-bottomed flask equipped with a magnetic stir bar was charged with 2-(4-tert-butoxycarbonyl)-2-oxopiperazin-1-yl)acetic acid (13.0 g, 50.3 mmol), 3,5-bis(trifluoromethyl)aniline (12.6 g, 55.3 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethylruonium hexafluorophosphate (HATU) (22.8 g, 60.0 mmol) in DMF (100 mL). Diisopropylethylamine (DIPEA) (10.3 g, 80.0 mmol) was added. The reaction mixture was stirred at room temperature for 16 h and then concentrated to ~60 mL by rotary evaporation. Saturated NaHCO₃ aqueous solution (200 mL) was added, and the mixture was extracted with EtOAc (2 × 200 mL) and water (200 mL), and was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated by rotary evaporation, and the residue was purified by flash chromatography on silica gel (CH₂Cl₂, then EtOAc/hexanes, 1:1 in v/v) followed by recrystallization from CH₂Cl₂/hexanes to give a white solid (20.0g, 85%).

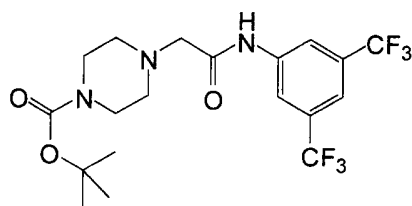
[00102] The solid (17 g, 36.2 mmol) was treated with saturated HCl in EtOAc (350 mL) for 10 min to afford the desired compound quantitatively. Purity (HPLC): 100%. ¹H NMR (400 MHz, D₂O) δ 3.61 (t, 2H, J=5.4 Hz), 3.71 (t, 2H, J=5.4Hz), 3.96 (s, 2H), 4.32 (s, 2H), 7.73 (s, 1H), 7.88 (s, 2H). ES-MS *m/z* 370.2 (M+H). Anal. Calcd. For C₁₄H₁₃F₆N₃O₂·1.0HCl·0.63H₂O: C, 40.37; H, 3.68; N, 10.09; Cl 8.51. Found: C, 40.42; H, 3.75; N, 10.00; Cl, 8.50.

[00103] Compounds 2-4 were prepared in an analogous manner.

Example 2: Synthesis of N-(3,5-bis(trifluoromethyl)phenyl)-2-(piperazin-1-yl)acetamide (Compound 5)

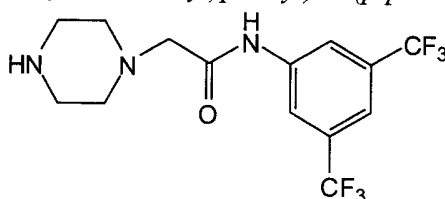


A. Synthesis of tert-butyl-4-(2-(3,5-bis(trifluoromethyl)phenylamino)-2-oxoethyl)piperazine-1-carboxylate



[00104] A mixture of N-(3,5-bis(trifluoromethyl)phenyl)-2-chloroacetamide (1.60 g, 5.23 mmol), tert-butyl piperazine-1-carboxylate (1.46 g, 7.85 mmol), K₂CO₃ (2.17 g, 15.7 mmol), and KI (cat.) in CH₃CN (50 mL) was stirred at room temperature overnight. The reaction was then diluted with EtOAc and washed with water. The organic layer was dried with Na₂SO₄, filtered, and the solvent was removed in vacuo to provide a solid. The solid was purified via automated flash chromatography (EtOAc/petroleum ether) to provide the product as a solid in excellent yield.

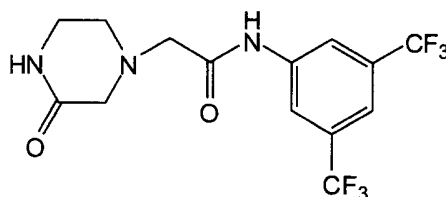
B. Synthesis of N-(3,5-bis(trifluoromethyl)phenyl)-2-(piperazin-1-yl)acetamide



[00105] A solution of tert-butyl 4-(2-(3,5-bis(trifluoromethyl)phenylamino)-2-oxoethyl)piperazine-1-carboxylate (2.00 g, 4.39 mmol) in CH₂Cl₂ (25 mL) was treated with 2M HCl in Et₂O (120 mL). The reaction was stirred at room temperature overnight. At this time, the solvent was removed under reduced pressure to provide the product as a white powder (HCl salt) in quantitative yield.

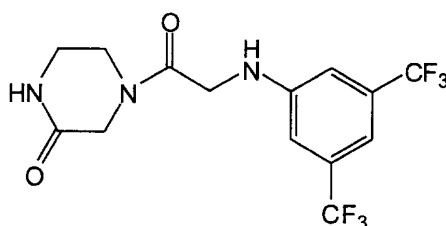
[00106] Compounds 6-8 were prepared in an analogous manner.

Example 3: Synthesis of N-(3,5-bis(trifluoromethyl)phenyl)-2-(3-oxopiperazin-1-yl)acetamide (Compound 9)



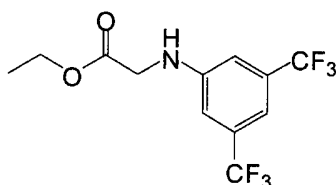
[00107] A mixture of N-(3,5-bis(trifluoromethyl)phenyl)-2-chloroacetamide (0.20 g, 0.65 mmol), piperazin-2-one (0.10 g, 0.98 mol), K₂CO₃ (0.18 g, 1.31 mmol), and KI (cat.) in CH₃CN (10 mL) was stirred overnight at room temperature. The reaction mixture was then diluted with EtOAc, washed with water, dried with Na₂SO₄, filtered, and the solvent was removed in vacuo to provide a white solid. The residue was purified by adding CH₂Cl₂, centrifuging, and pipetting off the supernatant (2 times). This provided the product in moderate yield and excellent purity.

Example 4: Synthesis of 4-(2-(3,5-bis(trifluoromethyl)phenylamino)acetyl)piperazin-2-one (Compound 10)



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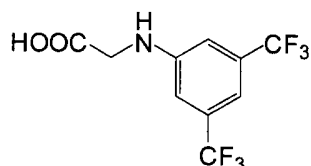
A. Synthesis of ethyl 2-(3,5-bis(trifluoromethyl)phenylamino)acetate



[00108] A mixture of 3,5-bis(trifluoromethyl)aniline (4.43 g, 19.33 mmol), ethyl 2-chloroacetate (2.37 g, 19.33 mmol), potassium carbonate (5.34 g, 38.66 mmol), potassium iodide (0.1 g, cat.), and acetonitrile (50 mL) was stirred at 20 °C for 2 days. The reaction mixture was then diluted with ethyl acetate (200 mL). The organic layer was subsequently washed with aqueous saturated sodium bicarbonate (2 × 20 mL) followed by water (2 × 20 mL), and the organic was then dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was diluted with

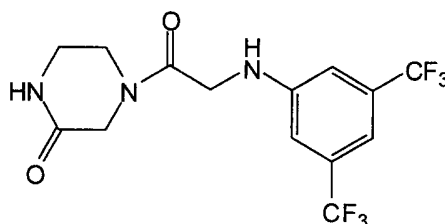
petroleum ether (20 mL). A white solid precipitated out to provide the desired compound (1.10 g, 18% yield). MS: 316.4 (M+1).

B. Synthesis of 2-(3,5-bis(trifluoromethyl)phenylamino)acetic acid



5
 [00109] A mixture of ethyl 2-(3,5-bis(trifluoromethyl)phenylamino)acetate (1.10 g, 3.48 mmol), lithium hydroxide (0.58 g, 13.93 mol), dioxane (5 mL), and water (5 mL) was stirred at room temperature for 3 h. The solvent was removed in vacuo, and the reaction product was then diluted with water (10 mL) and acidified with acetic acid to
 10 pH of about 4. A white solid precipitated to give the desired product (0.85 g, 85% yield). MS: 286.1 (M-1).

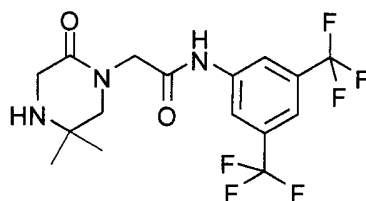
C. Synthesis of 4-(2-(3,5-bis(trifluoromethyl)phenylamino)acetyl)piperazin-2-one



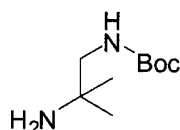
15 [00110] A mixture of 2-(3,5-bis(trifluoromethyl)phenylamino)acetic acid (0.20 g, 0.70 mmol), piperazin-2-one (0.07 g, 0.70 mmol), (O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium (0.27 g, 0.70 mmol), and *N,N*-diisopropylethylamine (0.11 g, 0.84 mmol) in anhydrous dimethyl formamide (5 mL) was stirred at 20 °C for 2 days. The volatile components were then removed in vacuo. The residue was then
 20 dissolved in ethyl acetate (100 mL), washed with saturated aqueous sodium bicarbonate solution (2 × 20 mL) followed by water (2 × 20 mL), and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo to provide the crude product, which was then purified using flash chromatography (ethyl acetate:petroleum ether 1:2) to obtain a white solid (0.20 g, 78% yield). MS: 370.6
 25 (M+1).

[00111] Compounds 11 and 12 were prepared in an analogous manner.

Example 5: Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-2-(5,5-dimethyl-2-oxopiperazin-1-yl)acetamide (Compound 13)

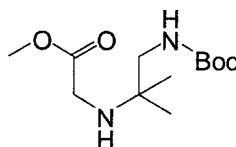


5 A. *Synthesis of tert-butyl 2-amino-2-methylpropylcarbamate*



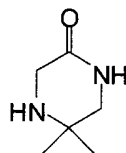
[00112] A mixture of 2-methylpropane-1, 2-diamine (1.8 g, 21 mmol), Boc_2O (2.0 g, 10 mmol), and triethylamine (3.0 ml, 21 mmol) in dichloromethane (5 mL) was stirred at room temperature for 1 day. The solution was concentrated to dryness by rotary evaporation, and the residue was purified by automated flash chromatography on silica gel (MeOH/dichloromethane: 10:1) to give a white solid (2.40 g, 86%).

B. *Synthesis of methyl 2-(1-(tert-butoxycarbonylamino)-2-methylpropan-2-ylamino)acetate*



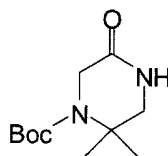
15 [00113] A mixture of *tert*-butyl 2-amino-2-methylpropylcarbamate (0.90 g, 4.8 mmol), methyl 2-chloroacetate (0.51 g, 4.8 mmol), and potassium carbonate (0.66 g, 4.8 mmol) in acetonitrile (5 mL) was stirred at room temperature for 1 day. The solution was concentrated to dryness by rotary evaporation and the residue was purified by automated flash chromatography on silica gel (Hexanes/EtOAc: 1/1) to give a white solid (0.54 g, 43%).

C. *Synthesis 5, 5 –dimethyl-3-oxopiperazin-2-one*



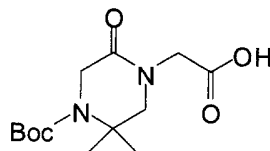
[00114] A mixture of 2-(1-(*tert*-butoxycarbonylamino)-2-methylpropan-2-ylamino)acetate (0.54 g, 2.07 mmol) and 2 N HCl in MeOH solution (5 mL) was stirred at room temperature for 3 hours. The solution was concentrated to dryness, and to the crude product were added triethylamine (1.0 mL, 7.0 mmol) and acetonitrile (5 mL). The mixture was heated at reflux overnight. The solution was concentrated to dryness by rotary evaporation, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes: from 30% to 100%) to give a white solid (0.245 g, 94%).

D. *Synthesis of tert-butyl 5, 5 –dimethyl-3-oxopiperazin-2-one*



[00115] A mixture of 5, 5-dimethylpiperazin-2-one (0.245 g, 1.90 mmol), Boc₂O (0.70 g, 3.5 mmol), and DIPEA (0.56 g, 4.4 mmol) in DMF (5 mL) was stirred at room temperature for 1 day. The solution was concentrated to dryness by rotary evaporation, and the residue was purified by automated flash chromatography on silica gel (EtOAc/hexanes: gradient elution from 30% to 100%) to give a white solid (0.40 g, 92%).

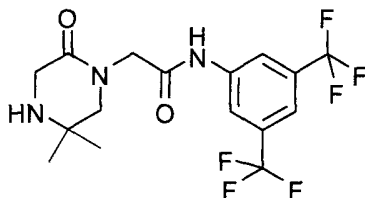
E. *Synthesis of 2-(4-(tert-butoxycarbonyl)-5, 5-dimethyl-2-oxopiperazin-1-yl)acetic acid*



[00116] This compound was prepared using the procedure as described for 2-(4-*tert*-butoxycarbonyl)-2-oxopiperazin-1-yl)acetic acid, using *tert*-butyl 5, 5 –dimethyl-

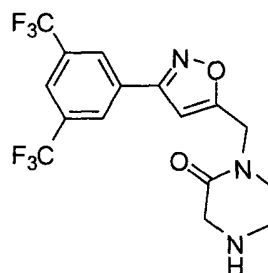
3-oxopiperazin-2-one (0.40 g, 1.7 mmol). The desired acid was obtained as a white solid (0.34 g, 70%).

F. Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-2-(5,5-dimethyl-2-oxopiperazin-1-yl)acetamide (Compound 13)

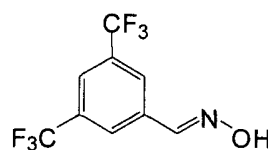


[00117] To a solution of 2-(4-(tert-butoxycarbonyl)-5,5-dimethyl-2-oxopiperazin-1-yl)acetic acid (0.34 g, 1.2 mmol), 3,5-bis(trifluoromethyl)aniline (0.191 g, 1.2 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (0.50 g, 1.3 mmol) in DMF (5 mL) was added DIPEA (0.350 g, 2.75 mmol). The reaction mixture was stirred at room temperature for 16 h, and the mixture was then concentrated to dryness. Saturated NaHCO₃ aqueous solution (10 mL) was added, and the mixture was extracted with EtOAc (20 mL). The extract was washed with saturated NH₄Cl aqueous solution (10 mL) and water (10 mL), and the extract was dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated by rotary evaporation, and the residue was purified by automated flash chromatography on silica gel (EtOAc/hexanes, 1: 2 in v/v) to give a white solid. The solid was treated with saturated HCl in EtOAc (10 mL) for 30 min. The acidic solution was neutralized with diluted K₂CO₃ solution to pH = 9 and extracted with EtOAc (3 × 30 mL). The combined extract was dried over anhydrous Na₂SO₄ to afford the titled compound (0.345 g, 72%). Purity (HPLC): 97.0%. ES-MS *m/z* 398.6 (M+H).

Example 6: Synthesis of 1-((3-(3,5-bis(trifluoromethyl)phenyl)isoxazol-5-yl)methyl)piperazin-2-one (Compound 14)

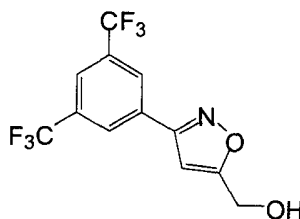


5 A. *Synthesis of (E)-3,5-bis(trifluoromethyl)benzaldehyde oxime*



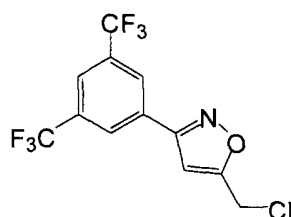
[00118] A mixture of 3,5-bis(trifluoromethyl)benzaldehyde (1.2 g, 5.0 mmol), hydroxyamine hydrochloride (0.69 g, 10 mmol), and sodium hydroxide (0.40 g, 10 mmol) in ethanol (95%, 20 mL) was refluxed overnight. The solution was
10 concentrated to dryness, and the residue was dissolved in EtOAc (20 mL) and washed with water (2 × 20 mL). The organic layer was dried and concentrated to give a white solid (1.23 g, 96%).

B. *Synthesis of (3-(3,5-bis(trifluoromethyl)phenyl)isoxazol-5-yl)methanol*



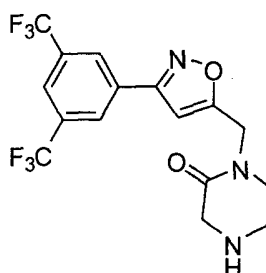
15 [00119] A mixture of (E)-3,5-bis(trifluoromethyl)benzaldehyde oxime (3.6 g, 14 mmol), N-chloro-succinimide (2.20g, 16.7 mmol) and pyridine (150 μL, 1.9 mmol) in THF (15 mL) was heated at 60°C for 30 min.. A solution of prop-2-yn-1-ol (1.0 mL, 15 mmol) and triethylamine (2.4 mL) in THF (2 mL) was added at 30°C. The
20 reaction mixture was stirred overnight and concentrated to dryness. The residue was dissolved in dichloromethane (20 mL) and washed with 1N HCl (20 mL × 2). The organic layer was dried and concentrated; the residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:4 v/v) to give a white solid (1.40 g, 27%).

C. *Synthesis of 3-(3,5-bis(trifluoromethyl)phenyl)-5-(chloromethyl)isoxazole*



[00120] A mixture of 3-(3,5-bis(trifluoromethyl)phenyl)isoxazol-5-yl)methanol
 5 (4) (1.40 g, 4.5 mmol), and thionyl chloride (1 mL, 13.9 mmol) in toluene (15 mL)
 was refluxed overnight. The reaction mixture was concentrated to dryness, and the
 residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:10 v/v)
 to give a brown oil (1.20 g, 81%).

10 D. *Synthesis of 1-((3-(3,5-bis(trifluoromethyl)phenyl)isoxazol-5-yl)methyl)piperazin-2-one*



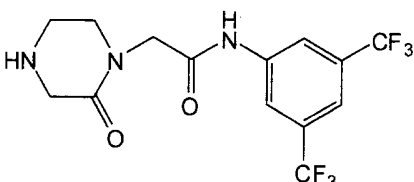
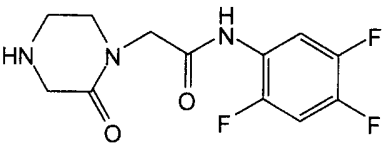
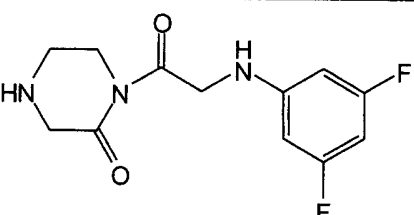
[00121] Under nitrogen, at room temperature, to a solution of 1-Boc-3-oxopiperazine (200 mg, 1 mmol) in anhydrous THF (5 mL) was added NaH (60% in
 15 mineral oil, 100 mg, 2.5 mmol) portionwise. After addition, the mixture was stirred at
 room temperature for 30 min and then at 65 °C for 1 h. After the mixture was cooled
 to room temperature, 3-(3,5-bis(trifluoromethyl)phenyl)-5-(chloromethyl)isoxazole
 (300 mg, 0.91mmol) was added. The reaction mixture was stirred at room
 temperature overnight. Water (5 mL) was added, and the solution was concentrated.
 20 Brine (100 mL) was added, and the reaction mixture was extracted with EtOAc (3 ×
 10 mL). The combined extracts were washed with water (10 mL) and dried over
 anhydrous Na₂SO₄. After filtration, the filtrate was concentrated by rotary
 evaporation, and the residue was purified by flash chromatography on silica gel
 (EtOAc/hexanes; 1/1 v/v) to give the desired product as a white solid. The solid was
 25 dissolved in trifluoroacetic acid (2 mL) and dichloromethane (2 mL), and the mixture
 was stirred at room temperature for 3 hours. The solution was concentrated to

dryness, neutralized with diluted K_2CO_3 solution to pH = 9, and extracted with EtOAc (3×30 mL). The combined extract was dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue obtained was purified by flash chromatography on silica gel (MeOH/dichloromethane: 1/20 v/v) to give the desired neutral product as a white solid. The solid was dissolved in dichloromethane and added 2N HCl ether solution to afford the titled compound (0.106 g, 47%). Purity (HPLC): 99.5%. ES-MS m/z 394.3 (M+H).

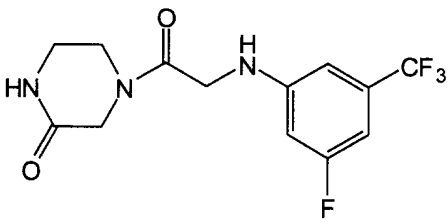
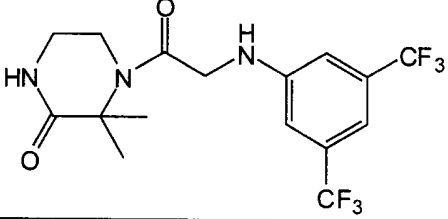
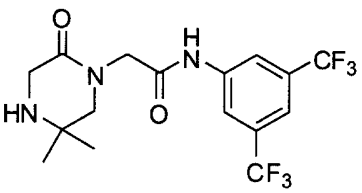
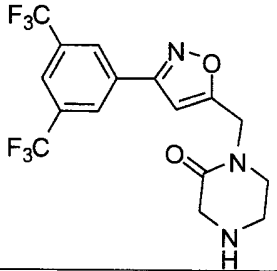
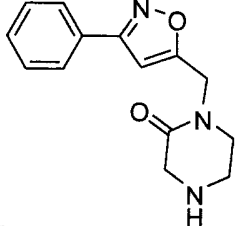
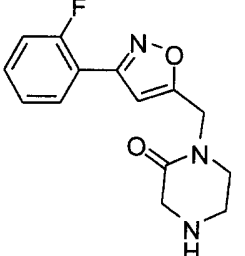
Example 7: Mass Spectrometric Analysis

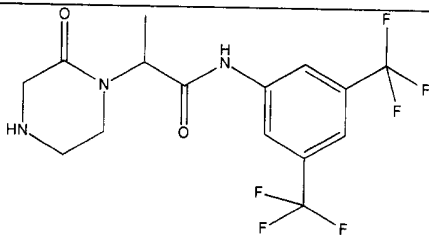
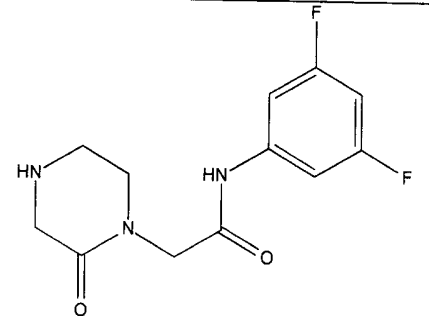
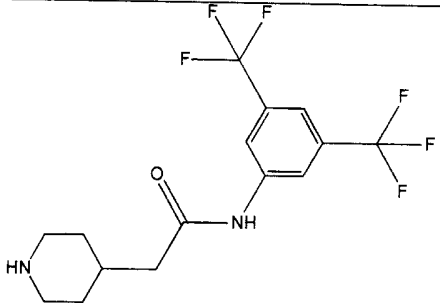
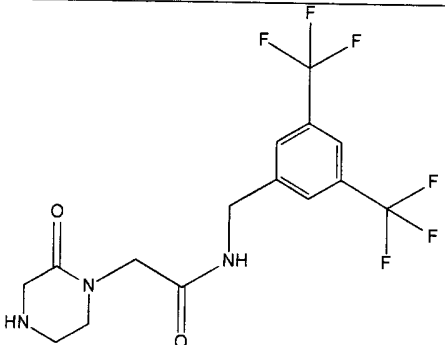
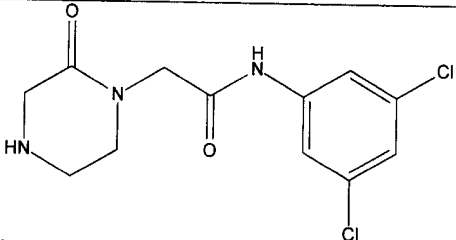
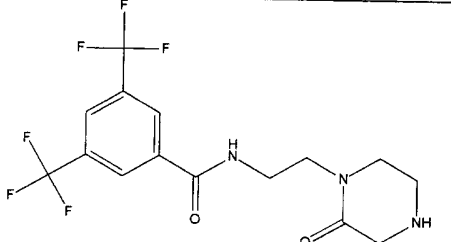
[00122] Following the general procedures set forth in Examples 1-6, the following compounds listed in Table 2 below were prepared. Mass spectrometry was employed with the final compound and at various stages throughout the synthesis as a confirmation of the identity of the product obtained (M+1). For the mass spectrometric analysis, samples were prepared at an approximate concentration of 1 μ g/mL in acetonitrile with 0.1% formic acid. Samples were then manually infused into an Applied Biosystems API3000 triple quadrupole mass spectrometer and scanned in Q1 in the range of 50 to 700 m/z .

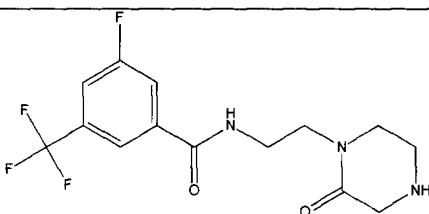
Table 2

Compound No.	Name	Structure	Mass Spec (m/z)
1	N-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxopiperazin-1-yl)acetamide		370.2
2	2-(2-oxopiperazin-1-yl)-N-(2,4,5-trifluorophenyl)acetamide		--
3	1-(2-(3,5-difluorophenylamino)acetyl)piperazin-2-one		--

Compound No.	Name	Structure	Mass Spec (m/z)
4	N-(3,5-bis(trifluoromethyl)phenyl)-2-(3,3-dimethyl-2-oxopiperazin-1-yl)acetamide		397.1
5	N-(3,5-bis(trifluoromethyl)phenyl)-2-(piperazin-1-yl)acetamide		355.1
6	N-(3,5-difluorophenyl)-2-(piperazin-1-yl)acetamide		255.1
7	2-(piperazin-1-yl)-N-(2,4,5-trifluorophenyl)acetamide		273.1
8	N-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(piperazin-1-yl)acetamide		305.1
9	N-(3,5-bis(trifluoromethyl)phenyl)-2-(3-oxopiperazin-1-yl)acetamide		369.1
10	4-(2-(3,5-bis(trifluoromethyl)phenylamino)acetyl)piperazin-2-one		369.1

Compound No.	Name	Structure	Mass Spec (m/z)
11	4-(2-(3-fluoro-5-(trifluoromethyl)phenylamino)acetyl)piperazin-2-one		319.1
12	4-(2-(3,5-bis(trifluoromethyl)phenylamino)acetyl)-3,3-dimethylpiperazin-2-one		397.1
13	N-(3,5-bis(trifluoromethyl)phenyl)-2-(5,5-dimethyl-2-oxopiperazin-1-yl)acetamide		397.1
14	1-((3-(3,5-bis(trifluoromethyl)phenyl)isoxazol-5-yl)methyl)piperazin-2-one		393.1
15	1-((3-phenylisoxazol-5-yl)methyl)piperazin-2-one		257.1
16	1-((3-(2-fluorophenyl)isoxazol-5-yl)methyl)piperazin-2-one		275.1

Compound No.	Name	Structure	Mass Spec (m/z)
17	N-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxopiperazin-1-yl)propanamide		383.29
18	N-(3,5-difluorophenyl)-2-(2-oxopiperazin-1-yl)acetamide		269.25
19	N-(3,5-bis(trifluoromethyl)phenyl)-2-(piperidin-4-yl)acetamide		354.29
20	N-(3,5-bis(trifluoromethyl)benzyl)-2-(2-oxopiperazin-1-yl)acetamide		383.29
21	N-(3,5-dichlorophenyl)-2-(2-oxopiperazin-1-yl)acetamide		302.16
22	N-(2-(2-oxopiperazin-1-yl)ethyl)-3,5-bis(trifluoromethyl)benzamide		383.29

Compound No.	Name	Structure	Mass Spec (m/z)
23	3-fluoro-N-(2-(2-oxopiperazin-1-yl)ethyl)-5-(trifluoromethyl)benzamide		333.28

Example 8: Cav3.2 Voltage-Clamp Electrophysiological Assays

[00123] Prior to recording currents from Cav3.2 T-type Ca^{2+} channels expressed in HEK cells, the culture media was replaced with extracellular solution (ECS) containing (in mM): 142 CsCl, 10 D-glucose, 2 CaCl_2 , 1 MgCl_2 , 10 HEPES, pH adjusted to 7.4 with CsOH. Borosilicate glass patch pipettes, pulled on a P-97 micropipette puller (Sutter Instruments, Novato, CA) with typical resistances of 2-4 MW, were backfilled with intracellular solution containing (in mM): 126.5 Cs-methanesulphonate, 2 MgCl_2 , 10 HEPES, 11 EGTA, 2 Na-ATP, pH adjusted to 7.3 CsOH. Voltages were recorded in the whole-cell configuration at room temperature ($\sim 21^\circ\text{C}$) using an Axopatch 200B (Molecular Devices, Sunnyvale, CA) patch-clamp amplifier. Recordings were low-pass filtered at 1 kHz (-3 dB 4-pole Bessel filter), digitized at 2 kHz with a Digidata 1322A interface (Molecular Devices), and acquired using pClamp 9.2 (Molecular Devices). No leak subtraction was used. Test compounds, prepared as 30 mM stock solutions in DMSO and diluted in extracellular buffer, were applied through a gravity driven multi-barrelled array of capillaries (24 gauge) connected to reservoirs controlled by solenoid valves. The effects of compounds on Cav3.2 slow and fast inactivation were evaluated using four different voltage protocols. The voltage dependence of fast and slow channel inactivation was examined using a two pulse protocol. Data were analyzed and fitted using OriginPro v.7.5 (OriginLab, Northampton, MA) software. Data obtained according to these methods are shown in Table 3.

