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(54) Title: PERMANENTLY CHARGED SODIUM AND CALCIUM CHANNEL BLOCKERS AS ANTI-INFLAMMATORY AGENTS

(57) Abstract: The invention provides compounds, compositions, methods, and kits for the treatment of neurogenic inflammation.

PERMANENTLY CHARGED SODIUM AND CALCIUM CHANNEL BLOCKERS AS ANTI-INFLAMMATORY AGENTS

Cross-Reference to Related Applications

This application claims benefit of U.S. Provisional Application No. 61/224,512, filed July 10, 2009, which is hereby incorporated by reference.

Field of the Invention

The invention provides compounds, methods and kits for the treatment of neurogenic inflammation.

Background of the Invention

The invention features methods and kits for the treatment of neurogenic inflammation by targeting nociceptors with drugs of low molecular weight, while minimizing effects on non-pain-sensing neurons or other types of cells. According to the method of the invention, small, hydrophilic drug molecules gain access to the intracellular compartment of pain-sensing neurons via entry through receptor/channels that are present in pain-sensing neurons but to a lesser extent or not at all in other types of neurons or in other types of tissue. Neurogenic inflammation is a mode of inflammation mediated by the efferent (motor) functions of sensory neurons, in which pro-inflammatory mediator molecules released in the periphery by pain-sensing neurons (nociceptors) both activate a variety of inflammatory pathways and also act on the vascular system to alter blood flow and capillary permeability.

Neurogenic inflammation contributes to the peripheral inflammation elicited by tissue injury, autoimmune disease, infection, exposure to irritants in a variety of tissues, and is thought to play an important role in the pathogenesis of numerous disorders (e.g. migraine, arthritis, rhinitis, gastritis, colitis, cystitis, and sunburn).

One way to reduce neurogenic inflammation is to block excitability in nociceptors, thereby preventing the activation of nociceptor peripheral terminals and the release of pro-inflammatory chemicals. Local anesthetics such as lidocaine and articaine act by inhibiting voltage gated ion channels in neurons. Local anesthetics are relatively hydrophobic molecules that gain access to their blocking site on the sodium channel by diffusing into or through the cell membrane. However, these anesthetics block sodium or calcium channels and thereby the excitability of all neurons, not just pain-sensing neurons. Thus, administration of local anesthetics produces unwanted or deleterious effects such as general numbness from block of low threshold pressure and touch receptors, motor deficits from block of motor axons and other complications from block of autonomic fibers. Local anesthetics also act on sodium channels on smooth muscle in the cardiovascular and respiratory systems producing deleterious effects.

Accordingly, there is a need for an approach to reducing neurogenic inflammation that selectively targets nociceptors.

Summary of the Invention

In a first aspect, the invention features a method for treating neurogenic inflammation in a patient, such as a human, by administering a therapeutically effective amount of a compound that is capable of entering a nociceptor through a channel-forming receptor present in the nociceptor when the receptor is activated and inhibiting a voltage-gated ion channel present in the nociceptor, wherein the compound does not substantially inhibit said channel when applied to the extracellular face of the channel and when the receptor is not activated. In certain embodiments, the compound is an inhibitor of voltage-gated sodium channels. Exemplary inhibitors of this class are QX-314, N-methyl-procaine, QX-222, N-octyl-guanidine, 9-aminoacridine and pancuronium. In other embodiments, the compound is a quarternary amine derivative or other charged derivative of a compound selected from riluzole, mexilitine, phenytoin, carbamazepine, procaine, articaine, bupivicaine, mepivicaine, tocainide,

prilocaine, diisopyramide, bencyclane, quinidine, bretylium, lifarizine, lamotrigine, flunarizine, and fluspirilene. In other embodiments, the compound is an inhibitor of calcium channels. Inhibitors of this class include D-890, CERM 11888, *N*-methyl-verapamil, *N*-methylgallopamil, *N*-methyl-devapamil, dodecyltrimethylammonium, and terpene compounds (e.g., sesquiterpenes), as well as charged derivatives (e.g., a quarternary amine derivative or a guanylated derivative) of verapamil, gallopamil, devapamil, diltiazem, fendiline, mibefradil, or farnesyl amine. Still other exemplary inhibitors of calcium channels can be described by Formulas XI-XIV) and in Tables 1, 2, and 3. In further embodiments, the ion channel inhibitor is a charged derivative (e.g., a quarternary amine derivative or a guanylated derivative) of any of compounds (1)-(563). Exemplary derivatives are described herein.

The channel-forming receptor can be activated prior to administering the compound by administration of a second compound that opens the channel. Alternatively, the channel-forming receptor can be activated by endogenous compounds present in the patient.

The invention also features a kit that includes a composition for treating neurogenic inflammation in a patient and instructions for the administration of the composition to a patient to treat neurogenic inflammation. The composition includes a compound that is capable of entering a nociceptor through a channel-forming receptor present in the nociceptor when the receptor is activated and inhibiting a voltage-gated ion channel present in the nociceptor, wherein the compound does not substantially inhibit said channel when applied to the extracellular face of the channel and when the receptor is not activated. In certain embodiments, the compound is an inhibitor of voltage-gated sodium channels or calcium channels, such as those described herein. In some embodiments, the compound is QX-314, N-methyl-procaine, QX-222, N-octyl-guanidine, 9-aminoacridine, pancuronium, or another low molecular weight, charged molecule that inhibits voltage-gated sodium channels when present inside of said nociceptor. In other embodiments, the compound is D-890, CERM 11888, *N*-methyl-verapamil, *N*-methylgallopamil, *N*-methyl-devapamil,

and dodecyltrimethylammonium; a quarternary amine derivative, of verapamil, gallopamil, devapamil, diltiazem, fendiline, mibefradil, or farnesyl amine; a compound according to any of Formulas(XI), (XII), (XIII-A), (XIII-B), (XIII-C), and (XIV); or a quarternary amine derivative or other charged derivative of any of compounds (1)-(563).

Any of the compositions, methods, and kits of the invention may optionally feature a second compound that activates the channel-forming receptor. In one embodiment, the second compound activates a channel-forming receptor selected from TRPV1, P2X(2/3), TRPA1, and TRPM8.

Activators of TRPV1 receptors include but are not limited to capsaicin, eugenol, camphor, clotrimazole, arvanil (N-arachidonoylvanillamine), anandamide, 2-aminoethoxydiphenyl borate (2APB), AM404, resiniferatoxin, phorbol 12-phenylacetate 13-acetate 20-homovanillate (PPAHV), olvanil (NE 19550), OLDA (*N*-oleoyldopamine), *N*-arachidonyldopamine (NADA), 6'-iodoresiniferatoxin (6'-IRTX), C18 N-acylethanolamines, lipoxygenase derivatives such as 12-hydroperoxyeicosatetraenoic acid, inhibitor cysteine knot (ICK) peptides (vanillotoxins), piperine, MSK195 (N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-2-[4-(2-aminoethoxy)-3-methoxyphenyl]acetamide), JYL79 (N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N'-(4-hydroxy-3-methoxybenzyl)thiourea), hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 10-shogaol, oleylgingerol, oleylshogaol, SU200 (N-(4-tert-butylbenzyl)-N'-(4-hydroxy-3-methoxybenzyl)thiourea), amylocaine, articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine (novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), and trimecaine. Other activators of TRPV1 receptors are described in O'Dell et al., *Bioorg Med Chem.* (2007) 15:6164-6149, and Sexton et al., *FASEB J* (2007) 21:2695-2703. Still other TRPV1 activators include black pepper compounds (e.g., Okumura

et al., *Biosci Biotechnol Biochem.* 74(5):1068-72 (2010) and Riera et al., *Br J Pharmacol.* 57(8):1398-409 (2009)), terpenoids (Iwasaki et al., *Life Sci.* 85(1-2)60-69 (2009)), nickel (Luebbert et al., *Pflugers Arch.* 459(5):737-50 (2010)), SA13353 ([1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea]; see, e.g., Tsuji et al., *Eur J Pharmacol.* 627(1-3):332-9 (2010)), oxidized linoleic metabolites (Patwardhan et al., *Proc Natl Acad Sci U S A.* 106(44):18820-4 (2009)), diallyl sulfides (Koizumi et al., *Biochem Biophys Res Commun.* 382(3):545-8 (2009)), and alkylamides derived from sanshool (Menozzi-Smarrito et al., *J Agric Food Chem.* 57(5):1982-9 (2009)).