Table 3

Compound	$V_{1/2}$ fast inactivation (mV)	$V_{1/2}$ slow inactivation (mV)	Fraction current remaining at -40 mV	τ recovery from fast inactivation (ms)	τ recovery from slow inactivation (ms)	Fraction of current recovered at 5.1 s interval
Control ECS	-61	-75	0.62	270	533	0.96
1	-66	*-80	0.51	311	**684	0.87
2	-65	-80	0.58	260	448	0.98
9		** -83	**0.32	**472	* 700	*0.80

$V_{1/2}$ voltage-dependence of half inactivation; * $P \leq 0.05$, ** $P < 0.005$

Example 9: Nav1.5/1.7/1.8 Voltage-Clamp Electrophysiological Assays

- 5 **[00124]** To examine the effects of compounds on enhancement of slow inactivation of Nav1.7 and Nav1.8 channels expressed in HEK cells the culture media was replaced with an extracellular solution containing (in mM): 137 NaCl, 4 KCl, 1.8 CaCl₂, 1 MgCl₂, 10 HEPES, 10 glucose, pH adjusted to 7.4 with NaOH. The intracellular solution contained (in mM): 130 KCl, 1 MgCl₂, 5 EGTA, 10 HEPES, 5
- 10 K₂ATP, adjusted to pH 7.3 with KOH. Whole-cell recordings, preparation and application of test compounds were performed in a similar manner to the Ca_v3.2 electrophysiological assays. Voltage protocols were applied to quantify the effects of test compounds to enhance slow inactivation for Nav1.7 and Nav1.8. Data obtained regarding inhibition of Nav 1.7 channels are shown in Table 4.

Table 4

Compound	Concentration tested	Fraction current remaining	n cells
1	30 μ M	0.40	6
10	10 μ M	0.91	4
	100 μ M	0.74	4
20	30 μ M	0.87	4
23	30 μ M	0.91	5

[00125] Inhibition of the TTX-resistant Nav1.5 sodium channel, a key cardiac ion channel, can have profound effects on the duration and amplitude of the cardiac action potential and can result in arrhythmias and other heart malfunctions. To assess the potential cardiac liability of compounds at an early stage in the drug discovery process, a Nav1.5 sodium channel screening assay is performed on Molecular Device's PatchXpress™ automated electrophysiology platform. Under voltage-clamp conditions, Nav1.5 currents were recorded from HEK cells expressing the human Nav1.5 channel in the absence and presence of increasing concentrations of the test compound to obtain an IC₅₀ value. The external recording solution contained (in mM): 90 TEACl, 50 NaCl, 1.8 CaCl₂, 1 MgCl₂, 10 HEPES, 10 glucose, adjusted to pH 7.4 with TEA-OH and to 300 mOsm with sucrose (if necessary), while the internal patch pipette solution contained (in mM): 129 CsF, 2 MgCl₂, 11 EGTA, 10 HEPES, 3 Na₂ATP adjusted to pH 7.2 with CsOH and to 290 mOsm with sucrose (if necessary). Nav1.5 channel currents were evoked using a cardiac action potential waveform at 1 Hz, digitized at 31.25 kHz and low-pass filtered at 12 kHz. As shown in Table 5, the tested compounds did not act as inhibitors of the cardiac Nav 1.5 channel and are thus selective inhibitors.

20

Table 5

Compound no.	HNA _v 1.5 Cardiac AP 1Hz IC ₅₀
1	100000
5	40000
9	80000

Example 10: L5/L6 Spinal Nerve Ligation (SNL) - Chung Pain Model

[00126] The Spinal Nerve Ligation is an animal model representing peripheral nerve injury generating a neuropathic pain syndrome. In this model experimental animals develop the clinical symptoms of tactile allodynia and hyperalgesia. L5/L6 Spinal nerve ligation (SNL) injury was induced using the procedure of Kim and Chung (Kim et al., *Pain* 50:355-363 (1992)) in male Sprague-Dawley rats (Harlan; Indianapolis, IN) weighing 200 to 250 grams.

10 [00127] Anaesthesia was induced with 2% isoflurane in O₂ at 2 L/min and maintained with 0.5% isoflurane in O₂. Rats were then shaved and aseptically prepared for surgeries. A 2 cm paraspinal incision was made at the level of L4-S2. L4/L5 was exposed by removing the transverse process above the nerves with a small rongeur. The L5 spinal nerve is the larger of the two visible nerves below the
15 transverse process and lies closest to the spine. The L6 spinal nerve is located beneath the corner of the slope bone. A home-made glass Chung rod was used to hook L5 or L6 and a pre-made slip knot of 4.0 silk suture was placed on the tip of the rod just above the nerve and pulled underneath to allow for the tight ligation. The L5 and L6 spinal nerves were tightly ligated distal to the dorsal root ganglion. The
20 incision was closed, and the animals were allowed to recover for 5 days. Rats that exhibited motor deficiency (such as paw-dragging) or failure to exhibit subsequent tactile allodynia were excluded from further testing.

[00128] Sham control rats underwent the same operation and handling as the experimental animals, but without SNL.

25 [00129] Prior to initiating drug delivery, baseline behavioural testing data is obtained. At selected times after infusion of the Test or Control Article behavioural data can then be collected again.

A. *Assessment of Tactile Allodynia – Von Frey*

[00130] The assessment of tactile allodynia consisted of measuring the withdrawal threshold of the paw ipsilateral to the site of nerve injury in response to probing with a series of calibrated von Frey filaments (innocuous stimuli). Animals were acclimated to the suspended wire-mesh cages for 30 min before testing. Each von Frey filament was applied perpendicularly to the plantar surface of the ligated paw of rats for 5 sec. A positive response was indicated by a sharp withdrawal of the paw. For rats, the first testing filament is 4.31. Measurements were taken before and after administration of test articles. The paw withdrawal threshold was determined by the non-parametric method of Dixon (Dixon, *Ann. Rev. Pharmacol. Toxicol.* 20:441-462 (1980)), in which the stimulus was incrementally increased until a positive response was obtained, and then decreased until a negative result was observed. The protocol was repeated until three changes in behaviour were determined ("up and down" method) (Chaplan et al., *J. Neurosci. Methods* 53:55-63 (1994)). The 50% paw withdrawal threshold was determined as $(10^{[X_f + k\delta]})/10,000$, where X_f = the value of the last von Frey filament employed, k = Dixon value for the positive/negative pattern, and δ = the logarithmic difference between stimuli. The cut-off values for rats were no less than 0.2 g and no higher than 15 g (5.18 filament); for mice no less than 0.03 g and no higher than 2.34 g (4.56 filament). A significant drop of the paw withdrawal threshold compared to the pre-treatment baseline is considered tactile allodynia. Rat SNL tactile allodynia were tested for Compounds 1-4 and 9-12 at 60 minutes compared to baseline and post-SNL. Compounds 1, 9, and 13 showed significant anti-allodynia as shown in Figure 1 and in Table 6 below.

Table 6

Compound no.	Rat SNL Tactile Allodynia (% Antiallodynia)		
	1 hour	2 hours	4 hours
1	52	55	37
3	1	--	4
9	36	--	--
10	10	13	15
11	9	4	1
12	9	11	42
13	16	8	5
19	47	39	32

B. Assessment of Thermal Hypersensitivity - Hargreaves

5 **[00131]** The method of Hargreaves and colleagues (Hargreaves et al., *Pain* 32:77-8 (1988)) can be employed to assess paw-withdrawal latency to a noxious thermal stimulus.

10 **[00132]** Rats may be allowed to acclimate within a Plexiglas enclosure on a clear glass plate for 30 minutes. A radiant heat source (e.g., halogen bulb coupled to an infrared filter) can then be activated with a timer and focused onto the plantar surface of the affected paw of treated rats. Paw-withdrawal latency can be determined by a photocell that halts both lamp and timer when the paw is withdrawn. The latency to withdrawal of the paw from the radiant heat source can be determined prior to L5/L6 SNL, 7-14 days after L5/L6 SNL but before drug, as well as after drug administration.

15 A maximal cut-off of 33 seconds is typically employed to prevent tissue damage. Paw withdrawal latency can be thus determined to the nearest 0.1 second. A significant drop of the paw withdrawal latency from the baseline indicates the status of thermal hyperalgesia. Antinociception is indicated by a reversal of thermal hyperalgesia to the pre-treatment baseline or a significant ($p < 0.05$) increase in paw

withdrawal latency above this baseline. Data is converted to % anti hyperalgesia or % anti nociception by the formula: $(100 \times (\text{test latency} - \text{baseline latency}) / (\text{cut-off} - \text{baseline latency}))$ where cut-off is 21 seconds for determining anti hyperalgesia and 40 seconds for determining anti nociception.

5

Example 11: 6 Hz Psychomotor Seizure Model of Partial Epilepsy

[00133] Compounds were evaluated for the protection against seizures induced by a 6 Hz, 0.2 ms rectangular pulse width of 3 s duration, at a stimulus intensity of 32 mA (CC97) applied to the cornea of male CF1 mice (20-30 g) according to procedures described by Barton et al, "Pharmacological Characterization of the 6 Hz Psychomotor Seizure Model of Partial Epilepsy," *Epilepsy Res.* 47(3):217-27 (2001). Seizures are characterised by the expression of one or more of the following behaviours: stun, forelimb clonus, twitching of the vibrissae and Straub-tail immediately following electrical stimulation. Animals were considered "protected" if following pre-treatment with a compound the 6 Hz stimulus failed to evoke a behavioural response as describe above. Exemplary results using this assay are shown in Table 7.

15

Table 7

Compound No.	Epilepsy 6 Hz (% protected)					Epilepsy 6 Hz (ED ₅₀)
	0.25 hr	0.5 hr	1 hr	2 hr	4 hr	
1	75	100	75	--	--	128
9	75	25	88	75	0	90
19	100	100	100	100	0	--

20

**Example 12: GAERS (Genetic Absence Epilepsy Rats from Strasbourg)
Epilepsy Model**

- [00134] The GAERS (Genetic Absence Epilepsy Rats from Strasbourg) is noted for its long and frequently recurring absence seizure episodes. Investigators have
5 determined, using electrophysiological recordings from neurons within the thalamus, that the activity and expression of the low-voltage calcium channels is significantly increased in GAERS. Eight female GAERS rats, bred in the Ludwig Institute for Cancer Research, were used for this study. Rats weighed between 180 and 250g and aged between 18 and 26 weeks at the start of the experiment.
- 10 [00135] Electrodes can be made by soldering together gold-plated sockets (220-S02 Ginder Scientific, VA, Canada), stainless steel teflon coated wire (SDR clinical technology, NSW, Australia) and a small stainless steel screw (1.4 × 3 mm, Mr. Specks, Australia). Animals can be anaesthetised with inhalation of Isoflurane in equal parts of medical air and oxygen (5% induction, 2.5 – 1.5% maintenance) or
15 alternatively by intraperitoneal injection with xylazine (10mg/kg) and ketamine (75 mg/kg). The animals can be fixated in a stereotaxic frame by means of ear bars. A midline incision on the scalp was made, skin and connective tissue is scraped and pushed laterally to expose underlying skull. Six holes are drilled bilaterally, two in the frontal bone and four in the parietal bone, approximately 2mm anterior to bregma,
20 and four and 10 mm posterior to bregma. Six electrodes are then implanted in the holes, and gold-plated sockets were clipped into 9-pin ABS plug (GS09PLG-220, Ginder Scientific, Canada). Two side-anchoring screws can be placed laterally into skull to improve strength of cap fixation. Caps can then be held in place with dental cement.
- 25 [00136] Post-operatively, animals are given the analgesic Rimadyl (4mg/kg), placed in their cages on a heat mat, and observed until recovery. Rats are caged separately throughout the study, weighed and health-checked daily, and are allowed 7 days to recover prior to commencement of the experimental procedures. Rats are typically allowed free access to rodent chow (brand, WA stock feeders) and water
30 under 12:12 light dark conditions in the Biological Research Facility of the Department of Medicine (RMH).
- [00137] Prior to first drug treatment, rats are tested for absence-type seizures, which are accompanied by generalised spike and wave discharges (SWD) on an EEG

recording. Testing, and all further experiments are performed in a quiet, well lit room with rats in their home cages. Rats are connected via 6-channel wire cables, which are cut and soldered to six gold-plated pins inserted into a 9 pin socket. Cables can be connected to a computer running Compumedics™ EEG acquisition software

5 (Melbourne, Australia). Three rats that do not have adequate baseline seizures at the start of the study can be commenced in week 2 and their treatments can be made up for at the end according to the schedule. On week 1, day 1, after the acclimation period following surgical implantation of subdural electrodes, four animals can be habituated with the cable connected for 15 minutes, and then have their SWDs

10 recorded for 60 minutes as baseline. Immediately following baseline, rats are given one of the test, reference, or control articles according to the treatment schedule, and target period is recorded from 15 minutes after injection for 120 minutes. Animals are monitored throughout the experiment, and are kept quietly wakeful during baseline and target periods.

15 [00138] The seizure expression for the 60 minutes pre-injection and 120 minutes post-injection EEG recording (starting 15 minutes post-drug administration) are quantified by marking the start and finish of the burst of SWDs. This can be done with the assistance of SWCFinder® software which has been custom designed to quantitate GAERS seizures, and researchers are blinded to the nature of the drug

20 administered, whereby the analysis is performed blinded. Standard criteria for GAERS seizures is an SWD burst of amplitude of more than three times baseline, a frequency of 7 to 12 Hz, and a duration of longer than 0.5s. From this, the total percent time spent in seizure over the 120 minutes post-injection EEG recording can be determined (percentage time in seizure) as the primary outcome variable.

25

Example 13: Mouse Rotarod Assay

[00139] To assess a compound's undesirable side effects (toxicity), animals were monitored for overt signs of impaired neurological or muscular function. In mice, the rotarod procedure (Dunham and Miya, *J. Am. Pharmacol. Assoc.* 46:208–209 (1957))

30 is used to disclose minimal muscular or neurological impairment (MMI). When a mouse is placed on a rod that rotates at a speed of 6 rpm, the animal can maintain its equilibrium for long periods of time. The animal is considered toxic if it falls off this rotating rod three times during a 1-min period. In addition to MMI, animals may

exhibit a circular or zigzag gait, abnormal body posture and spread of the legs, tremors, hyperactivity, lack of exploratory behavior, somnolence, stupor, catalepsy, loss of placing response and changes in muscle tone. Exemplary data obtained using this assay are shown in Table 8.

5

Table 8

Compound no.	% Impaired					TD ₅₀
	0.25 hr	0.5 hr	1 hr	2 hr	4 hr	
1	0	0	0	0	0	300
9	0	0	0	0	0	--
19	0	75	100	100	100	--

Example 14: Lamina Assay and Data*Recordings on Lamina I/II Spinal Cord Neurons.*

- 10 [00140] Male Wistar rats (P6 to P9 for voltage-clamp and P15 to P18 for current-clamp recordings) were anaesthetized through intraperitoneal injection of Inactin (Sigma). The spinal cord was then rapidly dissected out and placed in an ice-cold solution protective sucrose solution containing (in mM): 50 sucrose, 92 NaCl, 15 D-Glucose, 26 NaHCO₃, 5 KCl, 1.25 NaH₂PO₄, 0.5 CaCl₂, 7 MgSO₄, 1 kynurenic acid,
- 15 and bubbled with 5 % CO₂/ 95 % O₂. The meninges, dura, and dorsal and ventral roots were then removed from the lumbar region of the spinal cord under a dissecting microscope. The "cleaned" lumbar region of the spinal cord was glued to the vibratome stage and immediately immersed in ice cold, bubbled, sucrose solution. For current-clamp recordings, 300 to 350 μ m parasagittal slices were cut to preserve
- 20 the dendritic arbour of lamina I neurons, while 350 to 400 μ m transverse slices were prepared for voltage-clamped Na_v channel recordings. Slices were allowed to recover for 1 hour at 35 °C in Ringer solution containing (in mM): 125 NaCl, 20 D-Glucose, 26 NaHCO₃, 3 KCl, 1.25 NaH₂PO₄, 2 CaCl₂, 1 MgCl₂, 1 kynurenic acid, 0.1 picrotoxin, bubbled with 5 % CO₂/ 95 % O₂. The slice recovery chamber was then
- 25 returned to room temperature (20 to 22 °C) and all recordings were performed at this temperature.

[00141] Neurons were visualized using IR-DIC optics (Zeiss Axioskop 2 FS plus, Gottingen, Germany), and neurons from lamina I and the outer layer of lamina II were selected based on their location relative to the substantia gelatinosa layer. Neurons were patch-clamped using borosilicate glass patch pipettes with resistances of 3 to 6 MΩ. Current-clamp recordings of lamina I/II neurons in the intact slice, the external recording solution was the above Ringer solution, while the internal patch pipette solution contained (in mM): 140 KGluconate, 4 NaCl, 10 HEPES, 1 EGTA, 0.5 MgCl₂, 4 MgATP, 0.5 Na₂GTP, adjusted to pH 7.2 with 5 M KOH and to 290 mOsm with D-Mannitol (if necessary). Only tonic firing neurons were selected for current-clamp experiments, while phasic, delayed onset and single spike neurons were discarded (22). Recordings were digitized at 50 kHz and low-pass filtered at 2.4 kHz.

[00142] Data obtained according to this protocol are shown in Table 9.

Table 9

Compound no.	LAMINA I AND II			
	%Spike Change (Mean; % change from control)	% Spike Change SEM	% Spike Change P<0.05	EC ₅₀
1	-47.3	8.3	no	482
9	-35.5	12.1	no	--
19	-30.3	9.2	no	--

Example 15: Pharmacokinetic Parameters

[00143] Preliminary exposure characteristics of the compounds were evaluated in an in vivo Rat Early Pharmacokinetic (EPK) study design (Table 10), and the data show that the compounds are orally bioavailable. Male Sprague-Dawley rats were dosed via oral (PO) gavage in the detailed formulation. Blood samples were collected from the animals at 6 timepoints out to 4 hours post-dose. Pharmacokinetic analysis was performed on the LC-MS/MS measured concentrations for each timepoint of each compound. Exemplary data are shown in Table 10.

Table 10

Compound No.	Dose (mg/kg)	Route	Formulation	Dose Normalized C _{max} (nM)	Dose Normalized AUC (nM*h)	T _{max} (hr)
1	3	PO	PG	438	1,118	0.25
5	3	PO	PG	48	108	1.8
9	3	PO	PG	484	1,120	1.4
10	30	PO	10% DMSO/90% CMC	355	1,192	1.2
13	30	PO	10% DMSO/90% CMC	172	458	0.67
PG: Propylene glycol DMSO: Dimethyl sulfoxide CMC: 0.5% Carboxy methyl cellulose						

Other Embodiments

5 [00144] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice

10 within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth.

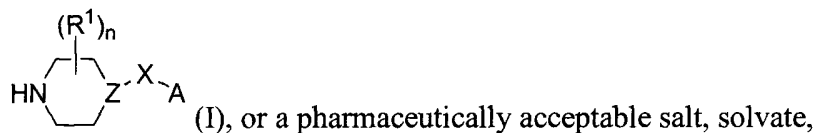
[00145] All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by

15 reference in its entirety.

Claims

What is claimed is:

1. A compound having a structure according to the following formula,

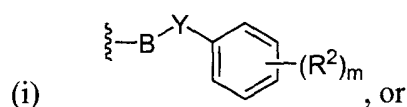
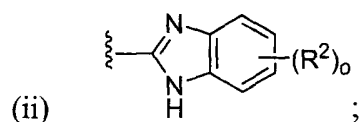


prodrug, or stereoisomer thereof, wherein

X is an optionally substituted alkylene (1-3C);

Z is N or CR⁴;

A is selected from



B is N-R³ or an optionally substituted isoxazolyl;

Y is a bond or an optionally substituted alkylene (1-3C)

m is an integer between 0-5;

n is an integer between 0-6;

o is an integer between 0-4;

each R¹ and R² is, independently, selected from halo, CN, NO₂,

COOR', CONR'₂, OR', SR', SOR', SO₂R', NR'₂, NR'(CO)R', and

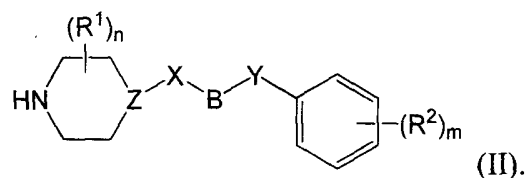
NR'SO₂R', wherein each R' is independently H or an optionally substituted group selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), and heteroalkynyl (2-6C); or R¹ and R² may

independently be one or more optionally substituted groups selected from alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), heteroalkyl (2-6C), heteroalkenyl (2-6C), or heteroalkynyl (2-6C); and wherein each R¹ may further be selected from =O and =NOR';

R³ is H or an optionally substituted alkyl (1-3C); and

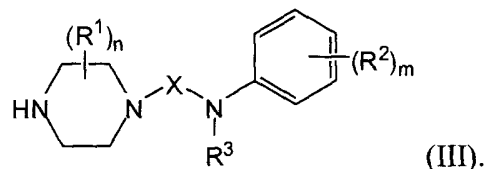
R⁴ is H, methyl, fluoro, hydroxyl or cyano.

2. The compound of claim 1, wherein said compound has a structure according to:

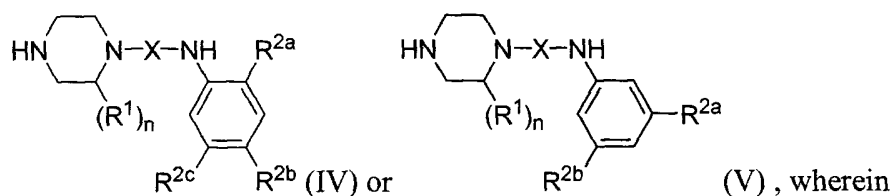


3. The compound of claim 2, wherein R^1 or R^2 is CF_3 or OCF_3 .
4. The compound of any of claims 1-3, wherein B is $N-R^3$.
5. The compound of any of claims 1-4, wherein X is substituted by $=O$.
6. The compound of claim 5, wherein X is $-CH_2C(=O)-$ or $-C(=O)CH_2-$.
7. The compound of claim 6, wherein X is $-CH_2C(=O)-$.
8. The compound of any of claims 1-7, wherein n is 0-3.
9. The compound of claim 8, wherein n is 0.
10. The compound of any of claims 1-9, wherein Y is a bond.
11. The compound of any of claims 1-10, wherein each R^1 is independently halo, methyl, CF_3 , or $=O$.
12. The compound of any of claims 1-11, wherein m is 0-3.
13. The compound of claim 12, wherein m is 2 or 3.
14. The compound of any of claims 1-13, wherein each R^2 is independently halo, methyl or CF_3 .
15. The compound of any of claims 1-14, wherein n is 1 and R^1 is $=O$.

16. The compound of claim 1, wherein said compound has a structure according to the following formula,



17. The compound of claim 16, wherein X is $-\text{CH}_2\text{C}(=\text{O})-$ or $-\text{C}(=\text{O})\text{CH}_2-$.
18. The compound of claim 17, wherein X is $-\text{CH}_2\text{C}(=\text{O})-$.
19. The compound of any of claims 16-18, wherein R^3 is H.
20. The compound of any of claims 16-19, wherein, independently, n is 0 or 1, and m is 2 or 3.
21. The compound of claim 20, wherein n is 1 and R^1 is $=\text{O}$.
22. The compound of any of claims 16-18, wherein said compound has a structure according to

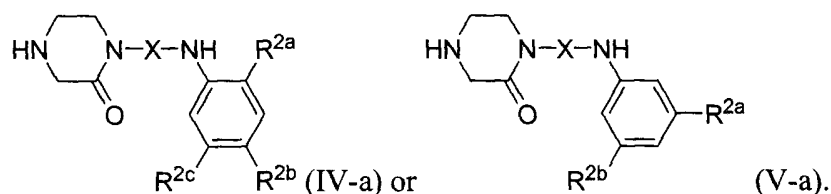


R^1 is $=\text{O}$;

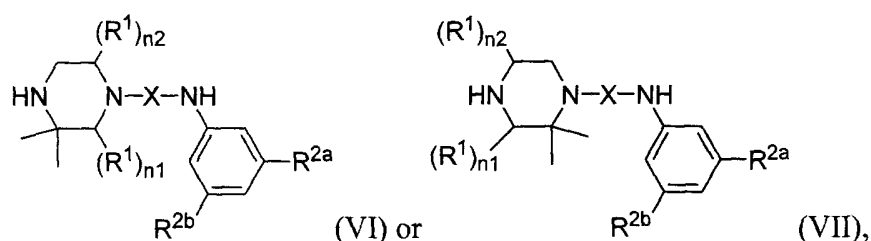
n is 0 or 1; and

each of R^{2a} , R^{2b} , and R^{2c} is selected, independently, from halogen and substituted 1C alkyl.

23. The compound of claim 22, wherein said compound has a structure according to



24. The compound of claim 22, wherein X is $-\text{CH}_2\text{C}(=\text{O})-$.
25. The compound of any of claims 16-18, wherein said compound has a structure according to



wherein

R^1 is $=\text{O}$;

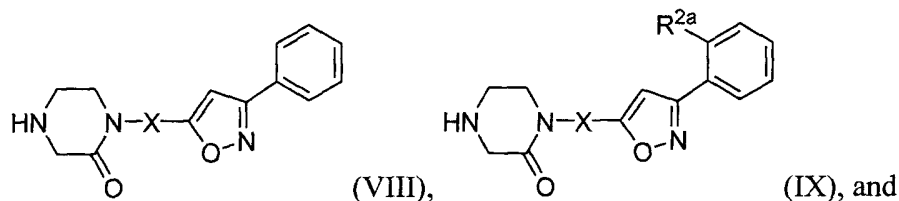
n_1 is 0 or 1;

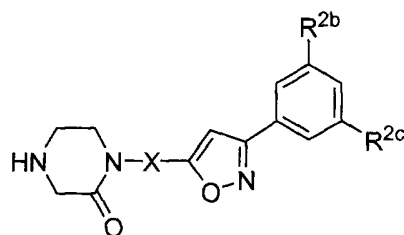
n_2 is 0 or 1; and

each R^{2a} , R^{2b} , and R^{2c} is selected, independently, from halogen and substituted 1C alkyl;

and wherein at least one of n_1 and n_2 is 0.