Still other activators of TRPV1 receptors include capsaicinoids and capsaicinoid analogs as described herein (e.g., vanilloids (e.g., N-vanillyl-alkanedienamides, N-vanillyl-alkanedienyls, and N-vanillyl-cis-monounsaturated alkenamides), capsiate, dihydrocapsiate, nordihydrocapsiate and other capsinoids, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, resiniferatoxin, tinyatoxin, civamide, N-phenylmethylalkenamide capsaicin derivatives, olvanil, N-[(4-(2-aminoethoxy)-3-methoxyphenyl)methyl]-9Z-octa-decanamide, N-oleyl-homovanillamide, triprenyl phenols (e.g., scutigeral), gingerols, piperines, shogaols, guaiacol, eugenol, zingerone, nuvanil, NE-19550, NE-21610, and NE-28345). Additional capsaicinoids, their structures, and methods of their manufacture are described in U.S. Patent Nos. 7,446,226 and 7,429,673, which are hereby incorporated by reference.

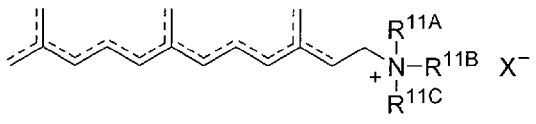
Activators of TRPA1 receptors include but are not limited to cinnamaldehyde, allyl-isothiocynanate, diallyl disulfide, icilin, cinnamon oil, wintergreen oil, clove oil, acrolein, hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 4-hydroxynonenal, methyl p-hydroxybenzoate, mustard oil, 3'-carbamoylbiphenyl-3-yl cyclohexylcarbamate (URB597), amylocaine, articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine

(novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), and trimecaine. Other activators of TRPA1 receptors are described in Taylor-Clark et al., *Mol Pharmacol* (2007) PMID: 18000030; Macpherson et al., *Nature* (2007) 445:541-545; and Hill et al., *J. Biol. Chem.* (2007) 282:7145-7153. Still otherTRPA1 activators include: fenamate NSAIDS (Hu et al., *Pflugers Arch.* 459(4):579-92 (2010)), congeners of AP18 (Defalco et al, *Bioorg Med Chem Lett.* 20(1):276-9 (2010)), tear gasses CN, CR, and CS (Brône et al., *Toxicol Appl Pharmacol.* 231(2):150-6 (2008)), nicotine (Talavera et al, *Nat Neurosci.* 12(10):1293-9 (2009)), Sichuan and Melegueta peppers (Riera et al., *Br J Pharmacol.* 157(8):1398-409 (2009)), diallyl sulfides nifedipine, nimodipine, nicardipine, and nitrendipine, L-type calcium channel agaonist BayK8644 (Fajardo et al., *Channels (Austin)* 2(6):429-38 (2008)), and isovellcral and polygodial (Escalera et al., *J. Biol. Chem.* 283(35):24136-44 (2008)).

Activators of P2X receptors include but are not limited to ATP, 2-methylthio-ATP, 2' and 3'-*O*-(4-benzoylbenzoyl)-ATP, and ATP5'-*O*-(3-thiotriphosphate).

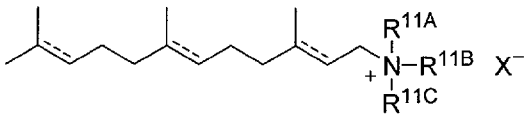
Activators of TRPM8 receptors include but are not limited to menthol, icilin, eucalyptol, linalool, geraniol, and hydroxycitronellal.

In another aspect, the invention features compounds according to Formula (XI),

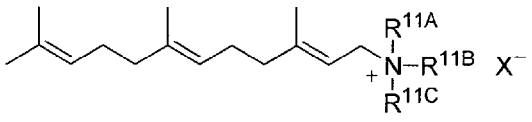


(XI),

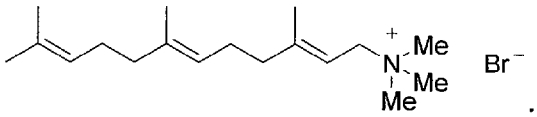
where each R^{11A}, R^{11B}, and R^{11C} is selected, independently, from H or C_{1-4} alkyl, and where 0, 1, 2, or 3 of the dashed bonds represents a carbon-carbon double bond (i.e., compounds of Formula (XI) can include 0, 1, 2, or 3 double bonds), provided that when 2 or 3 carbon-carbon double bonds are present, the double bonds are not adjacent to one another. In some embodiments, compounds of Formula (XI) can be represented by the following formula (XI-A),



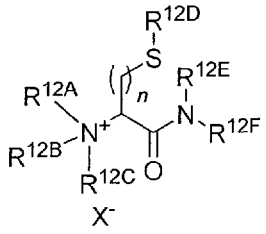
(XI-A), where each R^{11A}, R^{11B}, R^{11C}, and X is according to Formula (XI), and where each dashed bond represents an optional carbon-carbon double bond, or by formula (XI-B),



(XI-B), where each R^{11A}, R^{11B}, R^{11C}, and X is according to Formula (XI). In some embodiments, the compound of Formula (XI) is

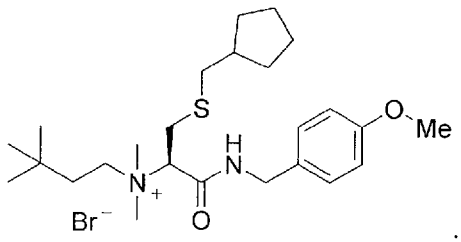


In another aspect, the invention features compounds according to Formula (XII),

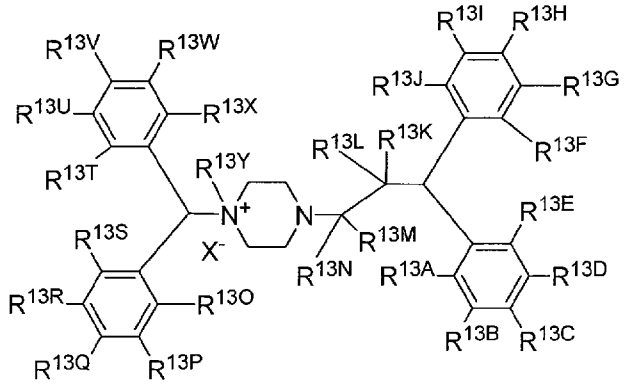


(XII), wherein

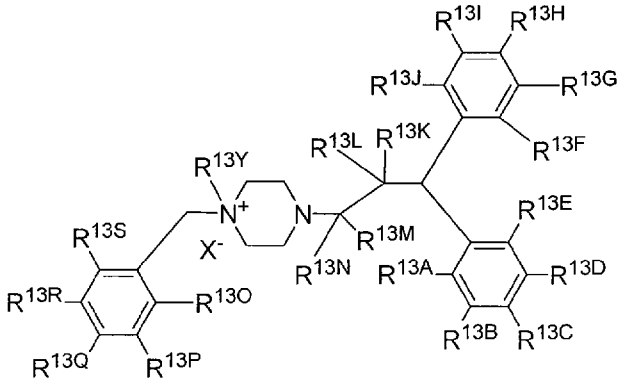
each of R^{12A}, R^{12B}, R^{12C}, and R^{12D} is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; or R^{12A} and R^{12B} together complete a heterocyclic ring having at least one nitrogen atom; n is an integer between 1-5; each of R^{12E} and R^{12F} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, or C_{3-10} alkheterocyclyl; and X is any pharmaceutically acceptable anion. In some embodiments, the compound has the following structure,



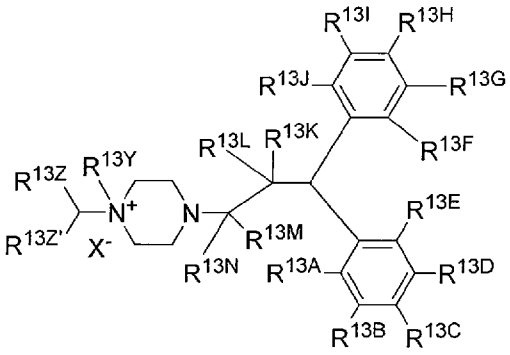
In another aspect, the invention features a compound having a structure according to one of the following formulas:



(XIII-A),



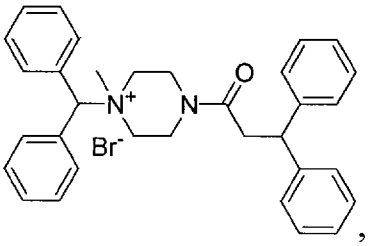
(XIII-B), or



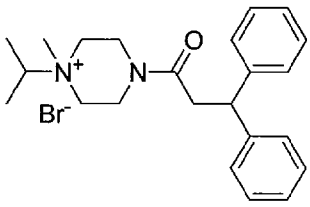
(XIII-C),

where each R^{13A}-R^{13J} and R^{13O}-R^{13T} is selected, independently, from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl, OR^{13AA}, $NR^{13AB}R^{13AC}$, $NR^{13AD}C(O)R^{13AE}$, $S(O)R^{13AF}$, $SO_2R^{13AG}R^{13AH}$, $SO_2NR^{13AI}R^{13AJ}$, SO_3R^{13AK}, CO_2R^{13AL}, $C(O)R^{13AM}$, and $C(O)NR^{13AN}R^{13AO}$; each of R^{13AA}-R^{13AO} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; each R^{13K}, R^{13L}, R^{13M}, and R^{13N} is, independently, H or C_{1-4} alkyl, or R^{13K} and R^{13L}, or R^{13M} and R^{13N}, combine to form C=O, or R^{13K} and R^{13M}

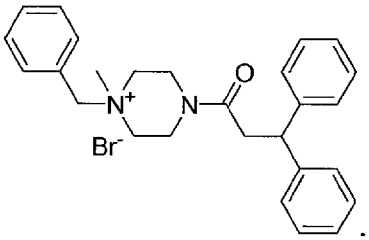
combine to form C=C; R^{13Y} is H or C_{1-4} alkyl; R^{13Z} and $R^{13Z'}$ are, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; and X^- is any pharmaceutically acceptable anion. In some embodiments, the compound is selected from the group consisting of:



,



, and



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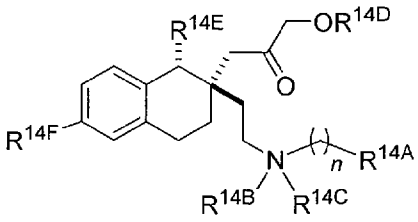
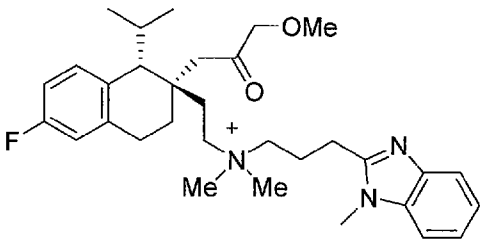
In another aspect, the invention features compounds according to the following formula,



(XIV),

where n is an integer between 0-5; R^{14A} is heterocyclyl, each of R^{14B}, R^{14C}, R^{14D}, and $R1^{4E}$ is, independently, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; and R^{14F} is selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkcnyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl, OR^{14G}, $NR^{14H}R^{141}$, $NR^{14J}C(O)R^{14K}$, $S(O)R^{14L}$, $SO_2R^{14M}R^{14N}$, $SO_2NR^{14O}R^{14P}$, SO_3R^{14Q}, CO_2R^{14R}, $C(O)R^{14S}$, and $C(O)NR^{14T}R^{14V}$; and each of R^{14G}-R^{13AO} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl. In some embodiments, the compound is



X^-, where X is a pharmaceutically acceptable anion.

The invention also features pharmaceutical compositions that include a compound according to any of Formulas (XI)-(XIV), or any of compounds (1)-(563), and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is formulated for oral, nasal, or inhalation administration.

In certain embodiments, the compounds, compositions, methods, and kits of the invention may be used to treat any disorder that is caused, wholly or in part, by neurogenic inflammation. Non-limiting examples of such disorders include asthma, rhinitis, conjunctivitis, arthritis, colitis, contact dermatitis, pancreatitis, chronic cough, sinusisitis (e.g., chronic rhinosinusistis), traumatic brain injury, sepsis (e.g., polymicrobial sepsis), tendinopathies chronic urticaria, rheumatic disease, acute lung injury, exposure to irritants, inhalation of irritants, pollutants or chemical warfare agents, eczema, cystitis, gastritis, urethritis, migraine headache, psoriasis, rhinitis, rosacea, sunburn, chemical warfare agents, inhaled tear gases, or inhaled pollutants.

Some methods and kits of the invention also feature one or more acetaminophens, NSAIDs, glucocorticoids, narcotics, tricyclic antidepressants, amine transporter inhibitors, anticonvulsants, antiproliferative agents, or immune modulators.

In another embodiment, the compositions are administered by intraarticular, surgical, intravenous, intramuscular, oral, rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, vaginal, intraurethral, intravesicular, intrathecal, epidural, mucosal, aural, or ocular administration by injection, inhalation, or direct contact. In yet another embodiment, the composition is formulated for controlled or sustained release over time.

By "biologically active" is meant that a molecule, including biological molecules, such as nucleic acids, peptides, polypeptides, and proteins, exerts a physical or chemical activity on itself or other molecule. For example, a "biologically active" molecule may possess, e.g., enzymatic activity, protein binding activity (e.g., antibody interactions), or cytotoxic activities (e.g., anti-cancer properties). Biologically active agents that can be used in the methods and kits described herein include, without limitation, an antibody or antibody fragment, an antibiotic, a polynucleotide, a polypeptide, a protein, an anti-cancer agent, a growth factor, and a vaccine.

By "inflammation" is meant any types of inflammation, such those caused by the immune system (immune-mediated inflammation) and by the nervous system (neurogenic inflammation), and any symptom of inflammation, including redness, heat, swelling, pain, and/or loss of function.

By "neurogenic inflammation" is meant any type of inflammation mediated by neurons (e.g. nociceptors) or any other component of the central or peripheral nervous system.

By "patient" is meant any animal. In one embodiment, the patient is a human. Other animals that can be treated using the methods and kits of the invention include, but are not limited to, non-human primates (e.g., monkeys, gorillas, chimpanzees), domesticated animals (e.g., horses, pigs, goats, rabbits, sheep, cattle, llamas), and companion animals (e.g., guinea pigs, rats, mice, lizards, snakes, dogs, cats, fish, hamsters, and birds).

Compounds useful in the invention include, but are not limited to, those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, esters, amides, thioesters, solvates, and polymorphs thereof, as well as racemic mixtures and pure isomers of the compounds described herein.

By "low molecular weight" is meant less than about 650 Daltons.

The term "pharmaceutically acceptable salt" represents those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation,

allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. The salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, isethionate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, mesylate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. These acid addition salts may also be referred to as "pharmaceutically acceptable anions." Representative alkali or alkaline earth metal salts include, but are not limited to, sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

In the generic descriptions of compounds of this invention, the number of atoms of a particular type in a substituent group is generally given as a range, e.g., an alkyl group containing from 1 to 4 carbon atoms or C_{1-4} alkyl. Reference to such a range is intended to include specific references to groups having each of the integer number of atoms within the specified range. For example, an alkyl group from 1 to 4 carbon atoms includes each of C_1, C_2, C_3, and C_4. A C_{1-12} heteroalkyl, for example, includes from 1 to 12 carbon atoms in addition to one or more heteroatoms. Other numbers of atoms and other types of atoms may be indicated in a similar manner.