26. The compound of claim 25, wherein both n_1 and n_2 are 0.
27. The compound of claim 1, wherein said compound has a structure selected from the group consisting of:



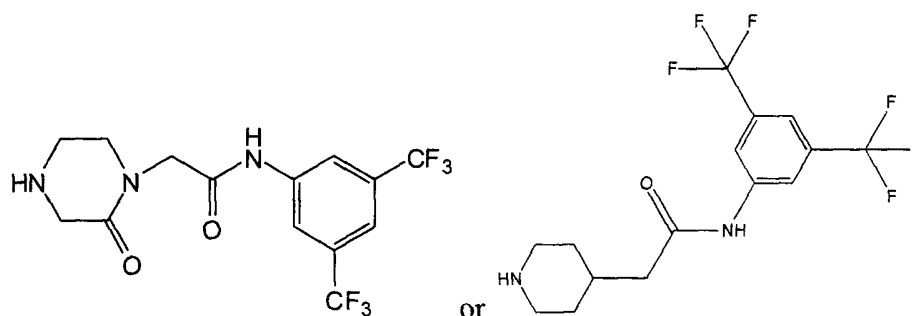


(X), wherein each R^{2a} , R^{2b} , and R^{2c} is selected, independently, from halogen and substituted 1C alkyl.

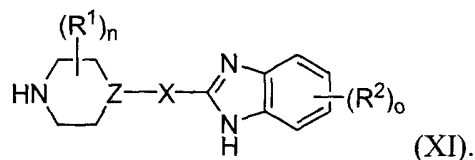
28. The compound of claim 27, wherein X is $-\text{CH}_2-$.
29. The compound of any of claims 22-28, wherein said halogen is fluoro and said substituted 1C alkyl is CF_3 .
30. The compound of claim 1, wherein said compound is selected from the group consisting of:
 - N-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxopiperazin-1-yl)acetamide;
 - 2-(2-oxopiperazin-1-yl)-N-(2,4,5-trifluorophenyl)acetamide;
 - 1-(2-(3,5-difluorophenylamino)acetyl)piperazin-2-one;
 - N-(3,5-bis(trifluoromethyl)phenyl)-2-(3,3-dimethyl-2-oxopiperazin-1-yl)acetamide;
 - N-(3,5-bis(trifluoromethyl)phenyl)-2-(piperazin-1-yl)acetamide;
 - N-(3,5-difluorophenyl)-2-(piperazin-1-yl)acetamide;
 - 2-(piperazin-1-yl)-N-(2,4,5-trifluorophenyl)acetamide;
 - N-(3-fluoro-5-(trifluoromethyl)phenyl)-2-(piperazin-1-yl)acetamide;
 - N-(3,5-bis(trifluoromethyl)phenyl)-2-(3-oxopiperazin-1-yl)acetamide;
 - 4-(2-(3,5-bis(trifluoromethyl)phenylamino)acetyl)piperazin-2-one;
 - 4-(2-(3-fluoro-5-(trifluoromethyl)phenylamino)acetyl)piperazin-2-one;
 - 4-(2-(3,5-bis(trifluoromethyl)phenylamino)acetyl)-3,3-dimethylpiperazin-2-one;
 - N-(3,5-bis(trifluoromethyl)phenyl)-2-(5,5-dimethyl-2-oxopiperazin-1-yl)acetamide;
 - 1-((3-(3,5-bis(trifluoromethyl)phenyl)isoxazol-5-yl)methyl)piperazin-2-one;
 - 1-((3-phenylisoxazol-5-yl)methyl)piperazin-2-one;
 - 1-((3-(2-fluorophenyl)isoxazol-5-yl)methyl)piperazin-2-one;
 - N-(3,5-bis(trifluoromethyl)phenyl)-2-(2-oxopiperazin-1-yl)propanamide;

N-(3,5-difluorophenyl)-2-(2-oxopiperazin-1-yl)acetamide;
 N-(3,5-bis(trifluoromethyl)phenyl)-2-(piperidin-4-yl)acetamide;
 N-(3,5-bis(trifluoromethyl)benzyl)-2-(2-oxopiperazin-1-yl)acetamide;
 N-(3,5-dichlorophenyl)-2-(2-oxopiperazin-1-yl)acetamide;
 N-(2-(2-oxopiperazin-1-yl)ethyl)-3,5-bis(trifluoromethyl)benzamide; and
 3-fluoro-N-(2-(2-oxopiperazin-1-yl)ethyl)-5-(trifluoromethyl)benzamide.

31. The compound of claim 1, wherein said compound is



32. The compound of claim 1, wherein said compound has a structure according to the following formula,



33. The compound of claim 32, wherein Z is N.

34. The compound of claim 32 or 33, wherein n is 0-3.

35. The compound of claim 34, wherein n is 0.

36. The compound of claim 32, wherein n is 1 and R₁ is =O.

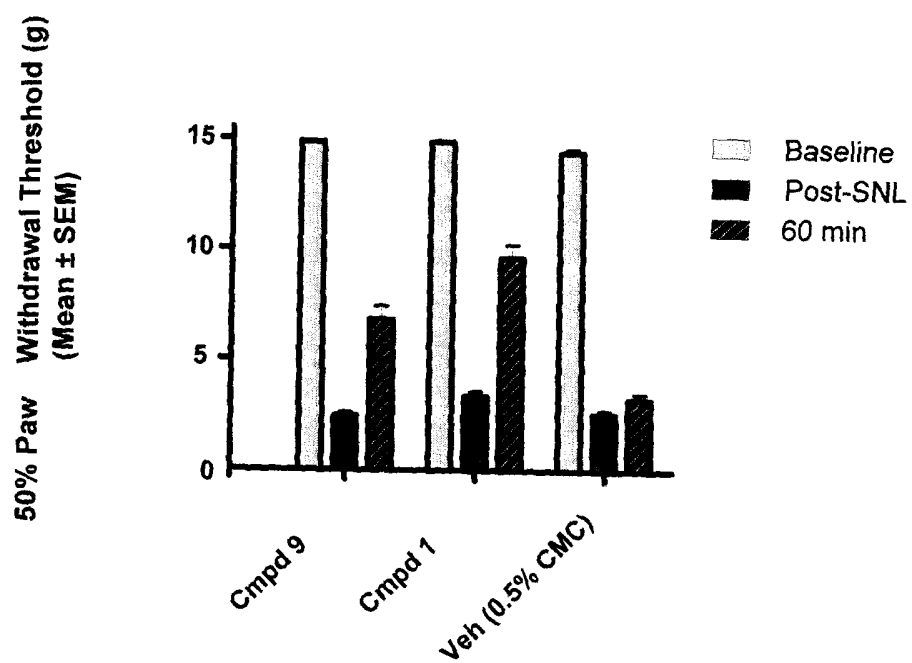
37. The compound of any of claims 32-36, wherein X is -CH₂C(=O)- or -C(=O)CH₂-.

38. The compound of claim 37, wherein X is -CH₂C(=O)-.

39. A pharmaceutical composition comprising the compound of any of claims 1-38 and a pharmaceutically acceptable carrier or excipient.
40. The pharmaceutical composition of claim 39, wherein said pharmaceutical composition is formulated in unit dosage form.
41. The pharmaceutical composition of claim 39, wherein said unit dosage form is a tablet, caplet, capsule, lozenge, film, strip, gelcap, or syrup.
42. A method to treat a condition modulated by sodium or calcium channels, or any combination thereof, said method comprising administering to a subject in need of such treatment an amount of the compound of any of claims 1-38 or the pharmaceutical composition of any of claims 39-41.
43. The method of claim 42, wherein said sodium or calcium channel is the $\text{Na}_v 1.7$, $\text{Na}_v 1.8$, or $\text{Ca}_v 3.2$ channel, or any combination thereof.
44. The method of claim 42, wherein said condition is pain, epilepsy, Parkinson's disease, depression, psychosis, or tinnitus.
45. The method of claim 44, wherein said psychosis is schizophrenia.
46. The method of claim 42, wherein said condition is pain or epilepsy.
47. The method of claim 46, wherein said pain is inflammatory pain or neuropathic pain.
48. The method of claim 46, wherein said pain is chronic pain.
49. The method of claim 48, wherein said chronic pain is peripheral neuropathic pain; central neuropathic pain, musculoskeletal pain, headache, visceral pain, or mixed pain.

50. The method of claim 49, wherein
- said peripheral neuropathic pain is post-herpetic neuralgia, diabetic neuropathic pain, neuropathic cancer pain, failed back-surgery syndrome, trigeminal neuralgia, or phantom limb pain;
 - said central neuropathic pain is multiple sclerosis related pain, Parkinson disease related pain, post-stroke pain, post-traumatic spinal cord injury pain, or pain in dementia;
 - said musculoskeletal pain is osteoarthritic pain and fibromyalgia syndrome; inflammatory pain such as rheumatoid arthritis, or endometriosis;
 - said headache is migraine, cluster headache, tension headache syndrome, facial pain, or headache caused by other diseases;
 - said visceral pain is interstitial cystitis, irritable bowel syndrome, or chronic pelvic pain syndrome; or
 - said mixed pain is lower back pain, neck and shoulder pain, burning mouth syndrome, or complex regional pain syndrome.
51. The method of claim 49, wherein said headache is migraine.
52. The method of claim 46, wherein said pain is acute pain.
53. The method of claim 44, wherein said acute pain is nociceptive pain or post-operative pain.
54. The method of claim 53, wherein said acute pain is post-operative pain.
55. A method of modulating a voltage-gated sodium channel or a calcium channel, said method comprising contacting a cell with the compound of any of claims 1-38, or the pharmaceutical composition of any of claims 39-41.

Figure 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/001386

<p>A. CLASSIFICATION OF SUBJECT MATTER</p> <p>IPC: C07D 241/08 (2006.01) , A61K 31/4462 (2006.01) , A61K 31/495 (2006.01) , A61K 31/496 (2006.01) , A61P 25/00 (2006.01) , C07D 211/34 (2006.01) , C07D 403/06 (2006.01) , C07D 413/06 (2006.01)</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>																							
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols)</p> <p>C07D 241/08 (2006.01) , A61K 31/4462 (2006.01) , A61K 31/495 (2006.01) , A61K 31/496 (2006.01) , A61P 25/00 (2006.01) , C07D 211/34 (2006.01) , C07D 403/06 (2006.01) , C07D 413/06 (2006.01)</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)</p> <p>STN Structure search in CAPlus</p>																							
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <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> <tbody> <tr> <td>P,X</td> <td>BAVETSIAS, V. et al. J. Med. Chem. 2010, 53, 5213-5228 (21 June 2010) *Scheme 4, compounds 29 (b) and (d)*</td> <td>1, 2, 4-10, 12, 14, and 16-19</td> </tr> <tr> <td>X</td> <td>IN1202/MUM/2007 (BABURAO, W. S. et al.) 21 June 2009 (21-06-2009) CA Registry number 946744-07-6</td> <td>1, 2, 4-10, 12, 14 and 16-19</td> </tr> <tr> <td>X</td> <td>GATAULLIN, R.R. et al. Pharmaceutical Chemistry Journal 1999, 33, 255-258 *compound VI (c)*</td> <td>1, 2, 4-10, 12-14, 16-20 and 39-41</td> </tr> <tr> <td>X</td> <td>GB 1434323 A (ICHTHYOL-GESELLSCHAFT CORDES, HERMANNI & Co.) 05 May 1976 (05-05-1976) *Table 1*</td> <td>1-10, 12-14, and 16-20</td> </tr> <tr> <td>P,X</td> <td>WO 2010080357 A1 (COGAN, D. et al.) 15 July 2010 (15-07-2010) *page 44*</td> <td>1, 8, 9, 12, 14, 32, 34 and 35</td> </tr> <tr> <td>X</td> <td>MOSS, N. et al. Bioorg. Med. Chem. Lett. 2009, 19, 2206-2210 (09 March 2009) *compound X*</td> <td>1, 8, 9, 12, 32, 34 and 35</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	P,X	BAVETSIAS, V. et al. J. Med. Chem. 2010, 53, 5213-5228 (21 June 2010) *Scheme 4, compounds 29 (b) and (d)*	1, 2, 4-10, 12, 14, and 16-19	X	IN1202/MUM/2007 (BABURAO, W. S. et al.) 21 June 2009 (21-06-2009) CA Registry number 946744-07-6	1, 2, 4-10, 12, 14 and 16-19	X	GATAULLIN, R.R. et al. Pharmaceutical Chemistry Journal 1999, 33, 255-258 *compound VI (c)*	1, 2, 4-10, 12-14, 16-20 and 39-41	X	GB 1434323 A (ICHTHYOL-GESELLSCHAFT CORDES, HERMANNI & Co.) 05 May 1976 (05-05-1976) *Table 1*	1-10, 12-14, and 16-20	P,X	WO 2010080357 A1 (COGAN, D. et al.) 15 July 2010 (15-07-2010) *page 44*	1, 8, 9, 12, 14, 32, 34 and 35	X	MOSS, N. et al. Bioorg. Med. Chem. Lett. 2009, 19, 2206-2210 (09 March 2009) *compound X*	1, 8, 9, 12, 32, 34 and 35
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X	GATAULLIN, R.R. et al. Pharmaceutical Chemistry Journal 1999, 33, 255-258 *compound VI (c)*	1, 2, 4-10, 12-14, 16-20 and 39-41																					
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X	MOSS, N. et al. Bioorg. Med. Chem. Lett. 2009, 19, 2206-2210 (09 March 2009) *compound X*	1, 8, 9, 12, 32, 34 and 35																					
<p>[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.</p>																							
<table border="1"> <tbody> <tr> <td>* Special categories of cited documents :</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"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)</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </tbody> </table>			* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"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)	"&" document member of the same patent family	"O" document referring to an oral disclosure, use, exhibition or other means		"P" document published prior to the international filing date but later than the priority date claimed										
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<p>Date of the actual completion of the international search</p> <p>28 October 2010 (20-10-2010)</p>		<p>Date of mailing of the international search report</p> <p>9 December 2010 (09-12-2010)</p>																					
<p>Name and mailing address of the ISA/CA</p> <p>Canadian Intellectual Property Office</p> <p>Place du Portage I, C114 - 1st Floor, Box PCT</p> <p>50 Victoria Street</p> <p>Gatineau, Quebec K1A 0C9</p> <p>Facsimile No.: 001-819-953-2476</p>		<p>Authorized officer</p> <p>Karla Randell (819) 956-6118</p>																					

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 42-54

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 42-54 are directed to a method for the treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claim 42, use to treat a condition modulated by sodium or calcium channels.

2. ☒ Claim Nos. : 1-29 and 39-55

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 :

These claim relate to an extremely large number of compounds. A complete search of the prior art could not be carried out. The search was restricted to the compounds of the examples, the compounds of Claim 1, part (ii) and partial searches of the compounds of Claim 1 part (I).

3. ☐ Claim Nos. :

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim 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 claim Nos. :

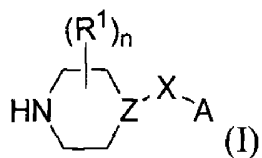
Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

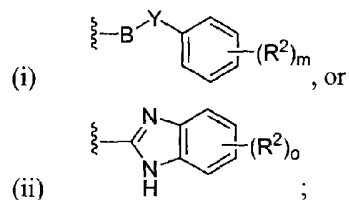
☐ No protest accompanied the payment of additional search fees.

Box No. IV **Text of the abstract (Continuation of item 5 of the first sheet)**

Compounds of formula (I) which are useful in ameliorating conditions characterized by unwanted sodium and/or calcium channel activity, particularly unwanted $\text{Na}_v 1.7$, $\text{Na}_v 1.8$, or $\text{Ca}_v 3.2$ channel activity are disclosed. Specifically, a series of compounds containing piperidine or piperazine linked through an amide, isoxazole or similar linker to an aryl ring are described and are shown to be useful for the treatment of pain or epilepsy.



A is selected from



INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZECHEL, C. et al. Bioorg. Med. Chem. Lett. 2003, 13, 165-169 *Table 1, intermediates of 11a, 11b and 20a*	1, 8, 9, 12, 32, 34, and 35
X	CA 2198084 A1 (BURKHOLDER, T.P. et al.) 29 February 1996 (29-02-29) *Example 31*	1, 8, 9, 12, 32, 34, and 35
X	WO 0121615 A1 (TAKAYAMA, K. et al) 29 March 2001 (29-03-2001) *CAS Registry number 330948-09-9*	1, 8, 9, 12, 32, 34, and 35
X	US 5559127 A (HARTMAN, G.D. et al.) 24 September 1996 (24-09-1996) *scheme 6, column 31, 32 and 41-42*	1, 8, 9, 12, 32, 34, and 35
X	CA 2022451 A1 (CARR, A.A. et al.) 02 April 1991 (02-04-1991) *Example 4*	1, 8, 9, 12, 32, 34, and 35
P,X	WO 2010053120 A1 (ISHII, T. et al.) 14 May 2010 (15-05-2010) *compounds 3 and 12*	1, 8, 9, 12, 14 and 32-35
X	CA 2497827 A1 (CARRUTHERS, N.I. et al.) 18 March 2004 (18-03-2004) *see examples*	1, 8, 9, 11-14, 32-35 and 39-41
X	WO 0250061 A1 (DARTOIS, C.G.Y. et al.) 27 June 2002 (27-06-2002) * Example 3 and 4*	1, 8, 9, 12, 14 and 32-35
X	PESSON, M.M. et al. Eur. J. Med. Chem. 1975, 10, 567-572 *intermediate 4j*	1, 8, 9, 12 and 32-35
P, X	WO 2010023196 A2 (PETERS, D. et al.) 04 March 2010 (04-03-2010) * Table 1*	1, 2, 4, 5, 8-10, 12-14, 16, 20, 39-41 and 42-55
P, X	WO 2010023197 A2 (PETERS, D. et al.) 04 March 2010 (04-03-2010) *whole document*	1, 2, 4-10, 12-14, 16-20, 29, 39-41, 42-55
X	CA 2711977 A1 (PETERS, D. et al) 23 July 2009 (23-07-2009) *whole document*	1-5, 8-10, 12-14, 16, 20, 22, 39-41 and 42-55
X	CA 2695496 A1 (PETERS, D. et al.) 05 February 2009 (05-02-2009) *whole document*	1, 2, 4, 8-10, 12-14, 16, 20, 39-41 and 42-55
X	US 5198449 A (SHANKLIN Jr., J. R.) 30 March 1993 (30-03-1993) *claims*	1-4, 8-10, 12-14, 16, 19, 20, 22 and 39-41
X	CAS Registry number 1027575-54-7 12 June 2008 (12-06-2008)	1, 2, 5, 8, 9, 10, 12 and 13
X	CA 2345210 A1 (SMALLHEER, J. M. et al.) 25 May 2000 (25-05-2000) *Scheme 1* and CAS Registry numbers 764635-79-2 and 270594-01-9	1, 2, 8-11 and 39-41
P, X	WO 2009146540 A1 (PAJOUHESH, H. et al.) 10 December 2009 (10-12-2009) *Example 1*	1-5, 8, 9, and 11-13
P, X	WO 2009136625 A1 (TSUZUKI, Y et al.) 12 November 2009 (12-11-2009) *compound formula (II)*	1,2, 4, 5, 8, 9, 12 and 13

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2703106 A1 (SUGASAWA, K. et al.) 30 April 2009 (30-04-2009) *compound 791*	1, 2, 4, 8, 9, 12 and 39-41
P, X	WO 2010102663 A1 (BESWICK, P.J. et al.) 16 September 2010 (16-09-2010) *Intermediate 11, 13 and 14*	1, 2, 4, 5, 8, 10-14, 16, 19 and 20
P, X	WO 2010087399 A1 (MARUMOTO S. et al.) 5 August 2010 (05-08-2010) *page 49*	1, 2, 4-6, 8, 9, 12-14, 16, 17, 19, 20 and 22
X	WO 2008109175 A1 (HARBESON, S.L. et al) 12 September 2008 (12-09-2008) *Example 4*	1, 2, 4-10, 12-14, and 16-20
X	US 20090105251 A1 (JONES, B. et al.) 23 April 2009 (23-04-2009) *example 33*	1, 2, 8, 10, 12, 14 and 39-41
X	CA 2659512 A1 (CLARK, R. B. et al) 21 December 2007 (21-12-2007) *example 151*	1, 2, 5, 8, 9, 10, 12 and 39-41
X	WO 2007118323 A1 (PAJOUHESH, H. et al.) 25 October 2007 (25-10-2007) *whole document, example 9*	1, 2, 8, 9, 10, 12, 14, 39-41, 42-55
X	CA 2605603 A1 (SEVERANCE, D. L. et al.) 02 November 2006 (02-11-2006) * example 28*	1, 2, 8, 9, 10, 12, 14 and 39-41
X	WO 2009064388 A2 (LIU, J.O. et al.) 22 May 2009 (22-05-2009) * pages 23 and 24*	1, 2, 4, 5, 8, 9, 12, 16 and 39-41
X	WO 2008157844 A1 (BISCHOFF, A. et al.) 24 December 2008 (24-12-2008) *scheme 1*	1, 2, 4, 5, 6, 8, 9, and 12
X	CA 2665736 A1 (MOFFAT, D.F.C. et al.) 02 May 2008 (02-05-2008) *example 14, page 81*	1, 2, 4, 8, 12 and 13

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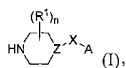
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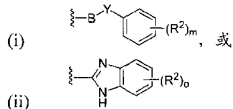
治疗疼痛和癫痫的取代的杂环衍生物

(57) 摘要

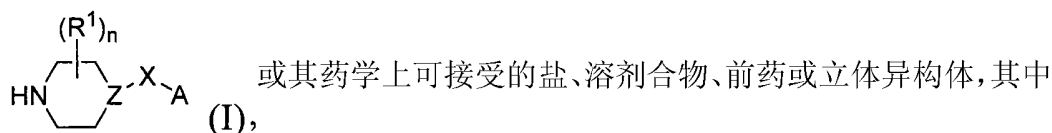
公开有效改善以不需要的钠和 / 或钙通道活性, 尤其是不需要的 Na_v 1.7, Na_v 1.8 或 Ca_v 3.2 通道活性为特征的疾病的式 (I) 化合物。具体说来, 描述含有通过酰胺或异噁唑或类似的连接剂连接至芳环的哌啶或哌嗪的一系列化合物并表明其可用于治疗疼痛和 / 或癫痫。A 选自式 (i) 或



(ii)。



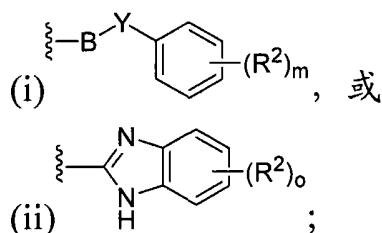
1. 一种具有根据下式的结构的化合物，



X 是任选取代的亚烷基 (1-3C)；

Z 是 N 或 CR⁴；

A 选自



B 是 N-R³ 或任选取代的异噁唑基；

Y 是键或任选取代的亚烷基 (1-3C)

m 是介于 0-5 之间的整数；

n 是介于 0-6 之间的整数；

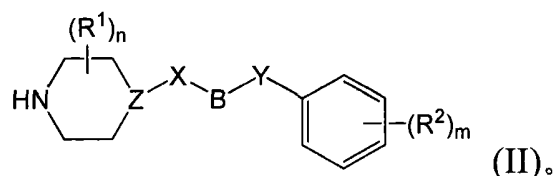
o 是介于 0-4 之间的整数；

各个 R¹ 和 R² 独立地选自卤代基、CN、NO₂、COOR'、CONR'₂、OR'、SR'、SOR'、SO₂R'、NR'₂、NR' (CO)R' 和 NR' SO₂R'，其中各个 R' 独立地为 H 或选自烷基 (1-6C)、烯基 (2-6C)、炔基 (2-6C)、杂烷基 (2-6C)、杂烯基 (2-6) 和杂炔基 (2-6C) 的任选取代的基团；或者 R¹ 和 R² 可独立地为选自烷基 (1-6C)、烯基 (2-6C)、炔基 (2-6C)、杂烷基 (2-6C)、杂烯基 (2-6C) 或杂炔基 (2-6C) 的一个或多个任选取代的基团；和其中各个 R¹ 可进一步选自 = O 和 = NOR'；

R³ 为 H 或任选取代的烷基 (1-3C)；和

R⁴ 为 H、甲基、氟代基、羟基或氰基。

2. 权利要求 1 的化合物，其中所述化合物具有根据下式的结构：



3. 权利要求 2 的化合物，其中的 R¹ 或 R² 为 CF₃ 或 OCF₃。

4. 权利要求 1-3 的任一项的化合物，其中的 B 是 N-R³。

5. 权利要求 1-4 的任一项的化合物，其中的 X 被 = O 取代。

6. 权利要求 5 的化合物，其中的 X 是 -CH₂C(=O)- 或 -C(=O)CH₂-。

7. 权利要求 6 的化合物，其中的 X 是 -CH₂C(=O)-。

8. 权利要求 1-7 的任一项的化合物，其中的 n 为 0-3。

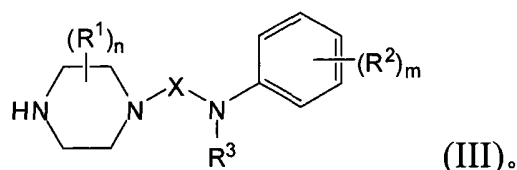
9. 权利要求 8 的化合物，其中的 n 为 0。

10. 权利要求 1-9 的任一项的化合物，其中的 Y 是键。

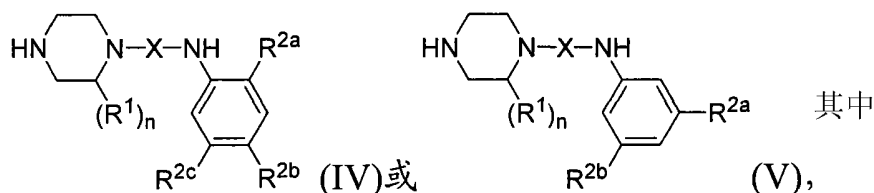
11. 权利要求 1-10 中任一种的化合物，其中各个 R¹ 独立地为卤代基、甲基、CF₃ 或 = O。

12. 权利要求 1-11 的任一项的化合物，其中的 m 是 0-3。

13. 权利要求 12 的化合物, 其中的 m 是 2 或 3。
 14. 权利要求 1-13 的任一项的化合物, 其中各个 R^2 独立地为卤代基、甲基或 CF_3 。
 15. 权利要求 1-14 的任一项的化合物, 其中 n 为 1 和 R^1 为 $=0$ 。
 16. 权利要求 1 的化合物, 其中所述化合物具有根据下式的结构,



17. 权利要求 16 的化合物, 其中的 X 为 $-CH_2C(=O)-$ 或 $-C(=O)CH_2-$ 。
 18. 权利要求 17 的化合物, 其中的 X 为 $-CH_2C(=O)-$ 。
 19. 权利要求 16-18 中任一项的化合物, 其中的 R^3 是 H 。
 20. 权利要求 16-19 中任一项的化合物, 其中独立地, n 是 0 或 1, 和 m 是 2 或 3。
 21. 权利要求 20 的化合物, 其中的 n 为 1 和 R^1 是 $=0$ 。
 22. 权利要求 16-18 中任一项的化合物, 其中所述化合物具有根据下式的结构