As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e., cycloalkyl. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 6 ring carbon atoms, inclusive. Exemplary cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups.

By "C_{1-4} alkyl" is meant a branched or unbranched hydrocarbon group having from 1 to 4 carbon atoms. A C_{1-4} alkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{1-4} alkyls include, without limitation, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and cyclobutyl.

By "C_{2-4} alkenyl" is meant a branched or unbranched hydrocarbon group containing one or more double bonds and having from 2 to 4 carbon atoms. A C_{2-4} alkenyl may optionally include monocyclic or polycyclic rings, in which each ring desirably has from three to six members. The C_{2-4} alkenyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-4} alkenyls include, without limitation, vinyl, allyl, 2-cyclopropyl-1-ethenyl, 1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, and 2-methyl-2-propenyl.

By "C_{2-4} alkynyl" is meant a branched or unbranched hydrocarbon group containing one or more triple bonds and having from 2 to 4 carbon atoms. A C_{2-4} alkynyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has five or six members. The C_{2-4} alkynyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-4} alkynyls include,

without limitation, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

By "C_{2-6} heterocyclyl" is meant a stable 5- to 7-membered monocyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of 2 to 6 carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from N, O, and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be covalently attached via any heteroatom or carbon atom which results in a stable structure, e.g., an imidazolinyl ring may be linked at either of the ring-carbon atom positions or at the nitrogen atom. A nitrogen atom in the heterocycle may optionally be quaternized. Preferably when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. Heterocycles include, without limitation, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl,

oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred 5 to 10 membered heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, tetrazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, isoxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, quinolinyl, and isoquinolinyl. Preferred 5 to 6 membered heterocycles include, without limitation, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, piperazinyl, piperidinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and tetrazolyl.

By "C_{6-12} aryl" is meant an aromatic group having a ring system comprised of carbon atoms with conjugated π electrons (e.g., phenyl). The aryl group has from 6 to 12 carbon atoms. Aryl groups may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has five or six members. The aryl group may be substituted or unsubstituted. Exemplary substituents include alkyl, hydroxy, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, fluoroalkyl, carboxyl, hydroxyalkyl, carboxyalkyl, amino, aminoalkyl, monosubstituted amino, disubstituted amino, and quaternary amino groups.

By "C_{7-14} alkaryl" is meant an alkyl substituted by an aryl group (e.g., benzyl, phenethyl, or 3,4-dichlorophenethyl) having from 7 to 14 carbon atoms.

By "C_{3-10} alkcycloalkyl" is meant an alkyl substituted by a cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl) having from 3-10 carbon atoms.

By "C_{3-10} alkheterocyclyl" is meant an alkyl substituted heterocyclic group having from 3 to 10 carbon atoms in addition to one or more heteroatoms (e.g., 3-furanylmethyl, 2-furanylmethyl, 3-tetrahydrofuranylmethyl, or 2-tetrahydrofuranylmethyl).

By "C_{1-7} heteroalkyl" is meant a branched or unbranched alkyl, alkenyl, or alkynyl group having from 1 to 7 carbon atoms in addition to1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O, S, and P. Heteroalkyls include, without limitation, tertiary amines, secondary amines, ethers, thioethers, amides, thioamides, carbamates, thiocarbamates, hydrazones, imines, phosphodiesters, phosphoramidates, sulfonamides, and disulfides. A heteroalkyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has three to six members. The heteroalkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, hydroxyalkyl, carboxyalkyl, and carboxyl groups. Examples of C_{1-7} heteroalkyls include, without limitation, methoxymethyl and ethoxyethyl.

By "halide" is meant bromine, chlorine, iodine, or fluorine.

By "fluoroalkyl" is meant an alkyl group that is substituted with a fluorine atom.

By "perfluoroalkyl" is meant an alkyl group consisting of only carbon and fluorine atoms.

By "carboxyalkyl" is meant a chemical moiety with the formula -(R)-COOH, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "hydroxyalkyl" is meant a chemical moiety with the formula -(R)-OH, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "alkoxy" is meant a chemical substituent of the formula -OR, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "aryloxy" is meant a chemical substituent of the formula -OR, wherein R is a C_{6-12} aryl group.

By "alkylthio" is meant a chemical substituent of the formula -SR, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "arylthio" is meant a chemical substituent of the formula -SR, wherein R is a C_{6-12} aryl group.

By "quaternary amino" is meant a chemical substituent of the formula -(R)-N(R')(R'')(R''')$^+$, wherein R, R', R'', and R''' are each independently an optionally substituted alkyl, heteroalkyl, alkaryl, alkcycloalkyl, alkheterocyclyl, alkenyl, alkynyl, heteroaryl, or aryl group as described herein. R may be an alkyl group linking the quaternary amino nitrogen atom, as a substituent, to another moiety. The nitrogen atom, N, is covalently attached to four carbon atoms of the alkyl, heteroalkyl, alkaryl, alkcycloalkyl, alkheterocyclyl, alkenyl, alkynyl, heteroaryl, and/or aryl groups, resulting in a positive charge at the nitrogen atom.

By "charged moiety" is meant a moiety which gains a proton at physiological pH thereby becoming positively charged (e.g., ammonium, guanidinium, or amidinium) or a moiety that includes a net formal positive charge without protonation (e.g., quaternary ammonium). The charged moiety may be either permanently charged or transiently charged.

As used herein, the term "parent" refers to a channel blocking compound which can be modified by quaternization or guanylation of an amine nitrogen atom present in the parent compound. The quaternized and guanylated compounds are derivatives of the parent compound. The guanidyl

derivatives described herein are presented in their uncharged base form. These compounds can be administered either as a salt (i.e., an acid addition salt) or in their uncharged base form, which undergoes protonation in situ to form a charged moiety.

By "therapeutically effective amount" means an amount sufficient to produce a desired result, for example, the reduction or elimination of neurogenic inflammation in a patient (e.g., a human) suffering from a condition, disease, or illness that is caused wholly or in part by neurogenic inflammation (e.g. asthma, arthritis, colitis, contact dermatitis, diabetes, eczema, cystitis, gastritis, migraine headache, psoriasis, rhinitis, rosacea, or sunburn).

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

Brief Description of the Drawings

Figure 1 is a graph showing the effect of intravenous QX-314 (0.4 mg/kg) on the edema elicited by injection of complete Freund's adjuvant (CFA) in the rat hindpaw determined by measuring the total volume of the hindpaw by plethysmography. The degree of swelling produced by injection of CFA is reduced by administration of QX-314 reflecting reduction in neurogenic edema resulting from the blockade of nociceptors by QX314. QX-314 by itself has no effect different from administration of saline.

Figure 2 shows the inhibition of voltage-dependent calcium channel current in a dorsal root ganglion (DRG) neuron by N-methyl-verapamil applied in the presence of capsaicin to open TRPV1 channels. Entry of the drug into the cell, and its blocking action, depends on applying the drug in the presence of capsaicin to activate the TRPV1 channels present in the neuronal membrane.

Detailed Description of the Invention

The present invention features methods and kits for the treatment of neurogenic inflammation by administering a positively-charged, voltage-gated ion channel inhibitor. In embodiments of the invention, the positively-charged,

voltage-gated ion channel inhibitor is administered alone or in combination with a TRP channel agonist such as capsaicinoid (e.g. capsaicin), mustard oil, or a "caine" drug (e.g., amylocaine, articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine (novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), or trimecaine)..

Voltage-gated ion channels in pain-sensing neurons are currently of great interest in developing strategies to treat neurogenic inflammation. Blocking voltage-dependent sodium channels in nociceptors can reduce or eliminate neurogenic inflammation by preventing activation of nociceptor peripheral terminals and the release of pro-inflammatory chemicals. A limitation in designing small organic molecules that inhibit sodium channels or calcium channels is that they must be active when applied externally to the target cell. The vast majority of such externally-applied molecules are hydrophobic and can pass through cell membranes. Accordingly, such molecules will enter all cells and thus exhibit no selectivity for affecting only nociceptors.

Some inhibitors, such as the quarternary ammonium derivative QX-314, are membrane-impermeant and are only effective when present inside the nociceptor cell, and thus must pass through through the cell membrane via a channel or receptor, such as a transient receptor potential ion channel (TRP channels, e.g., TRPAV1, TRPA1, TRPM8, and P2X(2/3)), in order to produce an effect. Under normal circumstances, most TRP channels in nociceptors are not active but require a noxious thermal, mechanical, or chemical stimulus to activate them. For example, TRP channels in nociceptors can be activated by an exogenous TRP ligand (i.e. TRP agonist) such as capsaicin, which opens the TRPV1 channel. Thus, one approach to selectively targeting nociceptors is to co-administer the membrane-impermeant ion channel inhibitor with an exogenous TRP ligand that permits passage of the inhibitor through the TRP

channel into the cell. In addition to capsaicin, the exogenous TRP ligand can also be another capsaicinoid, mustard oil, or lidocaine. In another example, TRP channels may be active in response to exogenous irritant activators such as inhaled acrolein from smoke or chemical warfare agents such as tear gas.

Under certain circumstances, TRP channels can be activated in the absence of exogenous TRP activators/ligands by endogenous inflammatory activators that are generated by tissue damage, infection, autoimmunity, atopy, ischemia, hypoxia, cellular stress, immune cell activation, immune mediator production, and oxidative stress. Under such conditions, endogenous molecules (e.g., protons, lipids, and reactive oxygen species) can activate TRP channels expressed on nociceptors, allowing membrane-impermeant, voltage-gated ion channel blockers to gain access to the inside of the nociceptor through the endogenously-activated TRP channels. Endogenous inflammatory activators of TRP channels include, for example, prostaglandins, nitric oxide (NO), peroxide (H_2O_2), cysteine-reactive inflammatory mediators like 4-hydroxynonenal, endogenous alkenyl aldehydes, endocannabinoids, and immune mediators (e.g., interleukin 1 (IL-1), nerve growth factor (NGF), and bradykinin).

Thus, the inventors have discovered that membrane-impermeant, positively-charged inhibitors of voltage-gated ion channels (e.g., quarternary ammonium derivatives, such as QX-314), alone or in combination with an exogenous TRP ligand, can be used to selectively target nociceptors in order to effectively treat (e.g., eliminate or alleviate) neurogenic inflammation in a patient (e.g., a human).

The invention is described in more detail below.

Neurogenic Inflammation

Inflammation is a complex set of responses to harmful stimuli that results in localized redness, swelling, and pain. Inflammation has two components, one driven by antigens and mediated by immune cells (immune-mediated inflammation) and one mediated by the nervous system (neurogenic

inflammation). Neurogenic inflammation results from the efferent functions of pain-sensing neurons (nociceptors), wherein neuropeptides and other chemicals that are pro-inflammatory mediators are released from the peripheral terminals of the nociceptors when they are activated. This release process is mediated by calcium influx and exocytosis of vesicles, and the pro-inflammatory mediators include substance P, neurokinin A and B (collectively known as tachykinins), and calcitonin gene-related peptide (CGRP).

The release of peripheral terminal chemicals stimulate a variety of inflammatory responses. First, the release of substance P can result in an increase in capillary permeability such that plasma proteins leak from the intravascular compartment into the extracellular space (plasma extravasation), causing edema. This can be detected as a wheal (a firm, elevated swelling of the skin) which is one component of a triad of inflammatory responses—wheal, red spot, and flare—known as the Lewis triple response. Second, the release of CGRP causes vasodilation, leading to increased blood flow. This can be detected as a flare, which is another component of the Lewis triple response.

Substance P also has a pro-inflammatory action on immune cells (e.g. macrophages, T-cells, mast cells, and dendritic cells) via their neurokinin-1 (NK1) receptor. This effect has been documented in allergic rhinitis, gastitis, and colitis, and represents an interface between the neurogenic and immune-mediated components of inflammation. Substance P released from one nociceptor may also act on NK1 receptors on neighboring nociceptors to sensitize or activate them, causing a spread of activation and afferent/efferent function.

These efferent functions of nociceptors can be triggered by: 1) Direct activation of a nociceptor terminal by a peripheral adequate stimulus applied to the terminal (e.g. a pinch); 2) Indirect antidromic activation of a non-stimulated nociceptor terminal by the axon reflex, wherein action potential input from one terminal of a nociceptor, upon reaching a converging axonal branch point in the periphery, results in an action potential traveling from the branch point down to the peripheral terminal of a non-stimulated terminal; and 3) Activation as a

result of activity in nociceptor central terminals in the CNS traveling to the periphery (e.g., primary afferent depolarization of central terminals produced by GABA can be sufficient to initiate action potentials traveling the "wrong way").

Neurogenic Inflammatory Disorders

In certain disorders, neurogenic inflammation contributes to the peripheral inflammation elicited by tissue injury, autoimmune disease, infection, and exposure to irritants in soft tissue, skin, the respiratory system, joints, the urogenital and GI tract, the liver, and the brain. Neurogenic inflammatory disorders include asthma, rhinitis, conjunctivitis, arthritis, colitis, contact dermatitis, diabetes, eczema, cystitis, gastritis, migraine headache, psoriasis, rhinitis, rosacea, and sunburn. pancreatitis, chronic cough, chronic rhinosinusistis, traumatic brain injury, polymicrobial sepsis, tendinopathies chronic urticaria, rheumatic disease, acute lung injury, exposure to irritants, inhalation of irritants, pollutants, or chemical warfare agents, as described herein.

Asthma

Asthma is a chronic respiratory disorder that is characterized by airway obstruction, bronchial hyperresponsiveness, and bronchial inflammation. Asthma can be induced by a variety of stimuli, including natural inhaled allergens (e.g. dust mites, pollen, and mold), household organic compounds (e.g. soap, perfume, shampoo, creams, and lotions), medications, industrial chemicals, food allergies, exercise, hormonal changes, and psychological stress. Patients who chronicically suffer from asthma experience episodes of hypersensitivity to such stimuli where the bronchi contract in spasms. During an asthma episode, inflammation of the airways causes bronchoconstriction and excess mucus production, making it difficult for the patient to breathe.

Cells responsible for airway hyperresponsiveness and obstruction include sensory and motor neurons as well as epithelial and smooth muscle

cells. Asthma is the result of a complex set of interactions between these cells and the immune system, particulatly the T-helper-2 cells which control the inflammatory process. There is growing evidence that communication between immune cells and neurons can be mediated by neurophilins, which are produced in increased concentrations by immune cells that enter the airways in an asthmatic episode. Neurophilins modify the functional activity of neuronal function, leading to altered neuropeptide and tachykinin production that results in neurogenic inflammation. (Renz et al. *Prog. Brain Res.* 146:325, 2004.) TRPV1 and TRPA1 channels also contribute to the neurogenic component of allergic asthma as well as cough and rhinitis.

Arthritis

Arthritis is a group of conditions involving inflammation and damage to the joints of the body. Arthritis can have many causes, including physical trauma and aging (osteoarthritis), autoimmune disease (rheumatoid arthritis and psoriatic arthritis), infection (septic arthritis), and gout (gouty arthritis).

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that principally affects the joints (synovitis), characterized by destruction of articular cartilage and bending/stiffness of the joints (ankylosis), and which leads to pain and substantial loss of mobility. RA can also cause inflammation in the skin, lungs, and kidneys. About 1% of the world population develops rheumatoid arthritis, with women having a three-fold higher risk than men.

The causes of autoimmunity in RA are not fully understood, but evidence suggests the involvement of abnormal B- and T-cell activation and the release of TNF and other cytokines. There has also been a causal link between cigarette smoke and RA. Studies have suggested that neurogenic inflammation makes an important contribution to the pathogenesis of joint pain in RA. See, for example, Levine et al. (*J. Immunol.* 135:843s, 1985), which showed that the severity of joint injury in RA is correlated with a greater local concentration of substance P.