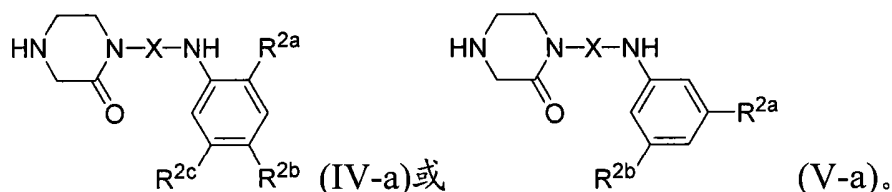


R^1 是 $=0$;

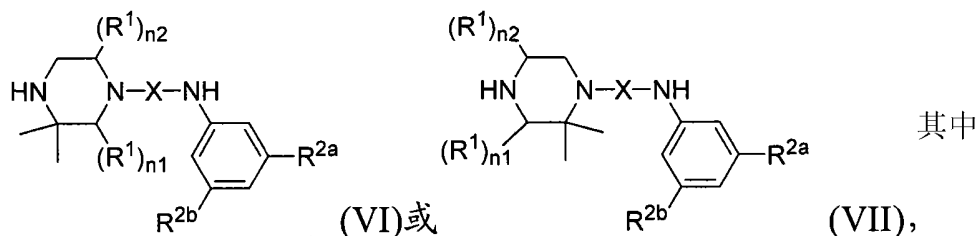
n 为 0 或 1; 和

R^{2a} 、 R^{2b} 和 R^{2c} 中的每一个独立地选自卤素和取代的 1C 烷基。

23. 权利要求 22 的化合物, 其中所述化合物具有根据下式的结构



24. 权利要求 22 的化合物, 其中的 X 是 $-CH_2C(=O)-$ 。
 25. 权利要求 16-18 中任一项的化合物, 其中所述化合物具有根据下式的结构



R^1 是 $=0$;

n_1 是 0 或 1;

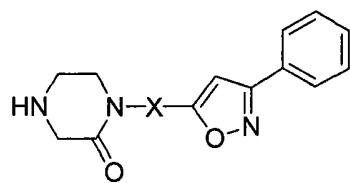
n_2 是 0 或 1; 和

R^{2a} 、 R^{2b} 和 R^{2c} 各自独立地选自卤素和取代的 1C 烷基;

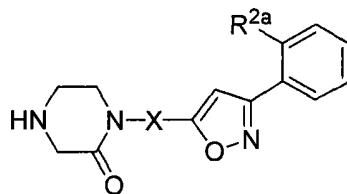
和其中 n_1 和 n_2 中至少一个是 0。

26. 权利要求 25 的化合物, 其中 n_1 和 n_2 都为 0。

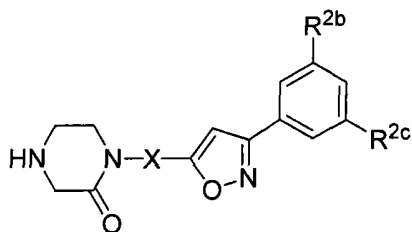
27. 权利要求 1 的化合物,其中所述化合物具有选自以下的结构:



(VIII)、



(IX)和



(X),

其中各个 R^{2a} 、 R^{2b} 和 R^{2c} 独立地选自卤素和取代的

1C 烷基。

28. 权利要求 27 的化合物,其中的 X 为 $-\text{CH}_2-$ 。

29. 权利要求 22-28 中任一项的化合物,其中所述的卤素为氟代基和所述取代的 1C 烷基为 CF_3 。

30. 权利要求 1 的化合物,其中所述的化合物选自:

N-(3,5-双(三氟甲基)苯基)-2-(2-氧代哌嗪-1-基)乙酰胺;

2-(2-氧代哌嗪-1-基)-N-(2,4,5-三氟苯基)乙酰胺;

1-(2-(3,5-二氟苯基氨基)乙酰基)哌嗪-2-酮;

N-(3,5-双(三氟甲基)苯基)-2-(3,3-二甲基-2-氧代哌嗪-1-基)乙酰胺;

N-(3,5-双(三氟甲基)苯基)-2-(哌嗪-1-基)乙酰胺;

N-(3,5-二氟苯基)-2-(哌嗪-1-基)乙酰胺;

2-(哌嗪-1-基)-N-(2,4,5-三氟苯基)乙酰胺;

N-(3-氟-5-(三氟甲基)苯基)-2-(哌嗪-1-基)乙酰胺;

N-(3,5-双(三氟甲基)苯基)-2-(3-氧代哌嗪-1-基)乙酰胺;

4-(2-(3,5-双(三氟甲基)苯基氨基)乙酰基)哌嗪-2-酮;

4-(2-(3-氟-5-(三氟甲基)苯基氨基)乙酰基)哌嗪-2-酮;

4-(2-(3,5-双(三氟甲基)苯基氨基)乙酰基)-3,3-二甲基哌嗪-2-酮;

N-(3,5-双(三氟甲基)苯基)-2-(5,5-二甲基-2-氧代哌嗪-1-基)乙酰胺;

1-((3-(3,5-双(三氟甲基)苯基)异噁唑-5-基)甲基)哌嗪-2-酮;

1-((3-苯基异噁唑-5-基)甲基)哌嗪-2-酮;

1-((3-(2-氟苯基)异噁唑-5-基)甲基)哌嗪-2-酮;

N-(3,5-双(三氟甲基)苯基)-2-(2-氧代哌嗪-1-基)丙酰胺;

N-(3,5-二氟苯基)-2-(2-氧代哌嗪-1-基)乙酰胺;

N-(3,5-双(三氟甲基)苯基)-2-(哌啶-4-基)乙酰胺;

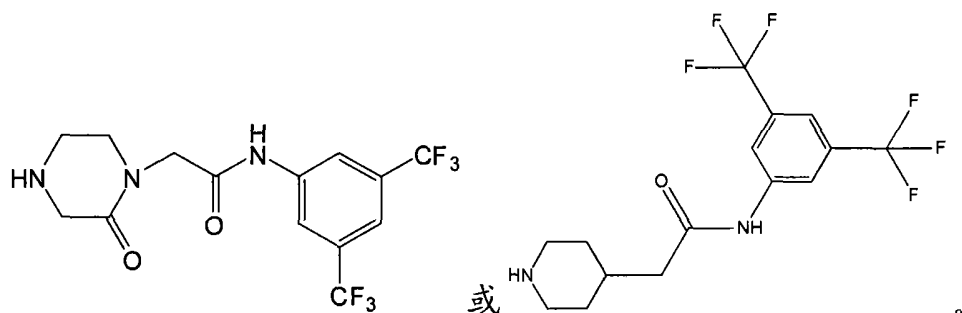
N-(3,5-双(三氟甲基)苄基)-2-(2-氧代哌嗪-1-基)乙酰胺;

N-(3,5-二氯苯基)-2-(2-氧代哌嗪-1-基)乙酰胺;

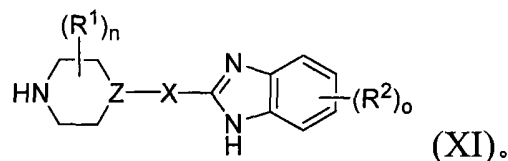
N-(2-(2-氧代哌嗪-1-基)乙基)-3,5-双(三氟甲基)苯甲酰胺;和

3-氟-N-(2-(2-氧代哌嗪-1-基)乙基)-5-(三氟甲基)苯甲酰胺。

31. 权利要求 1 的化合物,其中所述化合物为



32. 权利要求 1 的化合物,其中所述化合物具有根据下式的结构,



33. 权利要求 32 的化合物,其中的 Z 为 N。

34. 权利要求 32 或 33 的化合物,其中的 n 为 0-3。

35. 权利要求 34 的化合物,其中的 n 为 0。

36. 权利要求 32 的化合物,其中的 n 为 1 和 R₁ 是 = 0。

37. 权利要求 32-36 的任一项的化合物,其中的 X 为 -CH₂C(=O)- 或 -C(=O)CH₂-。

38. 权利要求 37 的化合物,其中的 X 是 -CH₂C(=O)-。

39. 一种含有权利要求 1-38 的任一项的化合物和药学上可接受的载体或赋形剂的药用组合物。

40. 权利要求 39 的药用组合物,其中所述的药用组合物被配制成单位剂型。

41. 权利要求 39 的药用组合物,其中所述的单位剂型为片剂、囊片剂、胶囊剂、锭剂、薄膜剂、小袋剂、软胶囊剂或糖浆剂。

42. 一种治疗受钠或钙通道或它们的任何组合调节的疾病的方法,所述方法包括给予需要此类治疗的受治疗者一定量的权利要求 1-38 的任一项的化合物,或权利要求 39-41 中任一项的药用组合物。

43. 权利要求 42 的方法,其中所述的钠和钙通道为 Na_v 1.7、Na_v 1.8 或 Ca_v 3.2 通道或它们的任何组合。

44. 权利要求 42 的方法,其中所述的疾病为疼痛、癫痫、帕金森氏病、抑郁症、精神病或耳鸣。

45. 权利要求 44 的方法,其中所述的精神病是精神分裂症。

46. 权利要求 42 的方法,其中所述的疾病为疼痛或癫痫。

47. 权利要求 46 的方法,其中所述的疼痛是炎性疼痛或神经性疼痛。

48. 权利要求 46 的方法,其中所述的疼痛是慢性疼痛。

49. 权利要求 48 的方法,其中所述的慢性疼痛是外周神经性疼痛、中枢神经性疼痛、肌肉骨骼痛、头痛、内脏疼痛或混合性疼痛。

50. 权利要求 49 的方法,其中

所述的外周神经性疼痛为带状疱疹后神经痛、糖尿病神经性疼痛、神经性癌痛、腰椎手术失败综合征、三叉神经痛或幻肢痛；

所述的中枢神经性疼痛是涉及多发性硬化的疼痛、涉及帕金森氏病的疼痛、中风后疼痛、外伤后骨髓损伤性疼痛或痴呆症中的疼痛；

所述的肌肉骨骼痛是骨关节痛和纤维肌痛综合征；炎性疼痛诸如类风湿性关节炎或子宫内膜移位症；

所述的头痛是偏头痛、丛集性头痛、紧张性头痛综合征、面痛或其它疾病引起的头痛；

所述的内脏疼痛是间质性膀胱炎，肠易激惹综合征或慢性骨盆疼痛综合征；或者

所述的混合性疼痛是腰痛、颈肩痛、灼口综合征或复杂性局部疼痛综合征。

51. 权利要求 49 的方法，其中所述的头痛是偏头痛。

52. 权利要求 46 的方法，其中所述的疼痛是急性疼痛。

53. 权利要求 44 的方法，其中所述的急性疼痛是伤害感受性疼痛或术后疼痛。

54. 权利要求 53 的方法，其中所述的急性疼痛是术后疼痛。

55. 一种调节电压门控钠通道或钙通道的方法，所述的方法包括用权利要求 1-38 的任一项的化合物或权利要求 39-41 中任一项的药用组合物接触细胞。

治疗疼痛和癫痫的取代的杂环衍生物

[0001] 相关申请的交叉参考

[0002] 本申请要求 2009 年 9 月 4 日提交的美国临时申请号 61/240,013 的优先权,其通过引用结合于本文中。

发明领域

[0003] 本发明涉及用来治疗与钙通道功能有关的疾病,尤其是与钠通道和 T-型钙通道活性有关的疾病的化合物。更具体地,本发明涉及含有哌嗪-N-芳基乙酰胺和哌嗪-芳基-异噁唑衍生物的化合物,其用于治疗疾病诸如癫痫、癌、疼痛、偏头痛、帕金森氏病、抑郁症、精神分裂症、精神病和耳鸣。

[0004] 发明背景

[0005] 电压门控钠 (Na_v) 通道存在于神经元和易激动组织,其中它们促成进程诸如膜兴奋和肌肉收缩 (Ogata 等, Jpn. J. Pharmacol. (2002) 88(4) 365-77)。来自单一 Na_v1 家族的 9 种不同跨膜 α -亚单位 ($\text{Na}_v1.1$ - 1.9) 与修饰通道功能的辅助 β -亚单位合并,形成功能性 Na_v 通道。在 9 种 Na_v1 α -亚单位同工型中,5 种表达于背根神经节,其中它们涉及调定静息膜电位和产生动作电位的阈值,还在持续去极化期间促成动作电位的上升及起动作 (upstroke as well as firing)。具体说来,河豚毒素 (TTX) 敏感的 $\text{Na}_v1.7$ 和 TTX-不敏感的 $\text{Na}_v1.8$ 通道亚型起到炎症和神经性疼痛的主要促成因素的作用 (Momin 等, Curr Opin Neurobiol. 18(4) :383-8, 2008 ;Rush 等, J Physiol. 579(Pt 1) :1-14, 2007)。

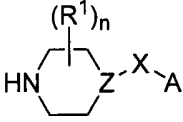
[0006] 钙通道介导多种正常生理学功能,还涉及多种人障碍。钙-介导的人障碍的实例包括但不限于先天性偏头痛、小脑性共济失调、心绞痛、癫痫、高血压、缺血和某些心率失常 (参见,例如,Janis 等,离子钙通道:其性质、功能、调节和临床意义 (1991) CRC Press, 伦敦)。T-型或低电压激活的通道描述在负电压下短暂地激活并对静息电位的变化高度敏感且涉及多种医学疾病的各类分子。例如,在缺乏基因表达的小鼠中,观察到抗失神发作 (absence seizures) 的 3.1 亚单位 (Kim 等, Mol Cell Neurosci 18(2) :235-245, 2001)。其它研究也已经涉及在癫痫的发展中的 3.2 亚单位 (Su 等, J Neurosci 22 :3645-3655, 2002)。

[0007] 因此,想要缓慢失活钠或缓慢失活钙通道的新的变构调节剂。调节剂可影响 $\text{Na}_v1.7$ 、 $\text{Na}_v1.8$ 或 $\text{Ca}_v3.2$ 通道中的一种或任何组合的缓慢失活的动力学和 / 或电压电位。

[0008] 发明概述

[0009] 本发明涉及用于受钠和 / 或钙通道调节的疾病的化合物。本发明化合物包括取代的哌啶 / 哌嗪-N-芳基乙酰胺、哌啶 / 哌嗪-N-芳基-异噁唑衍生物和哌啶 / 哌嗪-苯并咪唑衍生物。

[0010] 在第一个方面,本发明涉及一种具有根据下式的结构的化合物,

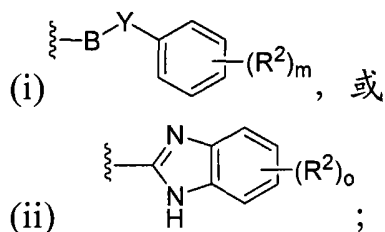
[0011]  或其药学上可接受的盐、溶剂合物、前药或立体异构体,其中 (I),

[0012] X 是任选取代的亚烷基 (1-3C) ;

[0013] Z 是 N 或 CR^4 ;

[0014] A 选自

[0015]



[0016] B 是 $N-R^3$ 或任选取代的异噁唑基 ;

[0017] Y 是键或任选取代的亚烷基 (1-3C) ;

[0018] m 是介于 0-5 之间的整数 ;

[0019] n 是介于 0-6 之间的整数 ;

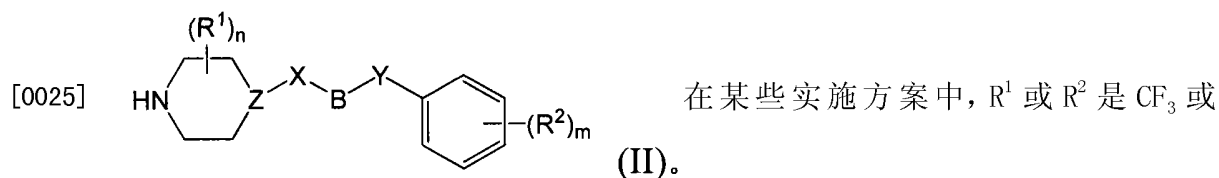
[0020] o 是介于 0-4 之间的整数 ;

[0021] 各个 R^1 和 R^2 独立地选自卤代基、CN、 NO_2 、 $COOR'$ 、 $CONR'_2$ 、 OR' 、 SR' 、 SOR' 、 SO_2R' 、 NR'_2 、 $NR'(CO)R'$ 、和 $NR'SO_2R'$, 其中各个 R' 独立地为 H 或选自烷基 (1-6C)、烯基 (2-6C)、炔基 (2-6C)、杂烷基 (2-6C)、杂烯基 (2-6) 和杂炔基 (2-6C) 的任选取代的基团 ; 或 R^1 和 R^2 可独立地为选自烷基 (1-6C)、烯基 (2-6C)、炔基 (2-6C)、杂烷基 (2-6C)、杂烯基 (2-6) 或杂炔基 (2-6C) 的一个或多个任选取代的基团 ; 和其中各个 R^1 可进一步选自 $=O$ 和 $=NOR'$;

[0022] R^3 为 H 或任选取代的烷基 (1-3C) ; 和

[0023] R^4 为 H、甲基、氟代基、羟基或氰基。

[0024] 在某些实施方案中, 化合物具有根据下式的结构 :



OCF_3 。

[0026] 在某些实施方案中, B 是 $N-R^3$ 。

[0027] 在其它实施方案中, X 被 $=O$ 取代。在另一些实施方案中, X 是 $-CH_2C(=O)-$ 或 $-C(=O)CH_2-$ 。在另一些实施方案中, X 是 $-CH_2C(=O)-$ 。

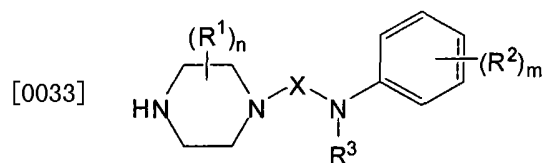
[0028] 在某些实施方案中, n 是 0-3 之间的整数。在某些实施方案中, n 为 0。

[0029] 在某些实施方案中, Y 是键。

[0030] 在某些实施方案中, R^1 独立地为卤代基、甲基、 CF_3 或 $=O$ 。

[0031] 在其它实施方案中, m 是 0-3。在另一些实施方案中, m 是 2 或 3。在某些实施方案中, R^2 独立地为卤代基、甲基或 CF_3 。

[0032] 在某些实施方案中, 化合物具有根据下式的结构,

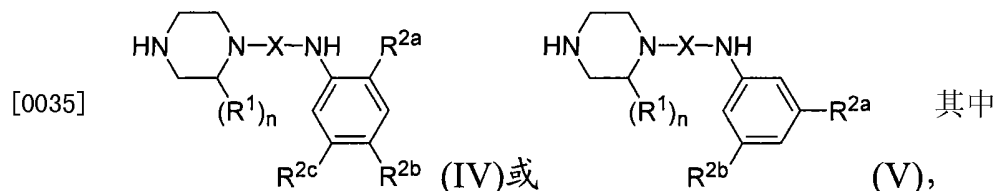


在某些实施方案中, X 是 $-\text{CH}_2\text{C}(=$

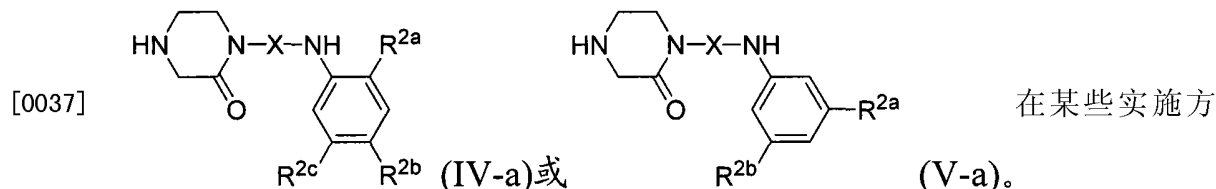
(III)。

$\text{O})-$ 或 $-\text{C}(=\text{O})\text{CH}_2-$ 。在另一些实施方案中, X 是 $-\text{CH}_2\text{C}(=\text{O})-$ 。在某些实施方案中, R^3 是 H。在其它实施方案中, 独立地, n 为 0 或 1 和 m 是 2 或 3。在又一些实施方案中, n 为 1 和 R^1 是 $=\text{O}$ 。

[0034] 在某些实施方案中, 化合物具有根据以下的结构

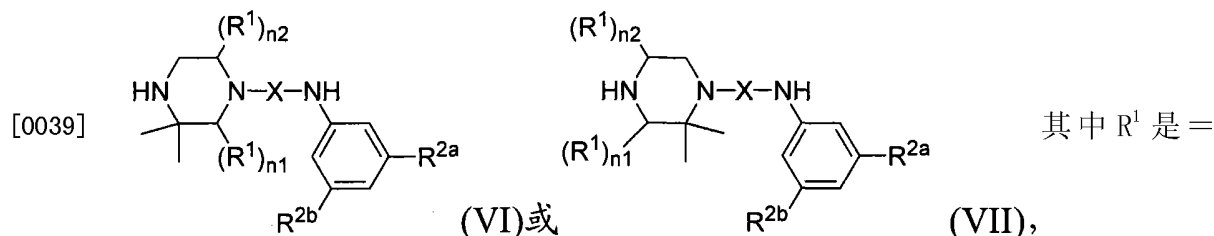


[0036] R^1 是 $=\text{O}$; n 为 0 或 1; 和 R^{2a} 、 R^{2b} 和 R^{2c} 各自独立地选自卤素和取代的 1C 烷基。在又一些实施方案中, 化合物具有根据以下的结构



案中, X 是 $-\text{CH}_2\text{C}(=\text{O})-$ 。

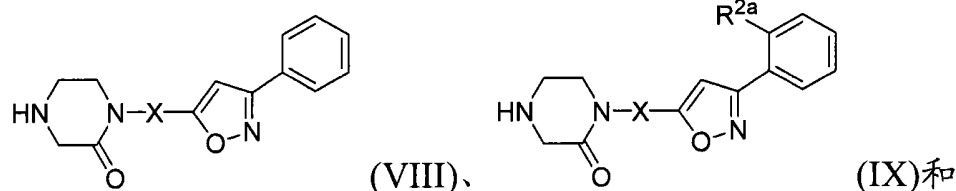
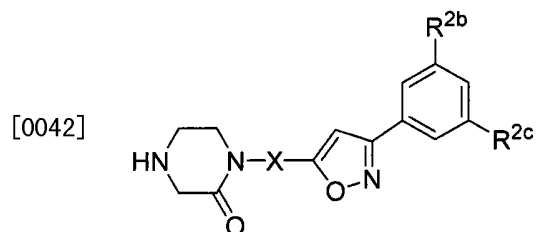
[0038] 在又一些实施方案中, 化合物具有根据以下的结构



O ; n_1 是 0 或 1; n_2 是 0 或 1; 各个 R^{2a} 、 R^{2b} 和 R^{2c} 独立地选自卤素和取代的 1C 烷基; 和其中 n_1 和 n_2 中至少一个是 0。在某些实施方案中, n_1 和 n_2 都为 0。

[0040] 在某些实施方案中, 化合物具有选自以下的结构:

[0041]



其中各个 R^{2a} 、 R^{2b} 和 R^{2c} 独立地选自卤素和取

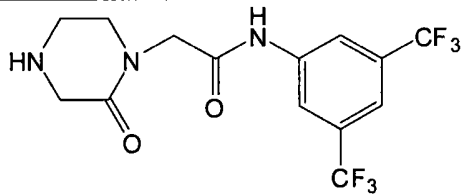
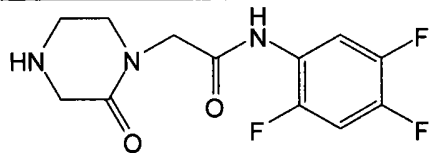
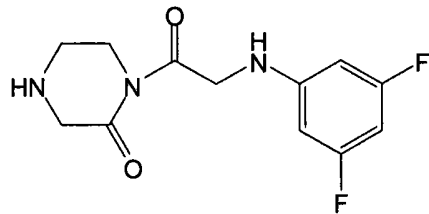
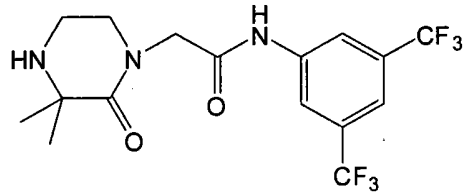
(X),

代的 1C 烷基。在某些实施方案中, X 是 $-\text{CH}_2-$ 。在其它实施方案中, 卤素是氟代基和取代 1C 烷基是 CF_3 。

[0043] 在某些实施方案中, 化合物选自表 1 中任何一种化合物。

[0044] 表 1

[0045]

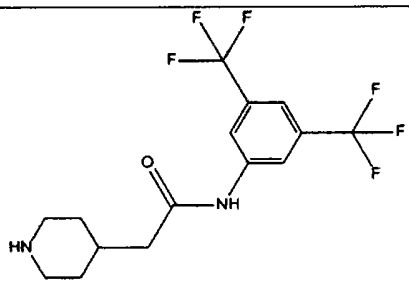
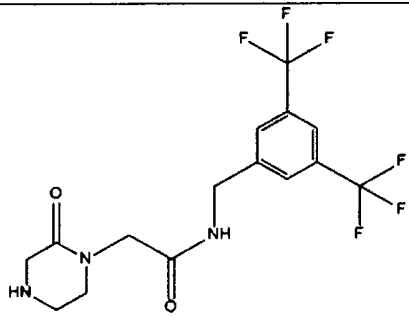
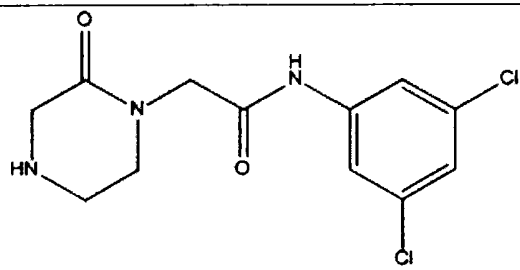
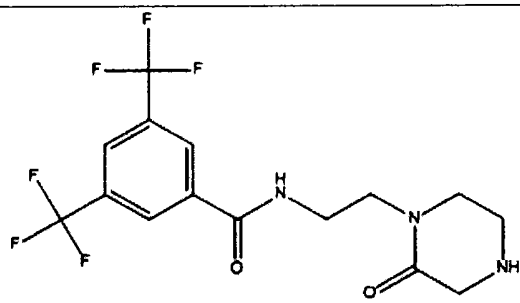
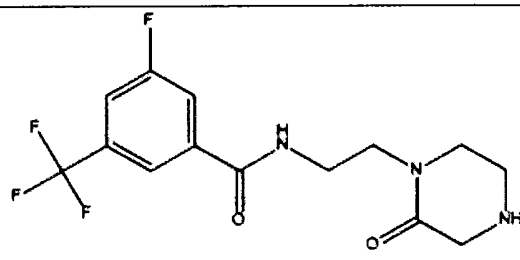
化合物号	名称	结构
1	N-(3,5-双(三氟甲基)苯基)-2-(2-氧代哌嗪-1-基)乙酰胺	
2	2-(2-氧代哌嗪-1-基)-N-(2,4,5-三氟苯基)乙酰胺;	
3	1-(2-(3,5-二氟苯基氨基)乙酰基)哌嗪-2-酮	
4	N-(3,5-双(三氟甲基)苯基)-2-(3,3-二甲基-2-氧代哌嗪-1-基)乙酰胺	

化合物号	名称	结构
5	N-(3,5-双(三氟甲基)苯基)-2-(哌嗪-1-基)乙酰胺	
6	N-(3,5-二氟苯基)-2-(哌嗪-1-基)乙酰胺	
7	2-(哌嗪-1-基)-N-(2,4,5-三氟苯基)乙酰胺	
8	N-(3-氟-5-(三氟甲基)苯基)-2-(哌嗪-1-基)乙酰胺	
[0046] 9	N-(3,5-双(三氟甲基)苯基)-2-(3-氧代哌嗪-1-基)乙酰胺	
10	4-(2-(3,5-双(三氟甲基)苯基氨基)乙酰基)哌嗪-2-酮	
11	4-(2-(3-氟-5-(三氟甲基)苯基氨基)乙酰基)哌嗪-2-酮	
12	4-(2-(3,5-双(三氟甲基)苯基氨基)乙酰基)-3,3-二甲基哌嗪-2-酮	