Colitis

Colitis is a group of chronic autoimmune disorders characterized by inflammation of the colon. Symptoms of colitis include pain, tenderness of the abdomen, fatigue, rapid weight loss, ulcers (ulcerative colitis), and gastrointestinal bleeding. Colitis can also be triggered by many foods, including alcohol, caffeine, dairy products, spicy foods, nuts, seeds, meats, refined sugar, and raw vegetables. It is known that neurogenic mechanisms are important to the inflammatory processes in colitis. For example, studies have shown that induced colitis inflammation in mice can be mitigated using NK-1 and CGRP receptor antagonists. (Nguyen et al. *Canadian J. Phys. Pharm.* 81:920, 2003.)

Contact Dermatitis

Contact dermatitis is the local irritation of superficial regions of the skin caused by contact with irritants or allergens. In North America, the most common causes of allergic contact dermatitis are plants such as poison ivy and poison oak. Common causes of irritant contact dermatitis are chemicals such as harsh soaps, detergents, and cleaning products. Symptoms of contact dermatitis include rash, blisters, wheals, hives, and burning itch. The role of neurogenic inflammation in contact dermatitis has been discussed, for example, in Guy, *AMA Arch. Derm. Syphilol.* 66:1, 1952.

Gastritis

Gastritis refers to a collection of disorders which induce inflammation of the stomach lining. Gastritis can be caused by excessive alcohol consumption, prolonged use of NSAIDs such as aspirin or ibuprofen, and chronic infection by bacteria (primarily *Helicobacter pylori*). Certain autoimmune disorders can also cause gastritis. Symptoms include internal bleeding, pain (especially in the upper abdomen), vomitting, and bloating. Gastritis can also lead to increased risk of stomach cancer.

Migraine

Migraine is a neurological disorder, more common in women than in men, that is characterized by headache, nausea, and altered perception. Migraine proceeds in several phases: 1) a prodrome phase that includes fatigue, food craving, neck stiffness, altered mood, and constipation or diarrhea; 2) an aura phase that includes disturbances of vision consisting of white/multicolored flashes of lights or dazzling lines, feelings of "pins-and-needles" in the hand and arm, auditory/olfactory hallucinations, vertigo, tingling /numbness of the face, and hypersensitivity to touch; 3) a pain phase that includes a throbbing headache accompanied by nausea, vomiting, blurred vision, nasal stuffiness, diarrhea, and local edema; and 4) a postdrome phase including fatigue and feelings of "hangover."

There are many theories about the cause of migraine. Among these is the theory that certain nerves, when irritated, release the pro-inflammatory mediators such as substance P that lead to neurogenic inflammation and associated pain.

Rhinitis

Rhinitis, known commonly as the running nose, is a disorder involving irritation and inflammation of internal nasal mucous membranes. Rhinitis is characterized by the generation of large amounts of mucus, producing running nose, nasal congestion, and post-nasal drip. According to recent estimates, more than 50 million people in the U.S. alone suffer from rhinitis yearly. Rhinitis is categoried into infective rhinitis (caused by bacterial infection), nonallergic rhinitis (caused by hormones, drugs, and foods), and allergic rhinitis (caused by immune reactions to allergens, e.g. hayfever). The role of neurogenic inflammation in the pathogenesis of rhinitis is similar to that of asthma, where enrivonmental substances enhance the immune response, leading to downstream release of substance P from neurons.

Cystitis

Cystitis is inflammation of the urinary bladder. There are several types of cystitis, including traumatic cystitis, interstitial cystitis, eosinophilic cystitis, radiation cystitis, and hemorrhagic cystitis. Interstitial cystitis, also known as painful bladder syndrome, is a disorder characterized by urination pain, urinary frequency, urgency, and pressure in the bladder. Unlike traumatic cystitis, interstitial cystitis has not been shown to be caused by bacterial infection. The cause of interstitial cystitis is unknown but has been proposed to involve neurogenic inflammation. For example, animal studies have shown that interstitial cystitis is correlated with both central and peripheral neural upregulation (Nazif et al., *Urology* 69:24-33 (2007)), and that acute bladder injury resulted in a significant increase in the release of substance P and CGRP (Lucioni et al., *BJU Int.* 101:366-370, 2008).

Additional Neurogenic Inflammatory Disorders

Additional neurogenic inflammatory disorders will be known to those skilled in the art, and include, but are not limited to sunburn, inflammatory conditions with a neurogenic component such as inflammation of blood vessels, eczema, rosacea, psoriasis, gingivitis, pancreatitis, chronic cough, chronic rhinosinusistis, traumatic brain injury, polymicrobial sepsis, tendinopathies chronic urticaria, acute lung injury, exposure to irritants, inhalation of irritants, pollutants, or chemical warfare agents.

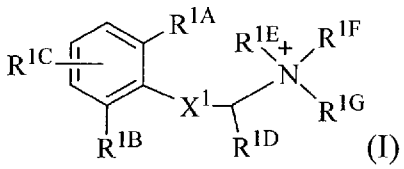
Inhibitors of Voltage-Gated Ion Channels

Inhibitors of voltage-gated ion channels that are suitable for use in the methods and kits of the invention for the treatment of neurogenic inflammation are desirably positively-charged, hydrophilic compounds. In one embodiment, the compounds are permanently charged (i.e., have a charge that is not transient). In another embodiment, the compounds are transiently charged. Suitable inhibitors of voltage-gated sodium channels include, but are not limited to, QX-314, N-methyl-procaine (QX-222), N-octyl-guanidine, 9-

aminoacridine, and pancuronium. Suitable inhibitors of voltage-gated calcium channels include, but are not limited to, D-890 (quaternary methoxyverapamil), CERM 11888 (quaternary bepridil), *N*-methyl-verapamil, *N*-methylgallopamil, *N*-methyl-devapamil, dodecyltrimethylammonium, and other compounds as described herein (see, e.g., charged derivatives of the compounds described in Tables 1 and 2).

Additionally, there are many known inhibitors of voltage-gated ion channels that would be of a suitable size to be useful in the methods of the invention (e.g., from about 100 to 4,000 Da, 100 to 3,000 Da, 100 to 2,000 Da, 150 to 1,500 Da, or even 200 to 1,200 Da) and that have amine groups, or can be modified to contain amine groups, that can be readily modified to be charged (e.g., as positively-charged quarternary amines, or as transiently charged, e.g., guanylated, compounds). Such inhibitors include, but are not limited to, riluzole, mexilitine, phenytoin, carbamazepine, procaine, tocainide, prilocaine, diisopyramide, bencyclane, quinidine, bretylium, lifarizine, lamotrigine, flunarizine, articaine, bupivicaine, mepivicaine, and fluspirilene.

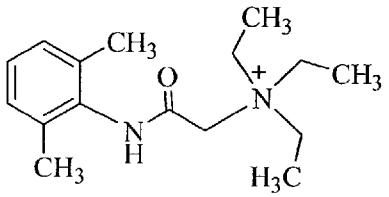
Compounds that can be used in the methods and kits of the invention for the treatment of inflammation include compounds of formulas I-X, below.



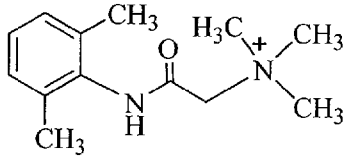
(I)

In formula I, each of R^{1A}, R^{1B}, and R^{1C} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{1H}, $NR^{1I}R^{1J}$, $NR^{1K}C(O)R^{1L}$, $S(O)R^{1M}$, $SO_2R^{1N}R^{1O}$, $SO_2NR^{1P}R^{1Q}$, SO_3R^{1R}, CO_2R^{1S}, $C(O)R^{1T}$, and $C(O)NR^{1U}R^{1V}$; and each of R^{1H}, R^{1I}, R^{1J}, R^{1K}, R^{1L}, R^{1M}, R^{1N}, R^{1O}, R^{1P}, R^{1Q}, R^{1R}, R^{1S}, R^{1T}, R^{1U}, and R^{1V} is, independently, selected from from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl X^1 is selected from $-CR^{1W}R^{1X}-$, $-NR^{1Y}C(O)-$, -OC(O)-, -SC(O)-, $-C(O)NR^{1Z}-$, $-CO_2-$, and -OC(S)-; and each of R^{1W}, R^{1X}, R^{1Y}, and R^{1Z} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; R^{1D} is selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; and each of R^{1E}, R^{1F}, and R^{1G}

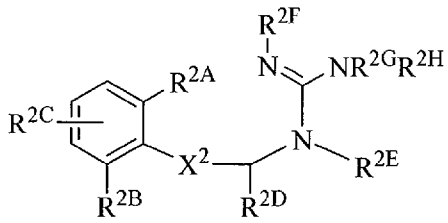
is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; or R^{1D} and R^{1G} together complete a heterocyclic ring having at least one nitrogen atom. In a preferred embodiment, X^1 is -NHC(O)-. Exemplary compounds of formula I include methylated quaternary ammonium derivatives of anesthetic drugs, such as N-methyl lidocaine, N,N-dimethyl prilocaine, N,N,N-trimethyl tocainide, N-methyl etidocaine, N-methyl ropivacaine, N-methyl bupivacaine, N-methyl levobupivacaine, N-methyl mepivacaine. These derivatives can be prepared using methods analogous to those described in Scheme 1. Compounds of formula I include QX-314 (CAS 21306-56-9) and QX-222 (CAS 21236-55-5) (below).



QX-314



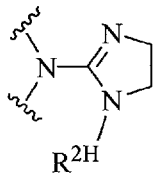
QX-222



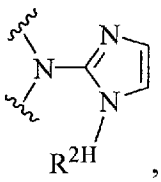
(II)

In formula II, each of R^{2A},R^{2B}, and R^{2C} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{2I}, $NR^{2J}R^{2K}$, $NR^{2L}C(O)R^{2M}$, $S(O)R^{2N}$, $SO_2R^{2O}R^{2P}$, $SO_2NR^{2Q}R^{2R}$, SO_3R^{2S}, CO_2R^{2T}, $C(O)R^{2U}$, and $C(O)NR^{2V}R^{2W}$; and each of R^{2I}, R^{2J}, R^{2K}, R^{2L}, R^{2M}, R^{2N}, R^{2O}, R^{2P}, R^{2Q}, R^{2R}, R^{2S}, R^{2T}, R^{2U}, R^{2V}, R^{2W} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; X^2 is selected from $-CR^{2X}R^{2Y}-$, $-NR^{2Z}C(O)-$, -OC(O)-, -SC(O)-, $-C(O)NR^{2AA}-$, $-CO_2-$, and -OC(S)-; and each of R^{2X}, R^{2Y}, R^{2Z}, and R^{2AA} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;R^{2D} is selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; R^{2E} is H or C_{1-4} alkyl; and each

of R^{2F}, R^{2G}, and R^{2H} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; or R^{2F} and R^{2G} together complete a heterocyclic ring having two nitrogen atoms. Where R^{2F} and R^{2G} form a heterocyclic ring having two nitrogen atoms, the resulting guanidine group is, desirably, selected from



and



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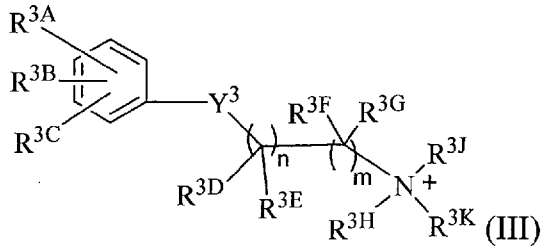
where R^{2H} is H or CH_3. Desirably, R^{2F} and R^{2G} combine to form an alkylene or alkenylene of from 2 to 4 carbon atoms, e.g., ring systems of 5, 6, and 7-membered rings. In a preferred embodiment, X^2 is -NHC(O)-. Exemplary compounds of formula II include N-guanidyl derivatives (e.g., $-C(NH)NH_2$ derivatives) of anesthetic drugs, such as desethyl-N-guanidyl lidocaine, N-guanidyl prilocaine, N-guanidyl tocainide, desethyl-N-guanidyl etidocaine, desbutyl-N-guanidyl ropivacaine, desbutyl-N-guanidyl bupivacaine, desbutyl-N-guanidyl levobupivacaine, desmethyl-N-guanidyl mepivacaine. These derivatives can be prepared using methods analogous to those described in Schemes 2-5.

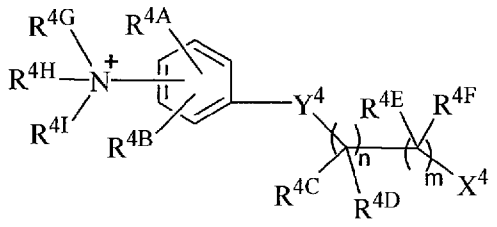
The guanidyl derivatives described herein (e.g., the compounds of formula II) are presented in their uncharged base form. These compounds can be administered either as a salt (i.e., an acid addition salt) or in their uncharged base form, which undergoes protonation in situ to form a charged moiety.

The synthesis of parent drugs of formulas I and II are described in the literature. See, for example, U.S. Patent No. 2,441,498 (synthesis of lidocaine), U.S. Patent No. 3,160,662 (synthesis of prilocaine), DE Patent No. 2235745 (synthesis of tocainide), DE Patent No. 2162744 (synthesis of etidocaine), PCT Publication No. WO85/00599 (synthesis of ropivacaine), U.S. Patent No. 2,955,111 (synthesis of bupivacaine and levobupivacaine), and U.S. Patent No. 2,799,679 (synthesis of mepivacaine).



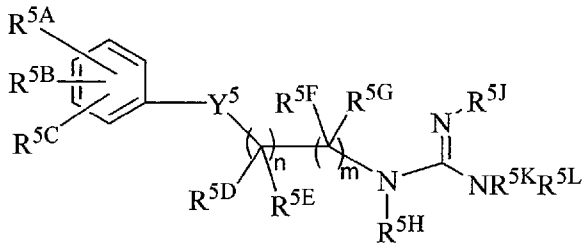
(III)

In formula III, n = 0-3 and m = 0-3, with (n+m) = 0-6; each of R^{3A}, R^{3B}, and R^{3C} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, OR^{3L}, $NR^{3M}R^{3N}$, $NR^{3O}C(O)R^{3P}$, $S(O)R^{3Q}$, $SO_2R^{3R}R^{3S}$, $SO_2NR^{3T}R^{3U}$, SO_3R^{3V}, CO_2R^{3W}, $C(O)R^{3X}$, and $C(O)NR^{3Y}R^{3Z}$; and each of R^{3L}, R^{3M}, R^{3N}, R^{3O}, R^{3P}, R^{3Q}, R^{3R}, R^{3S}, R^{3T}, R^{3U}, R^{3V}, R^{3W}, R^{3X}, R^{3Y}, R^{3Z} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; Y^3 is selected from from $-CR^{3AA}R^{3AB}-$, $-NR^{3AC}C(O)-$, -OC(O)-, -SC(O)-, $-C(O)NR^{3AD}-$, $-CO_2-$, and -OC(S)-; and each of R^{3AA}, R^{3AB}, R^{3AC}, and R^{3AD} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; each of R^{3D}, R^{3E}, R^{3F}, and R^{3G} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, and C_{3-10} alkheterocyclyl; each of R^{3H}, R^{3J}, and R^{3K} is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl. The quaternary nitrogen in formula III is identified herein as N'. Exemplary compounds of formula III include methylated quaternary ammonium derivatives of anesthetic drugs, such as N'-methyl procaine, N'-methyl proparacaine, N'-methyl allocain, N'-methyl encainide, N'-methyl procainamide, N'-methyl metoclopramide, N'-methyl stovaine, N'-methyl propoxycaine, N'-methyl chloroprocaine, N',N'-dimethyl flecainide, and N'-methyl tetracaine. These derivatives can be prepared using methods analogous to those described in Scheme 1.