[0047]

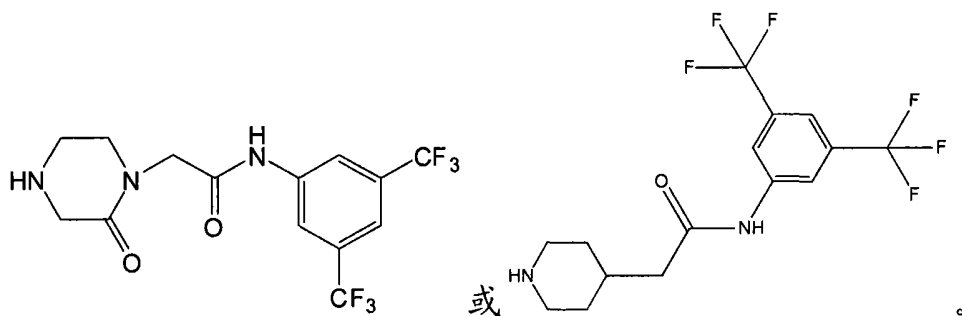
化合物号	名称	结构
13	N-(3,5-双(三氟甲基)苯基)-2-(5,5-二甲基-2-氧代哌嗪-1-基)乙酰胺	
14	1-((3-(3,5-双(三氟甲基)苯基)异噁唑-5-基)甲基)哌嗪-2-酮	
15	1-((3-苯基异噁唑-5-基)甲基)哌嗪-2-酮	
16	1-((3-(2-氟苯基)异噁唑-5-基)甲基)哌嗪-2-酮	
17	N-(3,5-双(三氟甲基)苯基)-2-(2-氧代哌嗪-1-基)丙酰胺	
18	N-(3,5-二氟苯基)-2-(2-氧代哌嗪-1-基)乙酰胺	

[0048]

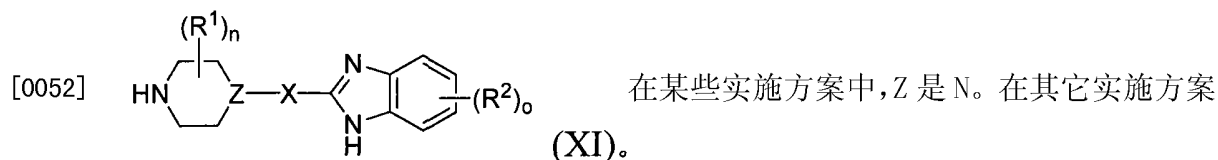
化合物号	名称	结构
19	N-(3,5-双(三氟甲基)苯基)-2-(哌啶-4-基)乙酰胺	
20	N-(3,5-双(三氟甲基)苄基)-2-(2-氧代哌嗪-1-基)乙酰胺	
21	N-(3,5-二氯苯基)-2-(2-氧代哌嗪-1-基)乙酰胺	
22	N-(2-(2-氧代哌嗪-1-基)乙基)-3,5-双(三氟甲基)苯甲酰胺	
23	3-氟-N-(2-(2-氧代哌嗪-1-基)乙基)-5-(三氟甲基)苯甲酰胺	

[0049] 在某些实施方案中,化合物是

[0050]



[0051] 在又一些实施方案中,化合物具有根据下式的结构,



中,n 为 0-3。在另一些实施方案中,n 为 0。在某些实施方案中,n 为 1 和 R_1 是 $=O$ 。在其它实施方案中,X 是 $-CH_2C(=O)-$ 或 $-C(=O)CH_2-$ 。在另一些实施方案中,X 是 $-CH_2C(=O)-$ 。

[0053] 在第二个方面,本发明涉及包含任何本文所述化合物(例如,根据式(I)-(XI)中任一种的化合物或 1-23 化合物中的任一种)和药学上可接受的载体或赋形剂的药用组合物。

[0054] 在某些实施方案中,将药用组合物配制成单位剂型。在其它实施方案中,单位剂型为片剂、囊片剂、胶囊剂、锭剂、薄膜剂、小袋剂、软胶囊剂或糖浆剂。

[0055] 在第三方面,本发明涉及治疗疾病(例如,疼痛或癫痫)的方法,其中的方法包括给予需要这样的治疗的受治疗者一定量(例如,有效量)的任何本文所述化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物 1-23 中的任一种)或任一种本文所述药用组合物。在某些实施方案中,疾病需要调节钠和/或钙通道活性(例如, $Na_v 1.7$ 、 $Na_v 1.8$ 或 $Ca_v 3.2$ 通道活性或钠和钙通道的任何组合的活性)。

[0056] 在某些实施方案中,疼痛是炎性疼痛或神经性疼痛。

[0057] 在其它实施方案中,疼痛是慢性疼痛。另一些实施方案中,慢性疼痛是外周神经性疼痛(例如,带状疱疹后神经痛、糖尿病神经性疼痛、神经性癌疼痛、腰椎手术失败综合征、三叉神经痛或幻肢痛)、中枢神经性疼痛(例如,多发性硬化涉及的疼痛、涉及帕金森氏病的疼痛、中风后疼痛、外伤后骨髓损伤性疼痛或痴呆症中的疼痛)、肌肉骨骼痛(例如,骨关节痛和纤维肌痛综合征;炎性疼痛诸如类风湿性关节炎或子宫内膜移位症)、头痛(例如,偏头痛、丛集性头痛、紧张性头痛综合征、面痛或其它疾病引起的头痛)、内脏疼痛(例如,间质性膀胱炎、肠易激惹综合征或慢性骨盆疼痛综合征)或混合疼痛(例如,腰痛、颈肩痛、灼口综合征或复杂性局部疼痛综合征)。

[0058] 在某些实施方案中,疼痛是急性疼痛(例如,伤害感受性疼痛或术后疼痛)。

[0059] 受钠和/或钙通道活性调节的示例的非限制性疾病包括疼痛、癫痫、偏头痛、帕金森氏病、抑郁症、精神分裂症、精神病或耳鸣。

[0060] 在第四方面,本发明涉及调节电压门控钠通道或钙通道的方法,其中的方法包括用任何本文所述化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物 1-23 中的任一种)或任一种本文所述药用组合物接触细胞。

[0061] 在另一方面,本发明涉及任何本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)在制备治疗任何本文所述的疾病(例如,需要钠和/或钙通道活性(例如, Na_v 1.7、 Na_v 1.8或 Ca_v 3.2通道活性或钠和钙通道的任何组合的活性)调节的疾病)的药物方面的用途。

[0062] 在某些实施方案中,两个或更多个特别描述的基团被结合进一种化合物:往往适于将具有如上所述的一个特征的一个特定实施方案与具有如上所述的一个或多个其它特征的一个或多个特定实施方案结合。

[0063] 如本文所用的,术语“烷基”、“烯基”和“炔基”包括未取代时仅含有C和H的直链、支链和环状单价取代基以及这些的组合。实例包括甲基、乙基、异丁基、环己基、环戊基乙基、2-丙烯基、3-丁炔基等。典型地,烷基、烯基和炔基含有1-8C(烷基)或2-8C(烯基或炔基)。在某些实施方案中,它们含有1-6C、1-4C、1-3C或1-2C(烷基);或2-6C、2-4C或2-3C(烯基或炔基)。而且,这些基团之一上的任何氢原子可被卤原子,尤其是氟代基或氯代基取代,且仍然在烷基、烯基和炔基的定义范围内。例如, CF_3 是1C烷基。这些基团也可被其它取代基取代。

[0064] 杂烷基、杂烯基和杂炔基被类似地定义,并在主链残基内含有至少一个碳原子而且还含有一个或多个O、S或N杂原子或它们的组合,借此杂烷基、杂烯基或杂炔基中的各个杂原子取代杂形式对应的烷基、烯基或炔基的一个碳原子。在优选实施方案中,杂烷基、杂烯基和杂炔基在该基团连着其它基团的各个末端含有C,存在的杂原子不位于末端位置。如本领域所理解的,这些杂形式不含有超过三个相邻的杂原子。在优选实施方案中,杂原子为O和/或N。

[0065] 在这个意义上,烷基被定义为1-6C,那么相应的杂烷基含有例如1-5C和至少一个N、O或S原子,以致杂烷基含有至少一个C原子和至少一个杂原子。类似地,当烷基被定义为1-6C或1-4C时,杂形式分别为1-5C或1-3C,其中至少一个C被O、N或S取代。因此,当烯基或炔基被定义为2-6C(或2-4C)时,那么相应的杂形式也会含有2-6C、N、O或S原子(或2-4),因为杂烯基或杂炔基含有至少一个碳原子和至少一个杂原子。此外,杂烷基、杂烯基或杂炔基取代基也可含有一个或多个羰基。杂烷基、杂烯基和杂炔基的实例有 CH_2OCH_3 、 $\text{CH}_2\text{N}(\text{CH}_3)_2$ 、 CH_2OH 、 $(\text{CH}_2)_n\text{NR}_2$ 、OR、COOR、CONR₂、 $(\text{CH}_2)_n\text{OR}$ 、 $(\text{CH}_2)_n\text{COR}$ 、 $(\text{CH}_2)_n\text{COOR}$ 、 $(\text{CH}_2)_n\text{SR}$ 、 $(\text{CH}_2)_n\text{SOR}$ 、 $(\text{CH}_2)_n\text{SO}_2\text{R}$ 、 $(\text{CH}_2)_n\text{CONR}_2$ 、NRCOR、NRCOOR、OCONR₂、OCOR等,其中R是H或烷基,其中的基团含有至少一个C,而取代基的多少与烷基、烯基和炔基的定义相一致。

[0066] 如本文所用的,术语“亚烷基”、“亚烯基”和“亚炔基”指具有确定大小的二价或三价基团,典型地,饱和基团为1-2C、1-3C、1-4C、1-6C或1-8C,和不饱和基团为2-3C、2-4C、2-6C或2-8C。它们包括未被取代时仅含C和H的直链、支链和环状形式以及这些的组合。如本文所述的化合物中的X示例的,因为它们是二价的,它们可将分子的两个部分连在一起。实例有亚甲基、亚乙基、亚丙基、环丙烷-1,1-二基、亚乙基、2-丁烯-1,4-二基等。这些基团可被典型地适于作为如本文提出的烷基、烯基和炔基的取代基的基团取代。因此,例如 $\text{C}=\text{O}$ 是被 $=\text{O}$ 取代的C1亚烷基。

[0067] 类似地定义杂亚烷基、杂亚烯基和杂亚炔基为具有确定大小的二价基团,典型地,饱和基团为1-3C、1-4C、1-6C或1-8C,不饱和基团为2-3C、2-4C、2-6C或2-8C。它们包括支链、支链和环状基团以及这些的组合,它们进一步在主链残基中含有至少一个碳原子而且

含有一个或多个 O、S 或 N 杂原子或它们的组合,从而杂亚烷基、杂亚烯基或杂亚炔基中的各个杂原子替代杂形式对应的亚烷基、亚烯基或亚炔基的一个碳原子。如本领域理解的,这些杂形式不含有超过三个相邻的杂原子。

[0068] “芳族”部分或“芳基”部分指对整个环系统的电子分布而言具有芳香特征的任何单环或稠环双环系统并包括单环或稠合双环部分诸如苯基或萘基;“杂芳族”或“杂芳基”也指含有选自 O、S 和 N 的一个或多个杂原子的这类单环或稠合双环系统。杂原子的包含要使包含的 5 元环以及 6 元环被认为是芳族的。因此,典型的芳族/杂芳族系统包括吡啶基、嘧啶基、咪唑基、苯并咪唑基、苯并三唑基、异喹啉基、喹啉基、苯并噻唑基、苯并呋喃基、噻吩基、呋喃基、吡咯基、噻唑基、噁唑基、咪唑基等。因为互变异构体在理论上可能的,苯二甲酰亚氨基也认为是芳族的。典型地,环系统含有 5-12 个环成员原子或 6-10 个环成员原子。在某些实施方案中,芳族或杂芳族部分是任选含有 1-2 个氮原子的 6 元芳族环系统。更具体地,所述部分是任选取代的苯基,2-、3- 或 4- 吡啶基,咪唑基,2- 或 4- 嘧啶基,噻吩基,苯并噻唑基或苯并咪唑基。甚至更具体地,这类部分为苯基、吡啶基或嘧啶基和甚至更具体地,其为苯基。

[0069] 卤代基可为任何卤原子,具体地为 F、Cl、Br 或 I,和更具体地是氟代基或氯代基。

[0070] 一般说来,取代基(例如,烷基、烯基、炔基或芳基(包括所有上述杂形式)本身可任选被另外的取代基取代。这些取代基的性质类似于就以上基本结构上的取代基所列举的那些。因此,如果取代基的实施方案是烷基,那么该烷基可任选被列为取代基的余下取代基取代,其中这有化学意义,且其中它不破坏烷基本身的大小限制;例如,对于这些实施方案,被烷基或被烯基取代的烷基只不过扩展碳原子的上限,而不包含在内。然而,被芳基、氨基、卤代基等取代的烷基会包含在内。例如,在基团被取代时,基团可被 1、2、3、4、5 或 6 个取代基取代。任选的取代基包括,但不限于:1C-6C 烷基或杂芳基、2C-6C 烯基或杂烯基、2C-6C 炔基或杂炔基、卤素;芳基、杂芳基、叠氮基($-N_3$)、硝基($-NO_2$)、氰基($-CN$)、酰氧基($-OC(=O)R'$)、酰基($-C(=O)R'$)、烷氧基($-OR'$)、酰氨基($-NR'C(=O)R''$ 或 $-C(=O)NRR'$)、氨基($-NRR'$)、羧酸($-CO_2H$)、羧酸酯($-CO_2R'$)、氨甲酰($-OC(=O)NR'R''$ 或 $-NRC(=O)OR'$)、羟基($-OH$)、异氰基($-NC$)、磺酸酯($-S(=O)_2OR$)、磺酰胺($-S(=O)_2NRR'$ 或 $-NRS(=O)_2R'$)或磺酰基($-S(=O)_2R$),其中各个 R 或 R' 独立地选自 H、1C-6C 烷基或杂芳基、2C-6C 烯基或杂烯基、2C-6C 炔基或杂炔基、芳基或杂芳基。取代基团可具有,例如,1、2、3、4、5、6、7、8 或 9 个取代基。

[0071] 如本文所用的,术语(例如,根据式(I)-(XI)中任一种的化合物或化合物 1-23 中的任一种)药物的“有效量”是足以产生有益或想要的结果诸如临床效果的量,和,“有效量”本身取决于所应用的上下文。例如,在给予作为钠或钙通道的调节剂的上下文中,药物的有效量是,例如,与未给予药物得到的响应相比,足以实现钠或钙通道活性改变的量。

[0072] 如本文所用的,术语“药用组合物”表示含有用药学上可接受的赋形剂配制的本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物 1-23 中的任一种)的组合物。在某些实施方案中,在政府监管机构许可作为治疗哺乳动物疾病的治疗方案的一部分下配制或出售该药用组合物。例如,可针对口服以单位剂型(例如,片剂、胶囊剂、囊片剂、软胶囊剂或糖浆剂);针对局部给药(例如,作为霜剂、凝胶剂、洗剂或软膏剂);针对静脉内给药(例如,作为不含微栓子的灭菌溶液剂和呈适于静脉内使用的溶剂系统);或以本

文所述的任何其它制剂配制药用组合物。

[0073] 如本文所用的,“药学上可接受的赋形剂”指并非本文所述的化合物的和具有对患者无毒和非炎性性质的任何成分(例如,可悬浮或溶解活性化合物的赋形剂)。赋形剂可包括,例如:抗粘着剂、抗氧化剂、粘合剂、包衣剂、压片助剂、崩解剂、染料(色料),润滑剂、乳化剂、填充料(稀释剂)、薄膜形成剂或包衣剂、调味剂、芳香剂、助流剂(促流剂)、润滑剂、防腐剂、印刷油墨、吸着剂、助悬剂或分散剂、甜味剂或水合水。示例的赋形剂包括,但不限于:丁羟甲苯(BHT)、碳酸钙、磷酸钙(二碱式)、硬脂酸钙、交联羧甲基纤维素、交联聚乙烯吡咯烷酮、柠檬酸、交联维酮、半胱氨酸、乙基纤维素、明胶、羟丙基纤维素、羟丙基甲基纤维素、乳糖、硬脂酸镁、麦芽糖醇、甘露醇、蛋氨酸、甲基纤维素、对羟基苯甲酸甲酯、微晶纤维素、聚乙二醇、聚乙烯吡咯烷酮、聚烯吡酮、预胶化淀粉、对羟基苯甲酸丙酯、棕榈酸视黄酯、虫胶、二氧化硅、羧甲基纤维素钠、柠檬酸钠、羟乙酸淀粉钠、山梨醇、淀粉(玉米)、硬脂酸、硬脂酸、蔗糖、滑石、二氧化钛、维生素A、维生素E、维生素C和木糖醇。

[0074] 如本文所用的,术语“药学上可接受的前药”表示,在正确的医学判断范围内,适于用来与具有过分的毒性、刺激、变应性响应等的人和动物的组织接触,与合理的利益/风险比相符,并对其打算的用途有效的本发明化合物的那些前药,在可能的情况下,以及本发明化合物的两性离子形式。

[0075] 如本文所用的,术语“药学上可接受的盐”表示本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)的那些盐,其在正确的医学判断范围内,适于用来与人和动物的组织接触,而无过分的毒性、刺激、变应性响应等,与合理的利益/风险比相符。药学上可接受的盐为本领域熟知。例如,药学上可接受的盐描述于:Berge等, J. Pharmaceutical Sciences 66:1-19, 1977 和药用盐:性质、选择和用途(P. H. Stahl 和 C. G. Wermuth 编辑), Wiley-VCH, 2008。可在本文所述的化合物的最终分离和纯化期间或分别使游离碱基团与适用的有机酸反应原位制备盐。

[0076] 本发明化合物可具有可电离基团以便能制备成药学上可接受的盐。这些盐可为涉及无机或有机酸的酸加成盐,或者,在本发明化合物的酸形式的情况下,可自无机或有机碱制备盐。化合物往往被制备成或用作按药学上可接受的酸或碱的加成产物制备的药学上可接受的盐。适用的药学上可接受的酸和碱为本领域熟知,诸如形成酸加成盐的盐酸、硫酸、氢溴酸、乙酸、乳酸、柠檬酸或酒石酸,和形成碱盐的氢氧化钾、氢氧化钠、氢氧化铵、咖啡碱、各种胺等。适当的盐的制备方法完全为本领域所确定。

[0077] 代表性的酸加成盐包括乙酸盐、己二酸盐、藻酸盐、抗坏血酸盐、天冬氨酸盐、苯磺酸盐、苯甲酸盐、硫酸氢盐、硼酸盐、丁酸盐、樟脑酸盐、樟脑磺酸盐、柠檬酸盐、环戊烷丙酸盐、二葡萄糖酸盐、十二烷基硫酸盐、乙磺酸盐、反丁烯二酸盐、葡庚糖酸盐、甘油磷酸盐、半硫酸盐、葡庚糖酸盐、己酸盐、氢溴酸盐、盐酸盐、氢碘酸盐、2-羟基-乙磺酸盐、乳糖醛酸盐、乳酸盐、月桂酸盐、月桂基硫酸盐、苹果酸盐、马来酸盐、丙二酸盐、甲磺酸盐、2-萘磺酸盐、烟酸盐、硝酸盐、油酸盐、草酸盐、棕榈酸盐、双羟萘酸盐、果胶酯酸盐、过硫酸盐、3-苯基丙酸盐、磷酸盐、苦味酸盐、特戊酸盐、丙酸盐、硬脂酸盐、琥珀酸盐、硫酸盐、酒石酸盐、硫氰酸盐、甲苯磺酸盐、十一酸盐、戊酸盐等。代表性的碱或碱土金属盐包括钠、锂、钾、钙、镁等以及无毒的铵、季铵和胺阳离子,包括但不限于铵、四甲基铵、四乙基铵、甲胺、二甲胺、三甲胺、三乙胺、乙胺等。

[0078] 如本文所用的术语“药学上可接受的溶剂合物”意指如本文描述的化合物（例如，根据式 (I)-(XI) 中任一种的化合物或化合物 1-23 中的任一种），其中适用溶剂的分子以晶格相结合。适用的溶剂是在给予的剂量下生理学上可耐受的。例如，可通过从包含有机溶剂、水或它们的混合物的溶液结晶、再结晶或沉淀，制备溶剂合物。适用的溶剂的实例有乙醇、水（例如，单-、二-和三-水合物）、N-甲基吡咯烷酮（NMP）、二甲亚砜（DMSO）、N,N'-二甲基甲酰胺（DMF）、N,N'-二甲基乙酰胺（DMAC）、1,3-二甲基-2-咪唑啉酮（DMEU）、1,3-二甲基-3,4,5,6-四氢-2-(1H)-嘧啶酮（DMPU）、乙腈（ACN）、丙二醇、乙酸乙酯、苄基醇、2-吡咯烷酮、苯甲酸苄酯等。当水是溶剂时，分子被称为“水合物”。

[0079] 如本文所用的术语“预防”指预防本文所述的疾病、障碍或病症（例如，疼痛（例如，慢性或急性疼痛）、癫痫、阿尔茨海默病、帕金森氏病、心血管疾病、糖尿病、癌、睡眠障碍、肥胖症、精神病诸如精神分裂症、膀胱过度活动症、肾病、神经保护、成瘾和男性节育）的一种或多种症状或病情的预防性治疗或治疗。例如，可在先于疾病、障碍或病症开始进行的事件之前（“预暴露性预防”）或之后（“暴露后预防”）着手预防性治疗。包括给予本文所述的化合物（例如，根据式 (I)-(XI) 中任一种的化合物或化合物 1-23 中的任一种）或其药学上可接受的盐或溶剂合物或其药用组合物的预防性治疗可为急性、短期或慢性的。在预防性治疗过程中所给予的剂量可有所不同。

[0080] 如本文所用的术语“前药”指例如，通过在血液中水解，在体内快速转变为上式母体化合物的化合物。本文所述的化合物的前药可为常规的酯。已经被用作前药的某些普通酯为苯基酯、脂族（C1-C8 或 C8-C24）酯、胆固醇酯、酰氧基甲基酯、氨基甲酸酯和氨基酸酯。例如，在其前药形式中的含有 OH 基团的化合物可在该位置被酰基化。在 T. Higuchi 和 V. Stella, 作为新的递药系统的前药, A. C. S. Symposium Series 的 14 卷、Edward B. Roche, 编辑, 药物设计中的生物可逆载体, 美国药物协会和 Pergamon 出版社, 1987 和 Judkins 等, Synthetic Communications, 26 (23) :4351-4367, 1996 中提供了全面的讨论, 它们分别通过引用结合于本文中。本发明化合物的前药优选适用于与人和动物的组织接触, 具有过分的毒性、刺激、变应性响应等, 与合理的利益 / 风险比相符并对其打算的用途有效。

[0081] 此外, 本发明化合物可通过共轭偶合至被设计来为靶向或为其它理由改变药物代谢动力学的物质上。因此, 本发明进一步包括这些化合物的共轭物。例如, 常常将聚乙二醇偶合至提高半衰期的物质; 可将化合物共价或非共价偶合至脂质体或偶合至其它特殊载体。往往也可通过连接剂部分将它们偶合至靶向试剂诸如抗体或肽模拟物。因此, 当被修饰以包含在这种类型的共轭物中时, 本发明还涉及化合物（例如, 根据式 (I)-(XI) 中任一种的化合物或化合物 1-23 中的任一种）。

[0082] 如本文所用的以及本领域完全理解的, “治疗”疾病或疾病的“治疗”（例如, 本文所述的疾病诸如疼痛（例如, 慢性或急性疼痛）、癫痫、阿尔茨海默病、帕金森氏病、心血管疾病、糖尿病、癌、睡眠障碍、肥胖症、精神病诸如精神分裂症、膀胱过度活动症、肾病、神经保护、成瘾和男性节育）是获得有益或想要的效果, 诸如临床效果的途径。有益或想要的效果可包括, 但不限于, 减轻或改善一种或多种症状或病情; 减少疾病、障碍或病症的严重程度; 稳定疾病、障碍或病症的状态（即, 不恶化）; 预防疾病、障碍或病症的传播; 延缓或减慢疾病、障碍或病症的发展; 疾病、障碍或病症的改善或缓和; 和无论可察觉还是不可察觉地的缓和（无论部分还是全部）。“减轻”疾病、障碍或病症意指, 与未治疗的程度和时间进程相

比,疾病、障碍或病症的程度和/或不想要的临床表现被减少和/或发展的时间进程被减慢或延长。

[0083] 术语“单位剂型”指适合作为人受治疗者和其它哺乳动物的统一剂量的物理上分开的单位,各单位含有任何合适的与一种或多种药用赋形剂一起的经计算以产生所需治疗效果的预定量活性物质。示例的非限制性单位剂型包括片剂(例如,咀嚼片剂)、囊片剂、胶囊剂(例如,硬胶囊剂或软胶囊剂)、锭剂、薄膜剂、小袋剂、软胶囊剂和糖浆剂。

[0084] 由于某些本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)易于形成酸加成盐,且这类盐可有利于处理和稳定,在某些实施方案中,化合物优选药学上可接受的盐。

[0085] 在某些情况下,本发明化合物含有一个或多个手性中心。本发明包括各种分离的立体异构形式以及呈不同手性程度的各立体异构体的混合物,包括外消旋混合物。它还涵盖可能形成的各种非对映异构体和互变异构体。

[0086] 本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)也用来制备用来治疗需要调节钠和/或钙通道活性,且尤其是 $\text{Na}_v 1.7$ 、 $\text{Na}_v 1.8$ 和 $\text{Ca}_v 3.2$ 通道活性或钠和钙通道的任何组合的活性的疾病的药物。

[0087] 通过以下详述、图和权利要求,本发明的其它特征和优点会显而易见。

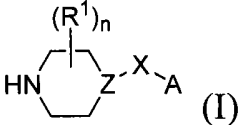
[0088] 图的简述

[0089] 图1显示与如在触诱异常性疼痛的 Von Frey 评估中测定的基线和 SNL 后相比,化合物1和9的抗痛觉异常作用。

[0090] 发明详述

[0091] 化合物

[0092] 本发明的特征在于,具有根据以下式的结构的化合物

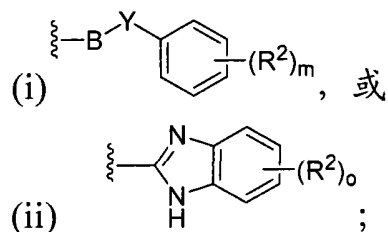
[0093]  或其药学上可接受的盐、溶剂合物、前药或立体异构体,其中

[0094] X 是任选取代的亚烷基(1-3C);

[0095] Z 是 N 或 CR^4 ;

[0096] A 选自

[0097]



[0098] B 是 N-R^3 或任选取代的异噁唑基;

[0099] Y 是键或任选取代的亚烷基(1-3C);

[0100] m 是介于 0-5 之间的整数;

[0101] n 是介于 0-6 之间的整数;

[0102] o 是介于 0-4 之间的整数;

[0103] 各个 R^1 和 R^2 独立地选自卤代基、CN、 NO_2 、 COOR' 、 CONR'_2 、 OR' 、 SR' 、 SOR' 、 $\text{SO}_2\text{R}'$ 、 NR'_2 、 $\text{NR}'(\text{CO})\text{R}'$ ，和 $\text{NR}'\text{SO}_2\text{R}'$ ，其中各个 R' 独立地为 H 或选自烷基 (1-6C)、烯基 (2-6C)、炔基 (2-6C)、杂烷基 (2-6C)、杂烯基 (2-6) 和杂炔基 (2-6C) 的任选取代的基团；或 R^1 和 R^2 可独立地为选自烷基 (1-6C)、烯基 (2-6C)、炔基 (2-6C)、杂烷基 (2-6C)、杂烯基 (2-6) 或杂炔基 (2-6C) 的一个或多个任选取代的基团；和其中各个 R^1 可进一步选自 $=\text{O}$ 和 $=\text{NOR}'$ ；

[0104] R^3 为 H 或任选取代的烷基 (1-3C)；和

[0105] R^4 为 H、甲基、氟代基、羟基或氰基。

[0106] 部位描述其它实施方案（例如，式 (II)-(XI) 和化合物 1-23）、合成这些化合物的示例性方法

[0107] 效用和给药

[0108] 本文所述的化合物（例如，根据式 (I)-(XI) 中任一种的化合物或化合物 1-23 中的任一种）用于本发明方法，尽管不囿于理论，并被认为通过其调节钠和 / 或钙通道活性，尤其是 $\text{Na}_v1.7$ 、 $\text{Na}_v1.8$ 或 $\text{Ca}_v3.2$ 通道的活性的能力发挥其所需的作用。这使其可用于治疗需要调节钠或 T- 型钙通道的某些疾病，包括疼痛、癫痫、偏头痛、帕金森氏病、抑郁症、精神分裂症、精神病和耳鸣。

[0109] 钠通道的调节

[0110] 9 种 $\text{Na}_v1\alpha$ -亚基同工型 $\text{Na}_v1.7$ 和 $\text{Na}_v1.8$ 通道亚型对炎症和神经性疼痛（同下页）两者起到主要促成因素的作用。近来，已经在 $\text{Na}_v1.7$ 通道中鉴别出导致获得通道功能 (Dib-Hajj 等, *Brain* 128:1847-1854, 2005) 或者更常见地导致通道功能损失 (Chatelier 等, *J. Neurophysiol.* 99:2241-50, 2008) 的突变体。这些突变体引起人的可遗传障碍诸如红斑肢痛症 (Yang 等, *J Med Genet.* 41(3)171-4, 2004)、阵发性剧痛症 (Fertleman 等, *Neuron.* 52(5)767-74, 2006) 和先天性痛觉丧失 (Cox 等, *Nature* 444(7121):894-8, 2006)。小鼠的行为研究已经表明，当在 $\text{Na}_v1.8$ -阳性神经元中基因剔除 $\text{Na}_v1.7$ 时，炎症和急性机械性感觉的疼痛减轻 (Nassar 等, *Proc Natl Acad Sci U S A.* 101(34):12706-11, 2004)。此外， $\text{Na}_v1.7$ 的 siRNA 减轻炎症痛觉过敏 (Yeomans 等, *Hum Gene Ther.* 16(2)271-7, 2005)。也已经采用分子技术击倒 (knockdown) $\text{Na}_v1.8$ ，显现出 $\text{Na}_v1.8$ 在炎性 (Khasar 等, *Neurosci Lett.* 256(1):17-20, 1998)、神经性和机械性痛觉过敏 (Joshi 等, *pain* 123(1-2):75-82, 2006) 中的作用，这已经表明，这些不同疼痛状况的维持的减弱。

[0111] 拉科酰胺 (Lacosamide) 是功能性氨基酸，它已经在神经性疼痛的几种动物模型中表现出作为止痛剂的效果，目前处于针对癫痫和糖尿病神经性疼痛的临床开发晚期。已经证实拉科酰胺的一种作用方式是通过以缓慢失活的通道构造选择性地抑制，抑制电压门控钠通道活性 (Sheets 等, *Journal of Pharmacology and Experimental Therapeutics*, 326(1)89-99(2008))。钠通道调节剂，包括临床相关化合物，可表现出显著的状态依赖性结合，其中快速且反复活化和失活的钠通道更易被阻断。在简化流程中，电压门控钠通道有四种不同的状态：开放、关闭、快速失活和缓慢失活。相信对于快速失活状态，典型的钠通道调节剂，诸如利多卡因，表现出最高的亲合性。然而，缓慢失活状态的改变也有临床相关性。

[0112] 钙通道的调节

[0113] 钙通过电压门控钙通道进入细胞，介导多种细胞和生理学响应，包括兴奋-收缩偶联、激素分泌和基因表达（例如，Miller 等, *Science* 235:46-52(1987)；Augustine 等，

Annu Rev Neurosci 10 :633-693(1987))。在神经元中,钙通道直接影响膜电位并促成电性质诸如兴奋、重复放电模式和起搏器活性。钙进入通过直接调节钙-依赖离子通道和调节钙-依赖酶诸如蛋白激酶 C 和钙调蛋白-依赖蛋白激酶 II 的活性进一步影响神经元功能。突触前神经末梢的钙浓度的增加引发神经递质的释放,它还影响发展中的神经元中的神经突触长出和生长锥迁移。

[0114] 钙通道介导多种正常生理功能,也涉及多种如本文所述的人障碍。例如,也已经表明,钙通道介导与神经性疼痛有关的神经元敏感化和超兴奋性过程的发展和维持,并为镇痛药的开发提供有吸引力的靶标(综述于 Vanegas 等, Pain 85 :9-18(2000))。已经根据其电生理学和药理学性质,将天然钙通道分为 T-、L-、N-、P/Q- 和 R- 型(综述于 Catterall, Annu Rev Cell Dev Biol 16 :521-555,2000 ;Huguenard,Annu Rev Physiol 58 :329-348, 1996)。L-、N- 和 P/Q- 型通道在更多正电势下活化(高电压活化)并表现出不同的动力学和电压-依赖性质(Id.)。可通过更负电势范围的活化和失活、快速失活、缓慢钝化和更小的单通道电导率,辨别 T- 型通道。已经从分子、药理学和电生理学上鉴别出 T- 型钙通道的三种亚型:这些亚型称为 α_{1G} 、 α_{1H} 和 α_{1I} (或者分别称为 Cav 3.1、Cav 3.2 和 Cav 3.3)。

[0115] T- 型钙通道涉及多种医学状况。在缺乏基因表达 3.1 亚型的小鼠中,观察到失神发作的抵抗(Kim 等, Mol. Cell Neurosci. 18(2) :235-245(2001))。其它研究也已经在癫痫的发展中涉及 3.2 亚型(Su 等, J. Neurosci. 22 :3645-3655(2002))。还有某些现有的抗惊厥药,诸如乙琥胺,通过阻断 T- 型通道起作用的证据(Gomora 等, Mol. Pharmacol. 60 : 1121-1132(2001))。

[0116] 低电压活化的钙通道高度表达于心血管系统的组织中。还有不断增加的证据表明, T- 型钙通道异常表达于癌细胞,并表明阻断这些通道可能除介导细胞凋亡之外还减少细胞增殖。最近的研究还表明,乳癌细胞中的 T- 型钙通道的表达是增殖状态依赖的,即,在快速复制阶段,通道以更高的水平表达,而一旦细胞处于非增殖状态,该通道的表达最小。因此,选择性地阻止钙通道进入癌细胞可能是预防肿瘤生长的有价值的手段(例如, PCT 专利申请号 WO 05/086971 和 W005/77082 ;Taylor 等, World J. Gastroenterol. 14(32) :4984-4991(2008) ;Heo 等, Biorganic&Medicinal Chemistry Letters 18 :3899-3901(2008))。

[0117] T- 型钙通道还可能涉及另外的其它疾病。最近的研究还表明, T- 型钙通道拮抗剂抑制小鼠的高脂肪膳食介导的体重增加。此外,给予选择性 T- 型通道拮抗剂减少体重和脂肪质量,同时增加瘦肌肉质量(例如, Uebele 等, The Journal of Clinical Investigation, 119(6) :1659-1667(2009))。T- 型钙通道也可能涉及疼痛(参见例如:美国专利公开号 2003/0086980 ;PCT 公开号 WO 03/007953 和 WO 04/000311)。除心血管疾病、癫痫(还参见美国专利申请号 2006/0025397)、癌和慢性或急性疼痛之外, T- 型钙通道还涉及糖尿病(美国专利公开号 2003/0125269)、睡眠障碍(美国专利公开号 2006/0003985)、帕金森氏病和精神病诸如精神分裂症(美国专利公开号 2003/0087799) ;膀胱过度活动症(Sui 等, British Journal of Urology International 99(2) :436-441(2007) ;美国专利公开号 2004/0197825)、肾病(Hayashi 等, Journal of Pharmacological Sciences 99 : 221-227(2005))、焦虑和酒精中毒(美国专利公开号 2009/0126031)、神经保护和男性节育。

[0118] 可根据本领域已知的方法（例如，在本文提供的参考文献中），测定本文所述的化合物（例如，根据式 (I)-(XI) 中任一种的化合物或化合物 1-23 中的任一种）对离子通道的调节。离子通道，例如，电压门控钠和钙离子通道的调节剂和医学化学或可以鉴别这类化合物的方法还描述于，例如：Birch 等，*Drug Discovery Today*, 9(9):410-418(2004)；Audesirk, “6 章 - 离子通道功能的电生理学分析,” *Neurotoxicology: Approaches and Methods*, 137-156(1995)；Camerino 等, “4 章：离子通道疾病的治疗方法,” *Advances in Genetics*, 64:81-145(2008)；Petkov, “16 章 - 离子通道,” *Pharmacology: Principles and Practice*, 387-427(2009)；Standen 等, “15 章 - 膜片钳方法和离子通道分析,” *Principles of Medical Biology*, 7 卷, 2 部分, 355-375(1997)；Xu 等, *Drug Discovery Today*, 6(24):1278-1287(2001)；和 Sullivan 等, *Methods Mol. Biol.* 114:125-133(1999)。还在实施例中提供举例的实验方法。

[0119] 疾病和病症

[0120] 可采用本文所述的化合物治疗的示例性疾病包括疼痛（例如，慢性或急性疼痛）、癫痫、阿尔茨海默病、帕金森氏病、糖尿病；癌；睡眠障碍；肥胖症；精神病诸如精神分裂症；膀胱过度活动症；肾病、神经保护和成瘾。例如，疾病可为疼痛（例如，神经性疼痛或术后疼痛）、癫痫、偏头痛、帕金森氏病、抑郁症、精神分裂症、精神病或耳鸣。

[0121] 如本文所用的癫痫包括但不限于部分性癫痫发作诸如颞叶癫痫、失神发作、全身性发作和强直性 / 阵挛性发作。

[0122] 如本文所用的癌症包括但不限于乳腺癌、神经母细胞瘤、眼癌、神经胶质瘤、前列腺癌、食道癌、纤维肉瘤、结肠直肠癌、嗜铬细胞瘤、腺癌、胰岛瘤、肺癌、黑素瘤和卵巢癌。

[0123] 如本文所用的急性疼痛包括但不限于伤害感受性疼痛和术后疼痛。慢性疼痛包括但不限于：外周神经性疼痛诸如带状疱疹后神经痛、糖尿病神经性疼痛、神经性癌疼痛、腰椎手术失败综合征、三叉神经痛、和幻肢痛；中枢神经性疼痛诸如多发性硬化相关疼痛、帕金森氏病相关疼痛、中风后疼痛、外伤后骨髓损伤性疼痛和痴呆症中的疼痛；肌肉骨骼痛诸如骨关节痛和纤维肌痛综合征；炎性疼痛诸如类风湿性关节炎和子宫内膜移位症；头痛诸如偏头痛、丛集性头痛、紧张性头痛综合征、面痛、其它疾病引起的头痛；内脏疼痛诸如间质性膀胱炎、肠易激惹综合征和慢性骨盆疼痛综合征；和混合性疼痛诸如腰痛、颈肩痛、灼口综合征和复杂性局部疼痛综合征。

[0124] 在治疗骨关节痛中，随着潜在的慢性疼痛的减轻，关节移动性也可改善。因此，采用本发明化合物治疗骨关节痛本来就包括采用这类化合物改善患有骨关节炎的患者的关节移动性。

[0125] 可在疼痛的任何标准动物模型中测试本文所述的化合物的效力。多种模型测试正常动物对强烈或伤害性刺激（生理学或伤害感受性疼痛）的敏感性。这些测试包括对热、机械和化学刺激的响应。热刺激通常涉及热刺激（典型地在 42-55℃ 间变化）的施加，包括，例如：对尾部的热辐射（甩尾试验）、后爪脚底表面的热辐射（足底测痛试验）、热板试验和将后爪或尾浸入热水中。浸入冷水、丙酮蒸发或冷板试验也可用来测试冷疼痛响应性。涉及机械刺激的测试典型地测量后爪对分等级的强度单丝 von Frey 毛发或对爪的持续压力刺激而产生退避反射的阈值（例如，Ugo Basile 痛觉仪 (analgesimeter)）。还可测量对标准针刺的响应持续时间。当采用化学刺激时，测量对皮肤、肌肉、关节或内部器官（例

如,膀胱或腹膜)施加或推注化学刺激物(例如,辣椒碱、芥子油、缓激肽、ATP、福尔马林、乙酸)的响应。

[0126] 此外,多种试验通过测定疼痛神经通路的外周或中枢部分的兴奋性改变评价痛觉敏化。在这点上,可通过反复的热刺激以及施加或推注敏化化学品(例如,前列腺素、缓激肽、组胺、血清素、辣椒碱或芥子油)介导外周敏化(即,高阈值伤害感受器的阈值和响应性的变化)。可通过伤害性刺激(例如,热)、化学刺激(例如,推注或施加化学刺激物)或感觉纤维的电激活,介导中枢敏化(即,外周疼痛纤维中的活性介导的中枢神经系统中神经元的兴奋性变化)。

[0127] 为测量外周炎症对疼痛敏感性的影响而开发的多种疼痛试验也可用来研究化合物的效力(Stein等, *Pharmacol. Biochem. Behav.* (1988) 31:445-451; Woolf等, *Neurosci.* (1994) 62:327-331)。此外,多种试验采用外周神经系统的损伤评价外周神经性疼痛。一个这样的实例是“轴索断裂疼痛模型(axotomy pain model)”(Watson, *J. Physiol.* (1973) 231:41)。其它类似试验包括涉及脊节段神经结扎(Kim和Chung *Pain* (1992) 50:355)、与部分神经损伤有关的Seltzer模型(Seltzer, *Pain* (1990) 43:205-18)、非伤害性神经损伤(spared nerve injur, SNI)模型(Decosterd和Woolf, *Pain* (2000) 87:149)、慢性压迫性损伤(CCI)模型(Bennett (1993) *Muscle Nerve* 16:1040)的SNL试验,涉及中毒性神经病诸如糖尿病(链佐星模型)、吡哆醇神经病、紫杉醇、长春新碱和其它抗肿瘤药介导的神经病的试验,涉及神经缺血、外周神经炎模型(例如,周围神经应用CFA)、采用HSV感染的带状疱疹后神经痛模型和压迫模型的试验。

[0128] 在全部以上试验中,例如,可根据行为、电生理学、神经化学或成像技术,评价测量结果,以检测神经活性变化。

[0129] 示例的疼痛模型还描述于本文提供的实施例中。

[0130] 除能调节特定的钠或钙通道外,还可希望化合物对表达于心脏的hERG K⁺通道具有极低的活性:以高效力阻断该通道的化合物可能引起致命的反应。参见,例如, Bowlby等,“hERG(KCNH2或K_v11.1K⁺通道:心律失常风险的筛查,”*Curr. Drug Metab.* 9(9):965-70(2008))。因此,对于调节钠或钙通道的化合物,也可能表现出hERG K⁺通道未被抑制,或者与对靶向的主要通道的抑制相比只有极少的抑制。类似地,可希望化合物不抑制细胞色素p450,药物解毒所需要的一种酶。这类化合物可能特别有益于本文所述的方法中。

[0131] 药用组合物

[0132] 为用作人和动物受治疗者的治疗,可将本发明化合物配制成药用或兽医用组合物。根据要治疗的受治疗者、给药方式和想要的治疗类型——例如,防止、预防或治疗——以与这些参数一致的方式配制化合物。这类技术的概述可发现于Remington:制药科学与实践,第21版, Lippincott Williams&Wilkins, (2005);和制药技术大全, J. Swarbrick和J. C. Boylan编辑, 1988-1999, Marcel Dekker, 纽约,它们分别通过引用结合于本文中。

[0133] 本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)可以组合物总重量的共计1-95%重量的量存在。可以适于关节内、经口、胃肠外(例如,静脉内、肌肉)、直肠、皮肤、皮下、局部、经皮、舌下、经鼻、阴道、囊内、尿道内、鞘内、硬膜外、经耳或眼给药的剂型,或者通过推注、吸入或与鼻、泌尿生殖器、胃肠道、生殖道或口腔粘膜直接接触,提供组合物。因此,药用组合物可呈,例如,片剂、胶囊剂、丸剂、粉末

剂、颗粒剂、混悬剂、乳剂、溶液剂、凝胶剂包括水凝胶剂、糊剂、软膏剂、霜剂、硬膏剂、涂敷剂 (drenches)、渗透递药装置、栓剂、灌肠剂、注射剂、植入物、喷雾剂、适于离子电渗递药的制剂或气雾剂的形式。可根据常规制药实践配制组合物。

[0134] 一般说来,为用于治疗,可单独、作为两种或更多种化合物的混合物或与其它药物联合,使用本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)。要与本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)联合的其它药物的实例将包括治疗相同适应症的药物。例如,在疼痛的治疗中,化合物可与另一种疼痛缓解治疗物诸如 NSAID 或选择性抑制 COX-2 的化合物或阿片或辅助镇痛剂诸如抗抑郁剂联合。要与本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)联合的潜在药物的另一实例将包括治疗不同但相关或有关的症状或适应症的药物。应根据给药途径,将化合物配制成易于递药的适当组合物。可以本领域已知的多种方法配制联合治疗的各化合物。例如,可一起或分开配制联合治疗中的第一种和第二种药物。为了同时或几乎同时给药,希望一起配制第一和第二种药物。

[0135] 如本领域熟知的,本发明化合物可被制备并作为包含有效量的本文所述的化合物(例如,根据式(I)-(XI)中任一种的化合物或化合物1-23中的任一种)和药学上可接受的载体或赋形剂的药用组合物使用。在某些实施方案中,组合物包括至少两种不同的药学上可接受的赋形剂或载体。

[0136] 以适于全身给药或外用或局部给药的方式制备制剂。全身制剂包括针对注射(例如,肌肉、静脉内或皮下注射)设计的那些,或者可针对经皮、经粘膜或口服而制备。制剂通常将包括稀释剂以及,在某些情况下,辅助剂、缓冲剂、防腐剂等。也可以脂质体组合物或作为微乳剂给予化合物。

[0137] 对于注射,可作为液体溶液剂或混悬剂,或者作为适于在注射前制成溶液剂或液体中的混悬剂的固体形式,或者作为乳剂,制备呈常规形式的制剂。适用的赋形剂包括,例如,水、盐水、葡萄糖、甘油等。例如,这类组合物还可包含一定量的无毒辅助物质诸如湿润剂或乳化剂、pH 缓冲剂等,诸如,乙酸钠、单月桂酸山梨醇酐酯等。

[0138] 还已经设计出药物的多种持续释放系统。参见,例如,美国专利号 5,624,677,其通过引用结合于本文中。

[0139] 全身给药还可包括相对地非侵入方法,诸如采用栓剂、透皮贴剂、透粘膜递药和鼻内给药。口服也适用本发明化合物。如本领域理解的,适用的形式包括糖浆剂、胶囊剂和片剂。

[0140] 对于动物或人受治疗者给药,本发明化合物的剂量可为,例如,0.01-50mg/kg(例如,0.01-15mg/kg 或 0.1-10mg/kg)。例如,剂量可为 10-30mg/kg。

[0141] 如本文所述,可以本领域已知的多种方式配制联合治疗中的各化合物。例如,可一起或分开配制联合治疗中的第一种和第二种药物。

[0142] 分别或分开配制的药物可包装在一起作为药剂盒。非限制性实例包括,但不限于,含有例如两个丸剂、一个丸剂和一种粉末剂、一个栓剂和一种在小瓶中的液体、两个外用霜剂等的药剂盒。药剂盒可包括有助于给予患者单位剂量的任选组成部分,诸如用于重新构成的粉末形式的小瓶、推注用注射器、定制的 IV 递药系统、吸入器等。此外,单位剂量药剂

盒可含有对于组合物制备和给予的说明书。可将药剂盒制备为用于一个患者的单次使用的单位剂量、特定患者多次使用的单位剂量（以不变剂量或其中个别化合物可随治疗进展而改变效价强度）；或者药剂盒可含有适于给予多个患者的多个剂量（“成批包装”）。可将药剂盒各组分组合为大包装盒、泡罩包装、瓶、管等。

[0143] 口服使用的制剂包括含有与无毒的药理学上可接受的赋形剂混合的活性成分的片剂。这些赋形剂可为，例如，惰性稀释剂或填充剂（例如，蔗糖、山梨醇、糖、甘露醇、微晶纤维素、淀粉包括马铃薯淀粉、碳酸钙、氯化钠、乳糖、磷酸钙、硫酸钙或磷酸钠）；粒化剂和崩解剂（例如，纤维素衍生物包括微晶纤维素、淀粉包括马铃薯淀粉、交联羧甲基纤维素钠、藻酸盐或藻酸）；粘合剂（例如，蔗糖、葡萄糖、山梨醇、阿拉伯胶、藻酸、藻酸钠、明胶、淀粉、预凝胶化淀粉、微晶纤维素、硅酸镁铝、羧甲基纤维素钠、甲基纤维素、羟丙基甲基纤维素、乙基纤维素、聚乙烯吡咯烷酮或聚乙二醇）；和润滑剂、助流剂和抗结合剂（例如，硬脂酸镁、硬脂酸锌、硬脂酸、二氧化硅、氢化植物油或滑石）。其它药理学上可接受的赋形剂可为着色剂、矫味剂、增塑剂、湿润剂、缓冲剂等。

[0144] 两种或多种化合物可在片剂、胶囊剂或其它媒介物中混合在一起，或者可分开。在一个实施例中，第一种化合物包含在片剂的内部，而第二种化合物在外部，以致大部分的第二种化合物在第一种化合物释放之前释放。

[0145] 也可作为可咀嚼片剂或作为硬明胶胶囊剂，其中的活性成分与惰性固体稀释剂（例如，马铃薯淀粉、乳糖、微晶纤维素、碳酸钙、磷酸钙或白陶土）混合，或者作为软明胶胶囊剂，其中的活性成分与水或油介质，例如，花生油、液体石蜡或橄榄油混合，提供口服用制剂。可采用，例如，混合器、流化床装置或喷雾干燥装备，以常规方法，用在上文对片剂和胶囊剂中提及的各种成分，制备散剂、颗粒剂和小丸剂。

[0146] 可对化合物的片剂、胶囊剂、小丸剂或颗粒剂制剂适当包衣，或者通过将化合物结合进适当基质，实现分散或扩散控制释放。控释包衣可能包括上述的一种或多种包衣物质和/或，例如，虫胶、蜂蜡、glycowax、蓖麻蜡、巴西棕榈蜡、硬脂醇、甘油单硬脂酸酯、甘油二硬脂酸酯、棕榈酸硬脂酸甘油醇酯、乙基纤维素、丙烯酸树脂、d1-聚乳酸、醋酸丁酸纤维素、聚氯乙烯、聚乙烯乙酸酯、乙烯基吡咯烷酮、聚乙烯、聚甲基丙烯酸酯、甲基丙烯酸甲酯、甲基丙烯酸2-羟基酯、甲基丙烯酸酯水凝胶、1,3-丁二醇、乙二醇甲基丙烯酸酯和/或聚乙二醇。在控释基质制剂中，基质材料还可包括，例如，水合甲基纤维素、巴西棕榈蜡和硬脂醇、卡波普934、硅酮、三硬脂酸甘油酯、丙烯酸甲酯-甲基丙烯酸甲酯、聚氯乙烯、聚乙烯和/或卤代碳氟化合物。

[0147] 可因口服而结合的本发明化合物和组合物的液体形式包括水溶液剂、适当矫味的糖浆剂、水性或油性混悬剂和用食用油诸如棉籽油、芝麻油、椰子油或花生油矫味的乳剂以及酞剂和类似的药用媒介物。

[0148] 通常，当给予人时，本发明组合中的任何化合物的口服剂量将取决于化合物的性质，并可容易地被本领域技术人员确定。典型地，这类剂量通常为约0.001mg-2000mg每日，理想地为约1mg-1000mg每日和更理想地为约5mg-500mg每日。至多200mg每日的剂量可能是必要的。

[0149] 如本文所述，联合治疗中的每种药物的给予，可独立地每日1-4次，持续一年，甚至患者可终生使用。可注明慢性、长期用药。

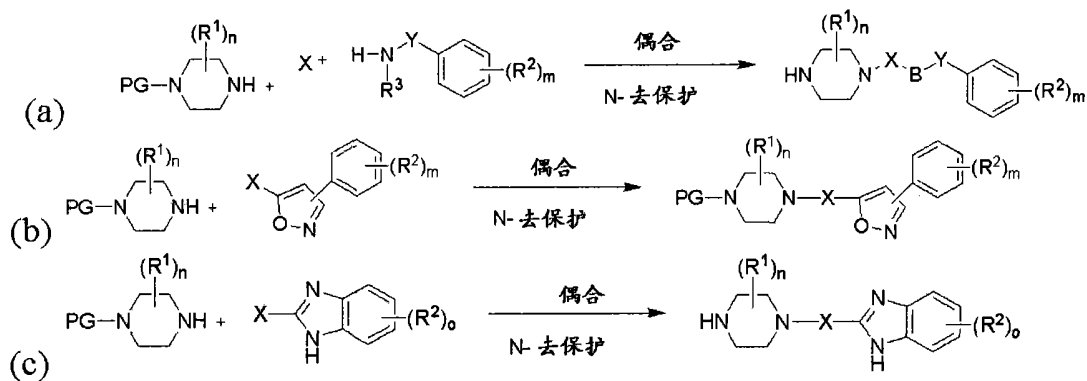
[0150] 合成

[0151] 打算用反应流程和实施例说明有代表性编号化合物的合成。因此,各实施例只意欲说明而不是限制本发明。可采用与本文所述方法结合的常规方法,合成未特别举例的其它化合物。

[0152] 如流程 1 中所示,可根据本领域已知的方法制备本文所述的化合物。

[0153] 流程 1

[0154]

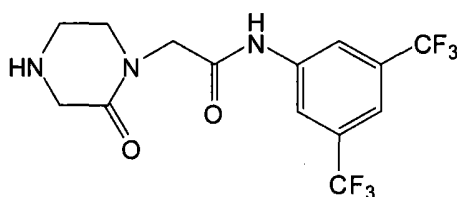


[0155] 在流程 1 中, PG 可为 H 或 N- 保护基团。如本文所用的术语“N- 保护基团”表示意欲在合成程序期间保护氨基免于不想要的反应的那些基团。常用的 N- 保护基团公开于 Greene, “有机合成中的保护基”, 第 3 版, (John Wiley&Sons, New York, 1999), 其通过引用结合于本文中。N- 保护基团包括酰基、芳酰基或氨基甲酰基; 含有磺酰基的基团; 氨基甲酸酯形成基团; 烷芳基诸如苄基; 和甲硅烷基。示例的 N- 保护基团包括甲酰基、乙酰基、苯甲酰基、特戊酰基、叔丁基乙酰基、丙氨酰基、苯基磺酰基、苄基、叔丁氧基羰基 (Boc) 和苄氧基羰基 (Cbz)。

实施例

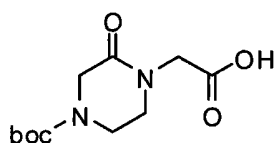
[0156] 实施例 1: N-(3,5- 双(三氟甲基)苯基)-2-(2- 氧代哌嗪-1-基)乙酰胺(化合物 1) 的合成

[0157]



[0158] A. 2-(4-叔丁氧基羰基)-2- 氧代哌嗪-1-基) 乙酸的合成

[0159]



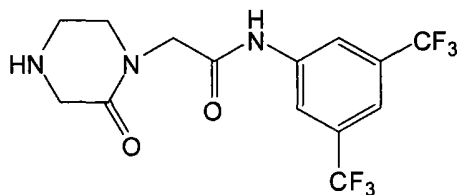
[0160] 在氮气和室温下,向 1-Boc-3- 氧代哌嗪 (10.4g, 51.9mmol) 的无水 DMF (100mL) 溶液分批加入 NaH (60% 矿物油中, 2.50g, 62.3mmol)。加入后,室温下搅拌混合物 30min 然后于 65℃ 下搅拌 1h。在混合物冷却至室温后,加入氯乙酸乙酯 (7.63g, 62.3mmol)。室温下搅

拌反应混合物 30min, 再于 65℃ 下搅拌 2h。加入水 (5mL), 浓缩溶液。加入盐水 (100mL), 用 EtOAc (5×100mL) 萃取反应混合物。用水 (100mL) 洗涤合并的萃取物, 经无水 Na₂SO₄ 干燥。过滤后, 经旋转蒸发浓缩滤液, 残余物经硅胶快速层析法 (EtOAc/ 己烷 :1/1v/v) 纯化, 得到呈白色固体的想要的产物 (13g, 87%)。

[0161] 使固体溶解于甲醇 (50mL) 并用 NaOH (2.5N, 50mL) 水溶液处理 2.5h。除去甲醇, 反复酸化残余水溶液 (每次小心地至 pH = 2), 然后用 EtOAc (10×100mL) 萃取。合并的萃取物经无水 Na₂SO₄ 干燥, 浓缩, 得到呈白色固体的酸 (11.2g, 85%)。

[0162] B. N-(3,5-双(三氟甲基)苯基)-2-(2-氧代哌嗪-1-基)乙酰胺的合成

[0163]



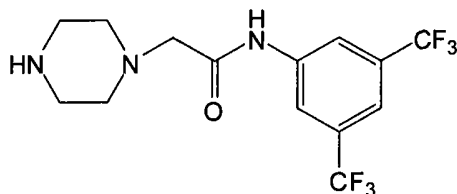
[0164] 向配有磁力搅拌棒的 500mL、单颈、圆底烧瓶中装入 DMF (100mL) 中的 2-(4-叔丁氧基羰基)-2-氧代哌嗪-1-基)乙酸 (13.0g, 50.3mmol)、3,5-双(三氟甲基)苯胺 (12.6g, 55.3mmol) 和 O-(7-氮杂苯并三唑-1-基)-N,N',N'-四甲基脲六氟磷酸酯 (HATU) (22.8g, 60.0mmol)。加入二异丙基乙胺 (DIPEA) (10.3g, 80.0mmol)。室温下搅拌反应混合物 16h, 然后通过旋转蒸发浓缩至约 60mL。加入饱和 NaHCO₃ 水溶液 (200mL) 用 EtOAc (2×200mL) 和水 (200mL) 萃取混合物, 再经无水 Na₂SO₄ 干燥。过滤后, 经旋转蒸发浓缩滤液, 残余物经硅胶快速层析法 (CH₂Cl₂, 然后 EtOAc/ 己烷, 1 : 1 in v/v) 纯化, 随后自 CH₂Cl₂/ 己烷再结晶, 得到白色固体 (20.0g, 85%)。

[0165] 用在 EtOAc (350mL) 中的饱和 HCl 处理固体 (17g, 36.2mmol) 10min, 定量得到想要的化合物。纯度 (HPLC) :100%。¹H NMR (400MHz, D₂O) δ 3.61 (t, 2H, J = 5.4Hz), 3.71 (t, 2H, J = 5.4Hz), 3.96 (s, 2H), 4.32 (s, 2H), 7.73 (s, 1H), 7.88 (s, 2H). ES-MS m/z 370.2 (M+H)。对 C₁₄H₁₃F₆N₃O₂ · 1.0HCl · 0.63H₂O 的分析计算值 :C, 40.37 ;H, 3.68 ;N, 10.09 ;Cl 8.51。实测值 :C, 40.42 ;H, 3.75 ;N, 10.00 ;Cl, 8.50。

[0166] 用类似方法制备化合物 2-4。

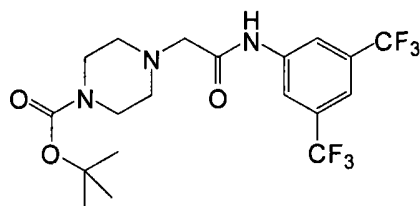
[0167] 实施例 2 :N-(3,5-双(三氟甲基)苯基)-2-(哌嗪-1-基)乙酰胺 (化合物 5) 的合成

[0168]



[0169] A. 4-(2-(3,5-双(三氟甲基)苯基氨基)-2-氧代乙基)哌嗪-1-羧酸叔丁酯的合成

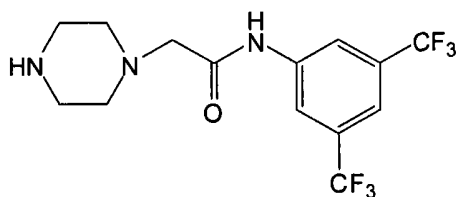
[0170]



[0171] 于室温下搅拌 N-(3,5-双(三氟甲基)苯基)-2-氯乙酰胺 (1.60g, 5.23mmol)、哌嗪-1-羧酸叔丁酯 (1.46g, 7.85mmol)、 K_2CO_3 (2.17g, 15.7mmol) 和 KI (cat.) 在 CH_3CN (50mL) 中的混合物过夜。然后用 EtOAc 稀释反应, 用水洗涤。有机层经 Na_2SO_4 干燥, 过滤, 真空除去溶剂, 得到固体。固体经自动快速层析法 (EtOAc/石油醚) 纯化, 以优异的得率得到呈固体的产物。

[0172] B. N-(3,5-双(三氟甲基)苯基)-2-(哌嗪-1-基)乙酰胺的合成

[0173]

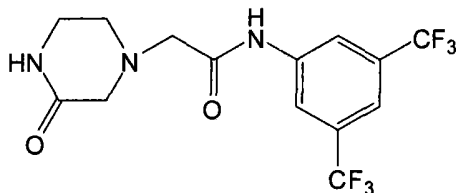


[0174] 用 Et_2O (120mL) 中的 2M HCl 处理 4-(2-(3,5-双(三氟甲基)苯基氨基)-2-氧代乙基)哌嗪-1-羧酸叔丁酯 (2.00g, 4.39mmol) 的 CH_2Cl_2 (25mL) 溶液。室温下搅拌反应过夜。此时, 在减少的压力下除去溶剂, 以定量得率得到呈白色粉末的产物 (HCl 盐)。

[0175] 用类似方法制备化合物 6-8。

[0176] 实施例 3: N-(3,5-双(三氟甲基)苯基)-2-(3-氧代哌嗪-1-基)乙酰胺 (化合物 9) 的合成

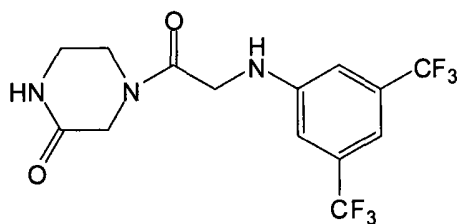
[0177]



[0178] 于室温下搅拌 N-(3,5-双(三氟甲基)苯基)-2-氯乙酰胺 (0.20g, 0.65mmol)、哌嗪-2-酮 (0.10g, 0.98mmol)、 K_2CO_3 (0.18g, 1.31mmol) 和 KI (cat.) 在 CH_3CN (10mL) 中的混合物过夜。然后用 EtOAc 稀释反应混合物, 用水洗涤, 经 Na_2SO_4 干燥, 过滤, 真空除去溶剂, 得到白色固体。通过加入 CH_2Cl_2 , 离心和吸去上清液 (2 次) 纯化残余物。以适度得率和优异纯度提供产物。

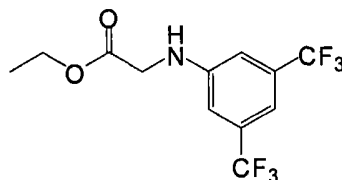
[0179] 实施例 4: 4-(2-(3,5-双(三氟甲基)苯基氨基)乙酰基)哌嗪-2-酮 (化合物 10) 的合成

[0180]



[0181] A. 2-(3,5-双(三氟甲基苯基氨基)乙酸乙基酯的合成

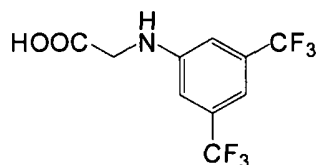
[0182]



[0183] 20℃下搅拌 3,5-双(三氟甲基)苯胺 (4.43g, 19.33mmol)、2-氯乙酸乙酯 (2.37g, 19.33mmol)、碳酸钾 (5.34g, 38.66mmol)、碘化钾 (0.1g, cat.) 和乙腈 (50mL) 的混合物 2 天。然后用乙酸乙酯 (200mL) 稀释反应混合物。随后先后用饱和碳酸氢钠水溶液 (2×20mL) 和水 (2×20mL) 洗涤有机层, 然后有机物经无水硫酸钠干燥。真空除去溶剂, 用石油醚 (20mL) 稀释残余物。沉淀出白色固体, 得到想要的化合物 (1.10g, 18% 得率)。MS: 316.4 (M+1)。

[0184] B. 2-(3,5-双(三氟甲基)苯基氨基)乙酸的合成

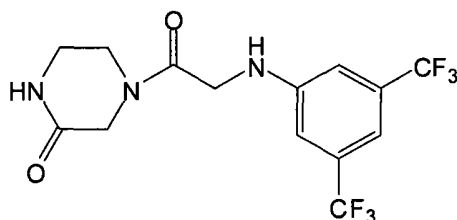
[0185]



[0186] 室温下搅拌 2-(3,5-双(三氟甲基)苯基氨基)乙酸乙酯 (1.10g, 3.48mmol)、氢氧化锂 (0.58g, 13.93mmol)、二氧杂环己烷 (5mL) 和水 (5mL) 的混合物 3h。真空除去溶剂, 然后用水 (10mL) 稀释反应产物, 用乙酸酸化至 pH 约 4。沉淀出白色固体, 得到想要的产物 (0.85g, 85% 得率)。MS: 286.1 (M-1)。

[0187] C. 4-(2-(3,5-双(三氟甲基)苯基氨基)乙酰基)哌嗪-2-酮的合成

[0188]



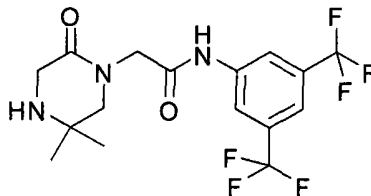
[0189] 20℃下搅拌 2-(3,5-双(三氟甲基)苯基氨基)乙酸 (0.20g, 0.70mmol)、哌嗪-2-酮 (0.07g, 0.70mmol)、(O-(7-氮杂苯并三唑-1-基)-N,N',N'-四甲基脒鎓 (0.27g, 0.70mmol) 和 N,N'-二异丙基乙胺 (0.11g, 0.84mmol) 在无水二甲基甲酰胺 (5mL) 中的混合物 2 天。然后真空除去挥发性组分。然后使残余物溶解于乙酸乙酯 (100mL), 先后用饱和碳酸氢钠水溶液 (2×20mL)、水 (2×20mL) 洗涤, 经无水硫酸钠干燥。然后真空除去溶剂, 得到粗产物, 然后采用快速层析法 (乙酸乙酯: 石油醚 1:2) 纯化它, 得到白色固体

(0.20g, 78%得率)。MS :370.6 (M+1)。

[0190] 用类似方法制备化合物 11 和 12。

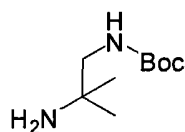
[0191] 实施例 5 :N-(3,5-双(三氟甲基)苯基)-2-(5,5-二甲基-2-氧代哌嗪-1-基)乙酰胺(化合物 13)的合成

[0192]



[0193] A. 2-氨基-2-甲基丙基氨基甲酸叔丁酯的合成

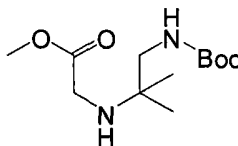
[0194]



[0195] 室温下搅拌 2-甲基丙烷-1,2-二胺(1.8g, 21mmol)、Boc₂O(2.0g, 10mmol) 和三乙胺(3.0ml, 21mmol) 在二氯甲烷(5mL) 中的混合物 1 天。经旋转蒸发浓缩溶液至干, 残余物经自动化硅胶快速层析法(MeOH/ 二氯甲烷:10 : 1) 纯化, 得到白色固体(2.40g, 86%)。

[0196] B. 2-(1-(叔丁氧羰基氨基)-2-甲基丙烷-2-基氨基)乙酸甲酯的合成

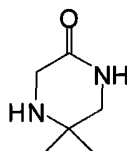
[0197]



[0198] 于室温下搅拌 2-氨基-2-甲基丙基氨基甲酸叔丁酯(0.90g, 4.8mmol)、2-氯乙酸甲酯(0.51g, 4.8mmol) 和碳酸钾(0.66g, 4.8mmol) 在乙腈(5mL) 中的混合物 1 天。经旋转蒸发浓缩溶液至干, 残余物经自动化硅胶快速层析法(己烷/EtOAc:1/1) 纯化, 得到白色固体(0.54g, 43%)。

[0199] C. 5,5-二甲基-3-氯代哌嗪-2-酮的合成

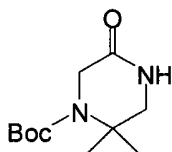
[0200]



[0201] 室温下搅拌 2-(1-(叔丁氧基羰基氨基)-2-甲基丙烷-2-基氨基)乙酸酯(0.54g, 2.07mmol) 和 2N HCl 在 MeOH 溶液(5mL) 中的混合物 3 小时。浓缩溶液至干, 向粗产物加入三乙胺(1.0mL, 7.0mmol) 和乙腈(5mL)。加热回流混合物过夜。经旋转蒸发浓缩溶液至干, 残余物经硅胶快速层析法(EtOAc/ 己烷:自 30%至 100%) 纯化, 得到白色固体(0.245g, 94%)。

[0202] D. 叔丁基 5,5-二甲基-3-氧代哌嗪-2-酮的合成

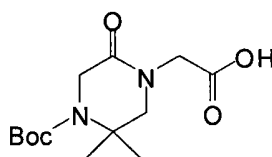
[0203]



[0204] 室温下搅拌 5,5-二甲基哌嗪-2-酮 (0.245g, 1.90mmol)、 Boc_2O (0.70g, 3.5mmol) 和 DIPEA (0.56g, 4.4mmol) 在 DMF (5mL) 中的混合物 1 天。经旋转蒸发浓缩溶液至干, 残余物经自动化硅胶快速层析法纯化 (EtOAc/己烷: 自 30% 至 100% 梯度洗脱) 得到白色固体 (0.40g, 92%)。

[0205] E. 2-(4-(叔丁氧基羰基)-5,5-二甲基-2-氧代哌嗪-1-基)乙酸的合成

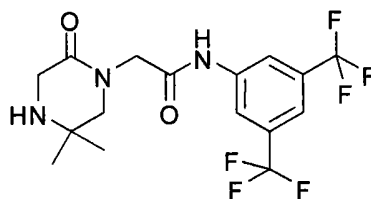
[0206]



[0207] 用如针对 2-(4-叔丁氧基羰基)-2-氧代哌嗪-1-基)乙酸所述的程序, 采用叔丁基 5,5-二甲基-3-氧代哌嗪-2-酮 (0.40g, 1.7mmol), 制备该化合物。得到呈白色固体的想要的酸 (0.34g, 70%)。

[0208] F. N-(3,5-双(三氟甲基)苯基)-2-(5,5-二甲基-2-氧代哌嗪-1-基)乙酰胺 (化合物 13) 的合成

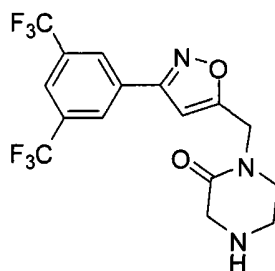
[0209]



[0210] 向 2-(4-(叔丁氧基羰基)-5,5-二甲基-2-氧代哌嗪-1-基)乙酸 (0.34g, 1.2mmol)、3,5-双(三氟甲基)苯胺 (0.191g, 1.2mmol) 和 O-(7-氮杂苯并三唑-1-基)-N,N,N',N'-四甲基脒六氟磷酸盐 (HATU) (0.50g, 1.3mmol) 的 DMF (5mL) 溶液加入 DIPEA (0.350g, 2.75mmol)。室温下搅拌反应混合物 16h, 然后将混合物浓缩至干。加入饱和 NaHCO_3 水溶液 (10mL), 用 EtOAc (20mL) 萃取混合物。用饱和 NH_4Cl 水溶液 (10mL) 和水 (10mL) 洗涤萃取物, 萃取物经无水 Na_2SO_4 干燥。过滤后, 经旋转蒸发浓缩滤液, 残余物经自动化硅胶快速层析法 (EtOAc/己烷, 1:2 (v/v)) 纯化, 得到白色固体。用在 EtOAc 中的饱和 HCl 处理 (10mL) 固体 30min。用稀 K_2CO_3 溶液中和酸性溶液至 $\text{pH} = 9$ 并用 EtOAc (3×30mL) 萃取。合并的萃取物经无水 Na_2SO_4 干燥, 得到标题化合物 (0.345g, 72%)。纯度 (HPLC): 97.0%。ES-MS m/z 398.6 (M+H)。

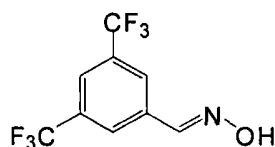
[0211] 实施例 6: 1-((3-(3,5-双(三氟甲基)苯基)异噁唑-5-基)甲基)哌嗪-2-酮 (化合物 14) 的合成

[0212]



[0213] A. (E)-3,5-双(三氟甲基)苯甲醛肟的合成

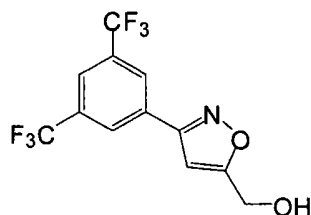
[0214]



[0215] 回流 3,5-双(三氟甲基)苯甲醛 (1.2g, 5.0mmol)、盐酸羟胺 (0.69g, 10mmol) 和氢氧化钠 (0.40g, 10mmol) 在乙醇 (95%, 20mL) 中的混合物过夜。浓缩溶液至干, 使残余物溶解于 EtOAc (20mL), 用水 (2×20mL) 洗涤。有机层经干燥和浓缩, 得到白色固体 (1.23g, 96%)。

[0216] B. (3-(3,5-双(三氟甲基)苯基)异噁唑-5-基)甲醇的合成

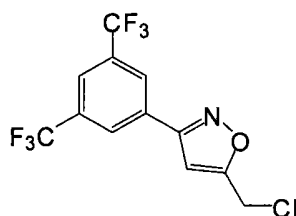
[0217]



[0218] 于 60℃ 下加热 (E)-3,5-双(三氟甲基)苯甲醛肟 (3.6g, 14mmol)、N-氯-琥珀酰亚胺 (2.20g, 16.7mmol) 和吡啶 (150 μL, 1.9mmol) 在 THF (15mL) 中的混合物 30min。30℃ 下加入丙-2-炔-1-醇 (1.0mL, 15mmol) 和三乙胺 (2.4mL) 的 THF (2mL) 溶液。搅拌反应混合物过夜, 浓缩至干。使残余物溶解于二氯甲烷 (20mL), 用 1N HCl (20mL×2) 洗涤。有机层经干燥和浓缩; 残余物经硅胶的快速层析法 (EtOAc/己烷, 1 : 4v/v) 纯化, 得到白色固体 (1.40g, 27%)。

[0219] C. 3-(3,5-双(三氟甲基)苯基)-5-(氯甲基)异噁唑的合成

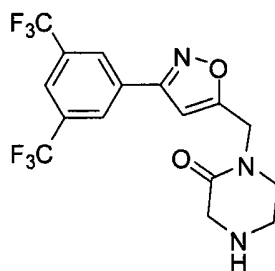
[0220]



[0221] 回流 (3-(3,5-双(三氟甲基)苯基)异噁唑-5-基)甲醇 (4) (1.40g, 4.5mmol) 和亚硫酸氯 (1mL, 13.9mmol) 在甲苯 (15mL) 中的混合物过夜。浓缩反应混合物至干, 残余物经硅胶快速层析法 (EtOAc/己烷, 1 : 10v/v) 纯化, 得到棕色油 (1.20g, 81%)。

[0222] D. 合成 1-((3-(3,5-双(三氟甲基)苯基)异噁唑-5-基)甲基)哌嗪-2-酮

[0223]



[0224] 在氮气、室温下,向 1-Boc-3-氧代哌嗪 (200mg, 1mmol) 的无水 THF (5mL) 溶液分批加入 NaH (60% 在矿物油中, 100mg, 2.5mmol)。加入后,室温下搅拌混合物 30min, 然后于 65℃ 下搅拌 1h。在混合物冷却至室温后,加入 3-(3,5-双(三氟甲基)苯基)-5-(氯甲基)异噁唑 (300mg, 0.91mmol)。室温下搅拌反应混合物过夜。加入水 (5mL), 浓缩溶液。加入盐水 (100mL), 用 EtOAc (3×10mL) 萃取反应混合物。用水 (10mL) 洗涤合并的萃取物, 经无水 Na₂SO₄ 干燥。过滤后, 经旋转蒸发浓缩滤液, 残余物经硅胶快速层析法 (EtOAc/ 己烷; 1/1v/v) 纯化, 得到呈白色固体的想要的产物。使固体溶解于三氟乙酸 (2mL) 和二氯甲烷 (2mL), 室温下搅拌混合物 3 小时。浓缩溶液至干, 用稀 K₂CO₃ 溶液中和至 pH = 9, 用 EtOAc (3×30mL) 萃取。合并的萃取物经无水 Na₂SO₄ 干燥, 浓缩至干。得到的残余物经硅胶的快速层析法 (MeOH/ 二氯甲烷 : 1/20v/v) 纯化, 得到呈白色固体的想要的中性产物。使固体溶解于二氯甲烷并加入 2N HCl 醚溶液, 得到标题化合物 (0.106g, 47%)。纯度 (HPLC) : 99.5%。ES-MS m/z 394.3 (M+H)。

[0225] 实施例 7 : 质谱分析

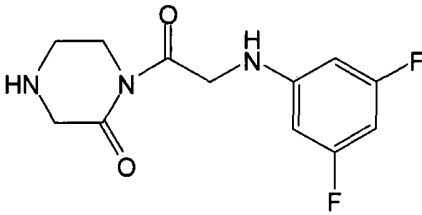
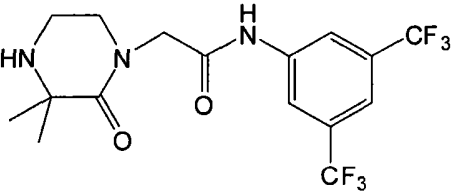
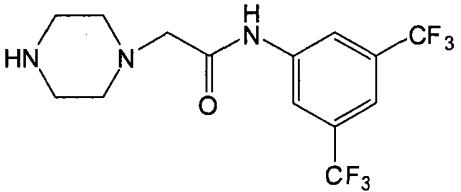
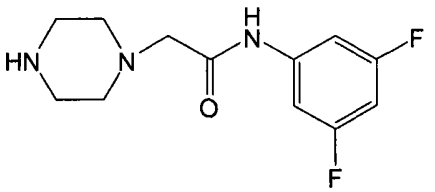
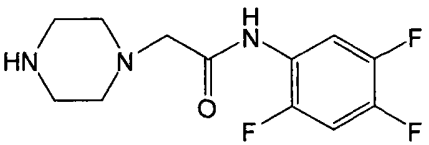
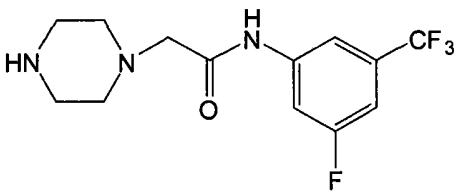
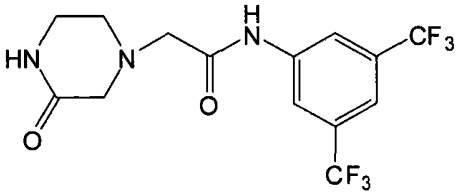
[0226] 按照实施例 1-6 中提出的通用程序, 制备下表 2 列出的以下化合物。就最终化合物和在合成期间的多个阶段采用质谱, 作为得到产物特征的确认 (M+1)。对于质谱分析, 以在含 0.1% 甲酸的乙腈中的约 1 μg/mL 浓度制备试样。然后将试样手工输入 Applied Biosystems API 3000 三重四极杆质谱仪并在 50-700m/z 范围以 Q1 扫描。

[0227] 表 2

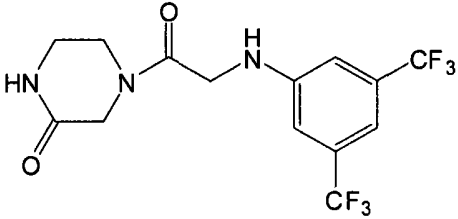
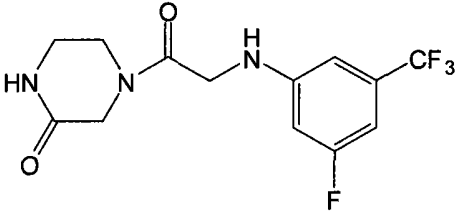
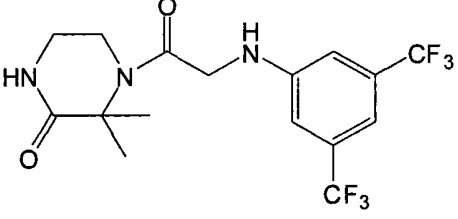
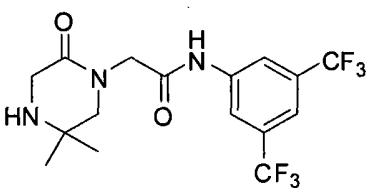
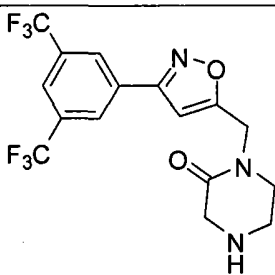
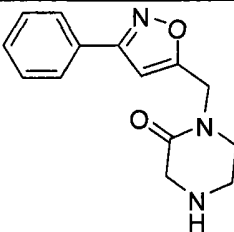
[0228]

化合物号	名称	结构	质谱 (m/z)
1	N-(3,5-双(三氟甲基)苯基)-2-(2-氧代哌嗪-1-基)乙酰胺		370.2
2	2-(2-氧代哌嗪-1-基)-N-(2,4,5-三氟苯基)乙酰胺		--

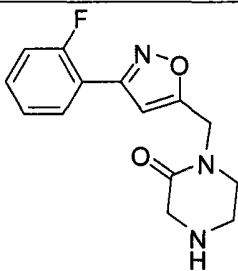
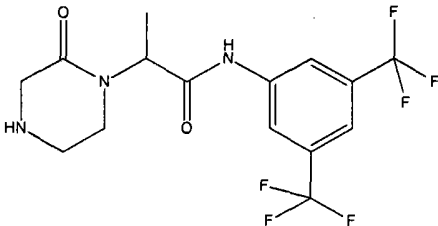
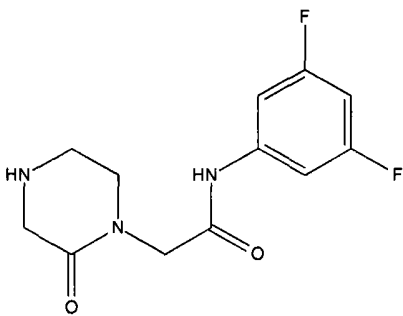
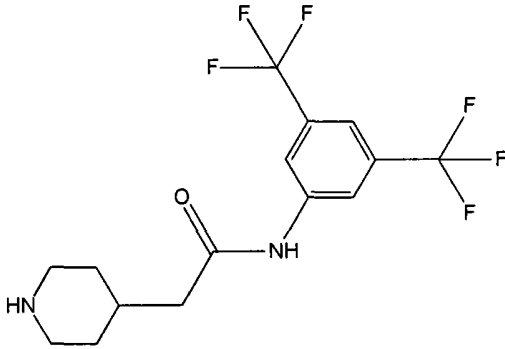
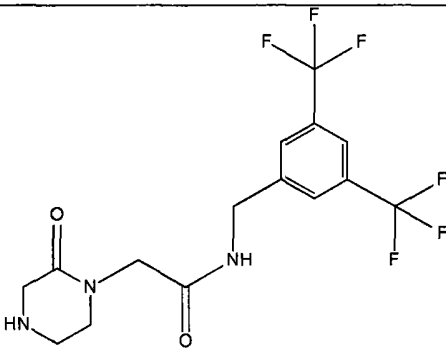
[0229]

化合物号	名称	结构	质谱 (m/z)
3	1-(2-(3,5-二氟苯基氨基)乙酰基)哌嗪-2-酮		--
4	N-(3,5-双(三氟甲基)苯基)-2-(3,3-二甲基-2-氧代哌嗪-1-基)乙酰胺		397.1
5	N-(3,5-双(三氟甲基)苯基)-2-(哌嗪-1-基)乙酰胺		355.1
6	N-(3,5-二氟苯基)-2-(哌嗪-1-基)乙酰胺		255.1
7	2-(哌嗪-1-基)-N-(2,4,5-三氟苯基)乙酰胺		273.1
8	N-(3-氟-5-(三氟甲基)苯基)-2-(哌嗪-1-基)乙酰胺		305.1
9	N-(3,5-双(三氟甲基)苯基)-2-(3-氧代哌嗪-1-基)乙酰胺		369.1

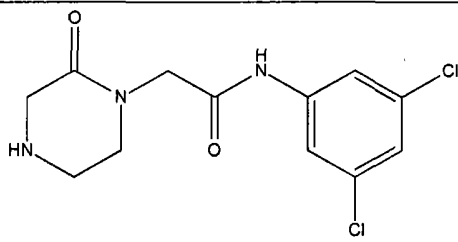
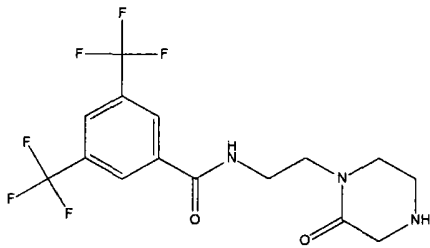
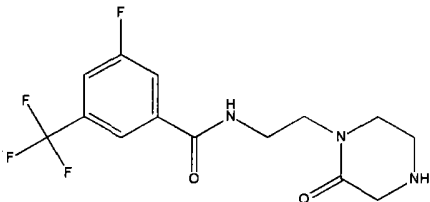
[0230]

化合物号	名称	结构	质谱 (m/z)
10	4-(2-(3,5-双(三氟甲基)苯基氨基)乙酰基)哌嗪-2-酮		369.1
11	4-(2-(3-氟-5-(三氟甲基)苯基氨基)乙酰基)哌嗪-2-酮		319.1
12	4-(2-(3,5-双(三氟甲基)苯基氨基)乙酰基)-3,3-二甲基哌嗪-2-酮		397.1
13	N-(3,5-双(三氟甲基)苯基)-2-(5,5-二甲基-2-氧代哌嗪-1-基)乙酰胺		397.1
14	1-((3-(3,5-双(三氟甲基)苯基)异噁唑-5-基)甲基)哌嗪-2-酮		393.1
15	1-((3-苯基异噁唑-5-基)甲基)哌嗪-2-酮		257.1

[0231]

化合物号	名称	结构	质谱 (m/z)
16	1-((3-(2-氟苯基)异噁唑-5-基)甲基)哌嗪-2-酮		275.1
17	N-(3,5-双(三氟甲基)苯基)-2-(2-氧代哌嗪-1-基)丙酰胺		383.29
18	N-(3,5-二氟苯基)-2-(2-氧代哌嗪-1-基)乙酰胺		269.25
19	N-(3,5-双(三氟甲基)苯基)-2-(哌啶-4-基)乙酰胺		354.29
20	N-(3,5-双(三氟甲基)苄基)-2-(2-氧代哌嗪-1-基)乙酰胺		383.29

[0232]

化合物号	名称	结构	质谱 (m/z)
21	N-(3,5-二氯苯基)-2-(2-氧代哌嗪-1-基)乙酰胺		302.16
22	N-(2-(2-氧代哌嗪-1-基)乙基)-3,5-双(三氟甲基)苯甲酰胺		383.29
23	3-氟-N-(2-(2-氧代哌嗪-1-基)乙基)-5-(三氟甲基)苯甲酰胺		333.28

[0233] 实施例 8 :Ca_v3.2 电压钳电生理学试验

[0234] 在纪录来自表达于 HEK 细胞中的 Ca_v3.2T- 型 Ca²⁺ 通道电流之前,用含有 (按 mM 计):142CsCl、10D- 葡萄糖、2CaCl₂、1MgCl₂、10HEPES、用 CsOH 调节 pH 至 7.4 的细胞外溶液 (ECS) 替代培养基。用含有 (以 mM 计):126.5Cs- 甲磺酸盐、2MgCl₂、10HEPES、11EGTA、2Na-ATP、pH 调节到 7.3CsOH 的细胞内溶液回填用 P-97 微量吸移管拉制仪 (micropipette puller) (Sutter Instruments, Novato, CA) 以典型的 2-4MW 阻力拉出的硼硅酸盐玻璃膜片吸液管 (Borosilicate glass patch pipettes)。室温 (约 21℃) 下以全细胞模式采用 Axopatch 200B (Molecular Devices, Sunnyvale, CA) 膜片钳放大器纪录电压。纪录以 1kHz (-3dB 4- 极 Bessel 滤波器) 的低通滤波,用 Digidata 1322A 界面 (Molecular Devices) 以 2kHz 数字化并采用 pClamp 9.2 (Molecular Devices) 获取。未用漏减 (leak subtraction)。通过连至由电磁阀控制的贮库的重力驱动的多管阵列毛细管 (24 规格 (gauge)) 施加作为 DMSO 中的 30mM 原料溶液并在细胞外缓冲溶液中稀释制备的测试化合物。采用 4 种不同的电压方案评价化合物对 Ca_v3.2 的缓慢和快速失活的作用。采用两种脉冲方案检测快速和缓慢通道失活的电压依赖。分析数据并采用 OriginPro v. 7.5 (OriginLab, Northampton, MA) 软件拟合。根据这些方法得到的数据表示于表 3。

[0235] 表 3

[0236]

化合物	$V_{1/2}$ 快速失活 (mV)	$V_{1/2}$ 缓慢失活 (mV)	-40 mV 下的残余电流份额	自快速失活的 τ 恢复 (ms)	自缓慢失活的 τ 恢复 (ms)	5.1 s 间隔下恢复的电流份额
对照 ECS	-61	-75	0.62	270	533	0.96
1	-66	*-80	0.51	311	**684	0.87
2	-65	-80	0.58	260	448	0.98
9		** -83	**0.32	**472	* 700	*0.80

[0237] $V_{1/2}$ 半失活的电压依赖 ;*P ≤ 0.05, **P < 0.005

[0238] 实施例 9 :Na_v1.5/1.7/1.8 电压钳电生理学试验

[0239] 为检测化合物对表达于 HEK 细胞的 Na_v1.7 和 Na_v1.8 通道的缓慢失活的促进作用,用含有 (以 mM 计) :137NaCl、4KCl、1.8CaCl₂、1MgCl₂、10HEPES、10 葡萄糖,用 NaOH 调节至 7.4pH 的细胞外溶液替代培养基。细胞内溶液含有 (以 mM 计) :130KCl、1MgCl₂、5EGTA、10HEPES、5K₂ATP,用 KOH 调节至 pH 7.3。用类似于 Ca_v3.2 电生理学试验的方法进行测试化合物的全细胞纪录、制备和应用。应用电压方案以量化测试化合物促进 Na_v1.7 和 Na_v1.8 缓慢失活的效果。就抑制 Na_v 1.7 通道得到的数据表示于表 4。

[0240] 表 4

化合物	测试浓度	残余电流份额	n 细胞
1	30 M	0.40	6
10	10 M	0.91	4
	100 M	0.74	4
20	30 M	0.87	4
23	30 M	0.91	5

[0242] 对抗 TTX 的 Na_v1.5 钠通道,关键的心脏离子通道的抑制可能对心脏动作电位的持续时间和幅度具有重大作用,并可能导致心率不齐和其它心脏功能障碍。为在药物开发过程的早期评价化合物的潜在心脏致病倾向,用 Molecular Device's PatchXpress™ 自动电生理学平台进行 Na_v1.5 钠通道筛查实验。在电压钳条件下,在缺乏和存在增加浓度的测试化合物的情况下,纪录来自表达人 Nav1.5 通道的 HEK 细胞的 Na_v1.5 电流,得到 IC₅₀ 值。外部纪录溶液含有 (以 mM 计) :90TEACl、50NaCl、1.8CaCl、1MgCl₂、10HEPES、10 葡萄糖,用 TEA-OH 调节至 pH 7.4 和用蔗糖调节至 300mOsm (如需要),而内贴片移液管溶液含有 (以 mM 计) :129CsF、2MgCl₂、11EGTA、10HEPES、3Na₂ATP,用 CsOH 调节至 pH 7.2 和用蔗糖调节至 290mOsm (如需要)。采用 1Hz 下的心脏动作电位波形产生 Na_v1.5 通道电流,以 31.25kHz 数字化并以 12kHz 低通滤波。如在表 5 中表示的,测试化合物不会起心脏 Na_v1.5 通道的抑制剂作用,因而是选择性抑制剂。

[0243] 表 5

[0244]

化合物号	HNA _v 1.5 心脏 AP 1Hz IC ₅₀
1	100000
5	40000
9	80000

[0245] 实施例 10 :L5/L6 脊神经结扎 (SNL)-Chung 疼痛模型

[0246] 脊神经结扎是表示产生神经性疼痛综合征的外周神经损伤的动物模型。在该模型中,实验动物发展触诱异常性疼痛和痛觉过敏的临床症状。采用 Kim 和 Chung 的程序 (Kim 等,Pain 50 :355-363(1992)) 介导体重 200-250 克的雄性 Sprague-Dawley 大鼠 (Harlan ; Indianapolis, IN) 的 L5/L6 脊神经结扎 (SNL) 损伤。

[0247] 用 O₂ 中的 2%异氟烷以 2L/min 介导麻醉并用 O₂ 中的 0.5%异氟烷维持。然后将大鼠剃毛和消毒,为手术作准备。以 L4-S2 的水平完成 2cm 椎旁切口。通过用小骨钳除去神经上面的横突暴露 L4/L5。L5 脊神经是在横突下面的两根可见神经中较大的那根,并最靠近脊椎。L6 脊神经位于斜骨角的下方。用自制玻璃 Chung 棒钩住 L5 或 L6,将预先打好的 4.0 丝缝线的活结 (slip knot) 置于正好在神经之上的棒的顶端并下拉以进行牢固结扎。将 L5 和 L6 脊神经远离背根神经节牢固地结扎。缝合切口,让动物恢复 5 天。表现出运动缺陷 (诸如拖爪 (paw-dragging)) 或不表现出随后的触诱异常性疼痛 (tactile allodynia) 的大鼠不包括在进一步的试验内。

[0248] 假手术对照大鼠经历与实验动物一样的相同手术和处理,但未进行 SNL。

[0249] 在开始递药前,得到基线行为测试数据。然后于输注测试或对照物后的选择时间再次收集行为数据。

[0250] A. 触诱异常性疼痛的评价 -Von Frey

[0251] 触诱异常性疼痛的评价包括测量对用一系列标刻度的 von Frey 细丝 (非伤害性刺激) 探测响应的神经损伤部位同侧爪的缩爪阈值。在试验前,使动物适应悬吊线网笼的环境 30。每根 von Frey 细丝垂直施加于大鼠结扎爪的跖面 5sec。用突然缩爪表示正响应。对于大鼠,第一根测试细丝为 4.31。在给予测试物之前和之后,进行测量。用 Dixon 非参数法 (Dixon, Ann. Rev. Pharmacol. Toxicol. 20 :441-462(1980)) 确定缩爪阈值,其中刺激逐渐增加,直到得到正响应,然后减少刺激直到观察到负结果。重复程序,直到确定行为的三种变化 (“上下”法) (Chaplan 等,J. Neurosci. Methods 53 :55-63(1994))。50%缩爪阈值确定为 $(10^{[X_f+k\delta]})/10,000$, 其中 X_f = 所用最后的 von Frey 细丝的值, k = 正 / 负模式的 Dixon 值和 δ = 刺激间的对数差。大鼠的临界值不低于 0.2g 和不高于 15g (5.18 细丝); 对于小鼠,不低于 0.03g 和不高于 2.34g (4.56 细丝)。与预先处理的基线相比,缩爪阈值的显著减弱认为是触诱异常性疼痛。与基线和 SNL 后相比,60 分钟时对化合物 1-4 和 9-12 测试大鼠 SNL 触诱异常性疼痛。如在图 1 和在下表 6 中显示的,化合物 1、9 和 13 表现出显著的抗异常性疼痛。

[0252] 表 6

化合物号	大鼠 SNL 触诱异常性疼痛 (%抗异常性疼痛)		
	1 小时	2 小时	4 小时
1	52	55	37
3	1	--	4
9	36	--	--
10	10	13	15
11	9	4	1
12	9	11	42
13	16	8	5
19	47	39	32

[0254] B. 热敏感性评价 -Hargreaves

[0255] 可采用 Hargreaves 和同事的方法 (Hargreaves 等, Pain 32:77-8(1988)) 评价对伤害性热刺激的缩爪潜伏期。

[0256] 可将大鼠置于透明玻璃板上的树脂玻璃罩内适应 30 分钟。然后可用计时器激活辐射热源 (例如, 连着红外过滤器的卤素灯泡) 并聚焦于要处理大鼠的感受爪的跖面。当缩爪时, 通过关闭灯和计时器的光电池可确定缩爪潜伏期。可确定 L5/L6SNL 前、L5/L6SNL 后但在给药前 7-14 天以及给药后对辐射热源的缩爪潜伏期。典型地采用最大截止值 (maximal cut-off) 33 秒预防组织损伤。因此可将缩爪潜伏期确定至最近似的 0.1 秒。缩爪潜伏期自基线的显著下降反映热痛觉过敏的情况。通过热痛觉过敏反转至预处理基线或缩爪潜伏期在该基线之上的显著 ($p < 0.05$) 增加表明抗伤害感受。用下式将数据转化为 % 抗痛觉过敏或 % 抗伤害感受: $(100 \times (\text{试验潜伏期} - \text{基线潜伏期}) / (\text{临界} - \text{基线潜伏期}))$, 其中对于确定抗痛觉过敏的临界值是 21 秒而对于确定抗伤害感受的是 40 秒。

[0257] 实施例 11: 部分型癫痫的 6Hz 精神运动型癫痫模型

[0258] 根据 Barton 等, “部分型癫痫的 6Hz 精神运动型癫痫模型的药理学特征”, Epilepsy Res. 47(3):217-27(2001) 描述的程序, 在施加于雄性 CF1 小鼠 (20-30g) 的眼角膜的 32mA (CC97) 刺激强度下, 评价化合物保护免于因 3s 持续时间的 6Hz、0.2ms 矩形脉冲宽度介导的癫痫。癫痫的特征在于表现出以下行为中的一种或多种: 紧随电刺激之后的晕眩、前肢阵挛、触须颤动和斯特劳布举尾反应 (Straub-tail)。如果在用化合物预处理后 6Hz 刺激未能引起如上所述的行为响应, 就认为动物“受保护”。采用该试验的示例结果表示于表 7。

[0259] 表 7

化合物号	癫痫 6 Hz (%受保护)					癫痫 6 Hz (ED ₅₀)
	0.25 hr	0.5 hr	1 hr	2 hr	4 hr	
[0260] 1	75	100	75	--	--	128
9	75	25	88	75	0	90
19	100	100	100	100	0	--

[0261] 实施例 12 :GAERS(来自 Strasbourg 的自发性失神癫痫大鼠) 癫痫模型

[0262] GAERS(来自 Strasbourg 的遗传性失神癫痫大鼠) 因其长期和频繁复发的失神癫痫发作而著名。采用来自丘脑内的神经元的电生理学纪录,研究者已经确认,在 GAERS 中的低电压钙通道的活性和表达显著增加。将饲养于 Ludwig 癌症研究院的 8 只雌性 GAERS 大鼠用于本研究。实验开始时的大鼠体重在 180 和 250g 之间,而年龄在 18 和 26 周之间。

[0263] 用焊接在一起的镀金插孔 (220-S02 Ginder Scientific, VA, 加拿大)、不锈钢聚四氟乙烯包裹线 (SDR clinical technology, NSW, 澳大利亚) 和小不锈钢螺钉 (1.4×3mm, Mr. Specks, 澳大利亚) 可制备电极。可用吸入等份额发医用空气和氧气 (5% 介导, 2.5-1.5% 保持) 中的异氟烷或作为选择地通过腹膜内推注赛拉嗪 (10mg/kg) 和氯胺酮 (75mg/kg) 麻醉动物。借助 ear bars 将动物固定在脑立体定位仪中。在中头皮开一个中线切口,剥开皮肤和相连组织,从侧面挤压以暴露表面下的颅骨。两侧钻 6 个孔,2 个在额骨,4 个在顶骨,在前囟前约 2mm,和在前囟后 4 和 10mm。然后将 6 个电极植入孔中,将镀金插孔插入 9 针 ABS 插座 (GS09PLG-220, Ginder Scientific, Canada)。两侧锚固螺钉从侧面放入颅骨提高封帽固定的强度。然后用牙齿粘固剂固定封帽。

[0264] 术后,给予动物镇痛剂 Rimadyl (4mg/kg),置于热垫上的它们的笼中,观察直到康复。整个研究中将大鼠单独关在笼中、每日称重并体检,在开始实验程序前允许恢复 7 天。通常在医学部门的生物研究设施 (Biological Research Facility of the Department of Medicine) (RMH) 中,在 12 : 12 光暗条件下,通常允许大鼠自由食用啮齿动物饲料 (rodent chow) (商标, WA stock feeders) 和水。

[0265] 在第一种药物处理前,测试大鼠的失神 - 型癫痫,根据 EEG 纪录,其伴有广泛性棘波发放 (SWD)。测试和其它全部实验都在安静、光照良好的房间内用在其笼舍中的大鼠进行。大鼠经 6 通道电缆线连接,其相交和焊接至插入 9 针插座的 6 根镀金针。电缆可连接至运行 Compumedics™ EEG 采集软件 (Melbourne, Australia) 的计算机。可在 2 周后着手处理在研究开始时未患适当基线癫痫的 3 只大鼠,可根据安排在最后弥补它们的处理。在手术植入硬膜下电极后适应环境时期后的第 1 周的第 1 天,可使 4 只动物习惯于连接电缆 15 分钟,然后纪录其 SWD 60 分钟作为基线。根据处理安排,立即按照基线给予大鼠测试物、参照或对照物中的一种,自推注后 15 分钟纪录目标周期 120 分钟。整个实验过程中监测动物,并在基线和目标周期期间保持安静地不眠。

[0266] 通过标记 SWD 的突然发作的开始和结束,针对 60 分钟预推注和 120 分钟推注后 EEG 纪录 (给药后的开始 15 分钟), 定量癫痫表现。这可借助为定量 GAERS 癫痫而特别定制的 SWCFinder ® 软件实现,研究者不知道给予药物的性质,从而进行盲分析。GAERS 癫痫的标准规范是超过三倍基线的振幅、7-12Hz 的频率和超过 0.5s 的持续时间的 SWD 突发。由

此,可将在整个推注后 120 分钟 EEG 纪录中的癫痫占用的总时间百分比(处于癫痫的时间百分比)测定作为主要结局参数。

[0267] 实施例 13:小鼠转棒实验

[0268] 为评价化合物的不想要的副作用(毒性),监测动物的损伤的神经或肌肉功能的显性标志。用转棒程序(Dunham and Miya, J. Am. Pharmacol. Assoc. 46:208-209(1957))揭示小鼠的最少肌肉或神经损伤(MMI)。当将小鼠放在以 6rpm 速度转动的棒上时,动物可保持其长时间的平衡。如果在 1 分钟时间内从该转棒下掉下 3 次,就认为动物中毒。除 MMI 外,动物还可能表现出环形或之字形步态、异常体姿和伸腿、战栗、活动过度、缺乏探索行为、嗜睡、木僵、僵住症、缺乏放置反应和肌肉张力变化。采用该实验得到的示例数据表示于表 8。

[0269] 表 8

化合物号	%损伤					TD ₅₀
	0.25 hr	0.5 hr	1 hr	2 hr	4 hr	
[0270] 1	0	0	0	0	0	300
9	0	0	0	0	0	--
19	0	75	100	100	100	--

[0271] 实施例 14:板层试验和数据

[0272] 根据板层 I/II 脊髓神经元的纪录。

[0273] 通过腹膜内推注 Inactin(Sigma),麻醉雄性 Wistar 大鼠(对于电压钳纪录 P6-P9 和对于电流钳纪录 P15-P18)。然后快速解剖出脊髓并置于冰冷溶液保护的蔗糖溶液中,其含有(以 mM 计):50 蔗糖、92NaCl、15D- 葡萄糖、26NaHCO₃、5KCl、1.25NaH₂PO₄、0.5CaCl₂、7MgSO₄、14- 羟基喹啉-2- 羧酸,并用 5% CO₂/95% O₂ 鼓气。在解剖显微镜下自脊髓的腰区除去脊膜、硬脊膜和后根和前根。将“干净的”腰区脊髓粘到振动切片机台并立即浸入冰冷、鼓泡通气的蔗糖溶液。对于电流钳纪录,切下 300-350 μm 矢状窦切片,保存板层 I 神经元的树突棘,而为电压钳 Na_v 通道纪录制备 350-400 μm 横切片。35℃下,在含有(以 mM 计):125NaCl、20D- 葡萄糖、26NaHCO₃、3KCl、1.25NaH₂PO₄、2CaCl₂、1MgCl₂、14- 羟基喹啉-2- 羧酸、0.1 印防己互毒素,用 5% CO₂/95% O₂ 鼓气的 Ringer 溶液中恢复 1 小时。然后将切片恢复室恢复至室温(20-22℃),该温度下做全部纪录。

[0274] 采用 IR-DIC 光学器件(Zeiss Axioskop 2FS plus, Gottingen, Germany)使神经元形象化,根据其相对于胶状质层的位置,自板层 I 和板层 II 的外层选择神经元。采用硼硅酸盐玻璃膜片吸液管,以 3-6MΩ 电阻,膜片箝制神经元。完整切片中的板层 I/II 神经元的电流钳纪录,外部纪录溶液是上述 Ringer 溶液,而内部膜片吸液管溶液含有(以 mM 计):140K 葡萄糖酸盐、4NaCl、10HEPES、1EGTA、0.5MgCl₂、4MgATP、0.5Na₂GTP,用 5M KOH 调节至 pH 7.2 和用 D- 甘露醇调节到 290mOsm(如需要)。对于电流钳实验仅选择紧张性放电神经元,而排除相延迟和单棘神经元(22)。在 50kHz 下数字化纪录并在 2.4kHz 下低通滤波。

[0275] 根据该方案得到的数据表示于表 9。

[0276] 表 9

化合物号	LAMINA I 和 II			
	%棘变化(平均; % 自对照物的变化)	%棘变化 SEM	%棘变化 P<0.05	EC ₅₀
1	-47.3	8.3	no	482
9	-35.5	12.1	no	--
19	-30.3	9.2	no	--

[0278] 实施例 15 : 药物代谢动力学参数

[0279] 用体内大鼠早期药物代谢动力学 (EPK) 研究设计评价化合物的初始暴露特征 (表 10), 数据表明, 化合物是口服生物可利用的。用详细制剂经口 (PO) 强饲对雄性 Sprague-Dawley 大鼠用药。在用药后 4 小时后的 6 个时间点从动物收集血样。用 LC-MS/MS 测量的各个化合物的各个时间点的浓度, 进行药物代谢动力学分析。示例的数据表示于表 10。

[0280] 表 10

[0281]

[0282]

化合物号	剂量 (mg/kg)	途径	制剂	正常剂量 Cmax (nM)	正常剂量 AUC (nM*h)	T _{max} (hr)
1	3	PO	PG	438	1,118	0.25
5	3	PO	PG	48	108	1.8
9	3	PO	PG	484	1,120	1.4
10	30	PO	10% DMSO/90% CMC	355	1,192	1.2
13	30	PO	10% DMSO/90% CMC	172	458	0.67
PG: 丙二醇 DMSO: 二甲亚砜 CMC: 0.5% 羧甲基纤维素						

[0283] 其它实施方案

[0284] 尽管已经结合其具体实施方案描述本发明, 但仍应理解, 进一步修饰是可能的, 且一般说来, 本申请打算涵盖根据本发明的原则的本发明的任何变化、应用或修改, 包括本公开的这类偏离也落在本发明所属领域内的已知或惯常的实践中并可适用于上文中提出的

必要特征。

[0285] 所有出版物、专利和专利申请都通过引用以其全文结合于本文中，以致如同专门和分别地表明各篇具体出版物、专利或专利申请都通过引用以其全文结合于本文中一样。

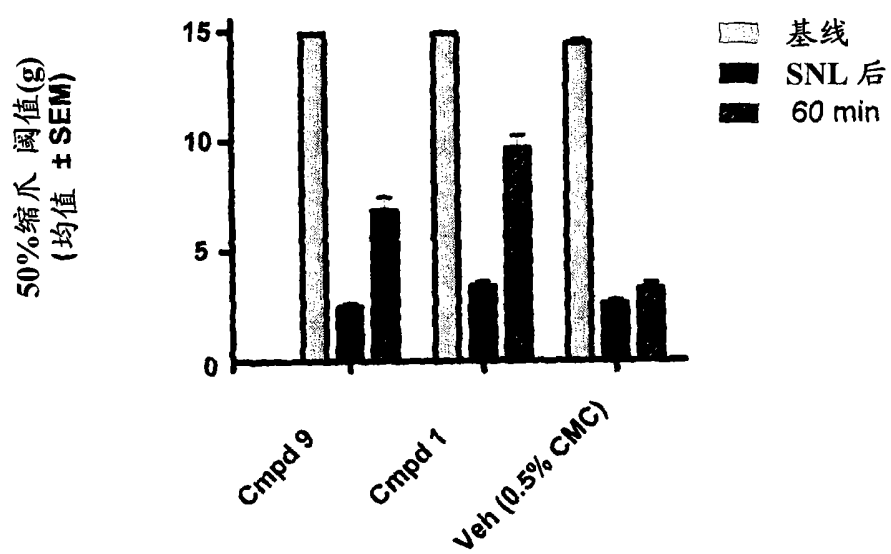


图 1