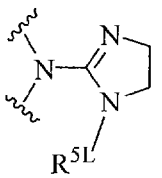
(IV)

In formula IV, n = 0-3 and m = 0-3, with (n+m) = 0-6; each of R^{4A} and R^{4B} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, OR^{4L}, $NR^{4M}R^{4N}$, $NR^{4O}C(O)R^{4P}$, $S(O)R^{4Q}$, $SO_2R^{4R}R^{4S}$, $SO_2NR^{4T}R^{4U}$, SO_3R^{4V}, CO_2R^{4W}, $C(O)R^{4X}$, and $C(O)NR^{4Y}R^{4Z}$; and each of R^{4L}, $R^{4M}R^{4N}$, R^{4O}, R^{4P}, R^{4Q}, R^{4R}, R^{4S}, R^{4T}, R^{4U}, R^{4V}, R^{4W}, R^{4X}, R^{4Y}, and R^{4Z} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; Y^4 is selected from $-CR^{4AA}R^{4AB}-$, $-NR^{4AC}C(O)-$, -OC(O)-, -SC(O)-, $-C(O)NR^{4AD}-$, $-CO_2-$, and -OC(S)-; and each of R^{4AA}, R^{4AB}, R^{4AC}, and R^{4AD} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;each of R^{4C}, R^{4D}, R^{4E}, and R^{4F} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, and C_{3-10} alkheterocyclyl; X^4 is selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and $NR^{4J}R^{4K}$; each of R^{4J} and R^{4K} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; and each of R^{4G}, R^{4H}, and R^{4I} is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl . The quaternary nitrogen in formula IV is identified herein as N". Exemplary compounds of formula III include methylated quaternary ammonium derivatives of anesthetic drugs, such as N",N",N"-trimethyl procaine, N",N",N"-trimethyl proparacaine, N",N",N"-trimethyl procainamide, N",N",N"-trimethyl metoclopramide, N",N",N"-trimethyl propoxycaine, N",N",N"-trimethyl chloroprocaine, N",N"-dimethyl tetracaine, N",N",N"-trimethyl benzocaine, and N",N",N"-trimethyl butamben. These derivatives can be prepared using methods analogous to those described in Scheme 1.

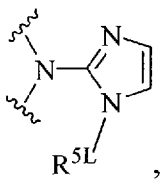


(V)

In formula V, n = 0-3 and m = 0-3, with (n+m) = 0-6; each of R^{5A}, R^{5B}, and R^{5C} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, OR^{5M}, $NR^{5N}R^{5O}$, $NR^{5P}C(O)R^{5Q}$, $S(O)R^{5R}$, $SO_2R^{5S}R^{5T}$, $SO_2NR^{5U}R^{5V}$, SO_3R^{5W}, CO_2R^{5X}, $C(O)R^{5Y}$, and $C(O)NR^{5Z}R^{5AA}$; and each of R^{5M}, R^{5N}, R^{5O}, R^{5P}, R^{5Q}, R^{5R}, R^{5S}, R^{5T}, R^{5U}, R^{5V}, R^{5W}, R^{5X}, R^{5Y}, R^{5Z}, and R^{5AA} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; Y^5 is selected from $-CR^{5AB}R^{5AC}-$, $-NR^{5AD}C(O)-$, -OC(O)-, -SC(O)-, $-C(O)NR^{5AE}-$, $-CO_2-$, and -OC(S)-; and each of R^{5AB}, R^{5AC}, R^{5AD}, and R^{5AE} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; each of R^{5D}, R^{5E}, R^{5F}, and R^{5G} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, and C_{3-10} alkheterocyclyl; R^{5H} is H or C_{1-4} alkyl; and each of R^{5J}, R^{5K}, and R^{5L} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; or R^{5J} and R^{5K} together complete a heterocyclic ring having two nitrogen atoms. Where R^{5J} and R^{5K} form a heterocyclic ring having two nitrogen atoms, the resulting guanidine group is, desirably, selected from



and



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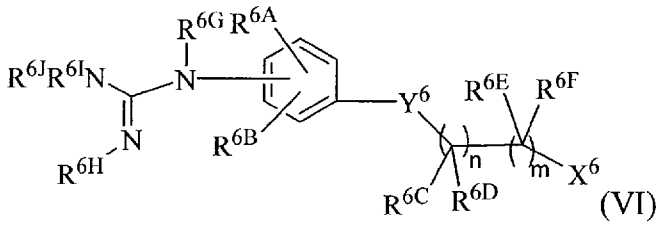
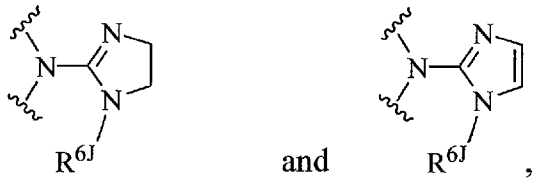
where R^{5L} is H or CH_3. Desirably, R^{5J} and R^{5K} combine to form an alkylene or alkenylene of from 2 to 4 carbon atoms, e.g., ring systems of 5, 6, and 7-membered rings. The guanylated nitrogen in formula V is identified herein as N'. Exemplary compounds of formula V include N-guanidyl derivatives (e.g., $-C(NH)NH_2$ derivatives) of anesthetic drugs, such as such as desethyl-N'-guanidyl procaine, desethyl-N'-guanidyl proparacaine, desethyl-N'-guanidyl

allocain, desmethyl-N'-guanidyl encainide, desethyl-N'-guanidyl procainamide, desethyl-N'-guanidyl metoclopramide, desmethyl-N'-guanidyl stovaine, desethyl-N'-guanidyl propoxycaine, desethyl-N'-guanidyl chloroprocaine, N'-guanidyl flecainide, and desethyl-N'-guanidyl tetracaine. These derivatives can be prepared using methods analogous to those described in Schemes 2-5.



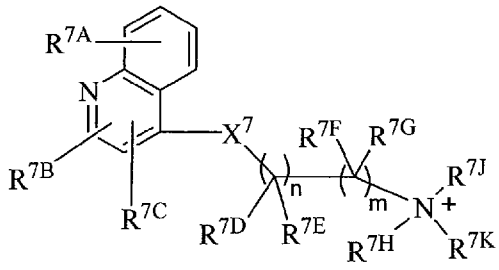
(VI)

In formula VI, n = 0-3 and m = 0-3, with (n+m) = 0-6; each of R^{6A} and R^{6B} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, OR^{6K}, $NR^{6L}R^{6M}$, $NR^{6N}C(O)R^{6O}$, $S(O)R^{6P}$, $SO_2R^{6Q}R^{6R}$, $SO_2NR^{6S}R^{6T}$, SO_3R^{6U}, CO_2R^{6V}, $C(O)R^{6W}$, and $C(O)NR^{6X}R^{6Y}$; and each of R^{6K},R^{6L}, R^{6M}, R^{6N}, R^{6O}, R^{6P}, R^{6Q}, R^{6R}, R^{6S}, R^{6T}, R^{6U}, R^{6V}, R^{6W}, R^{6X}, and R^{6Y} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; Y^6 is selected from $-CR^{6Z}R^{6AA}-$, $-NR^{6AB}C(O)-$, -OC(O)-, -SC(O)-, $-C(O)NR^{6AC}-$, $-CO_2-$, and -OC(S)-; and each of R^{6Z}, R^{6AA}, R^{6AB}, and R^{6AC} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; each of R^{6C}, R^{6D}, R^{6E}, and R^{6F} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, and C_{3-10} alkheterocyclyl; X^6 is selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and $NR^{6AD}R6^{AE}$; each of R^{6AD} and R^{6AE} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; R^{6G} is H or C_{1-4} alkyl; and each of R^{6H}, R^{6I}, and R^{6J} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; or R^{6H} and R^{6I} together complete a heterocyclic ring having two nitrogen atoms. Where R^{6H} and R^{6I} form a heterocyclic ring having two nitrogen atoms, the resulting guanidine group is, desirably, selected from



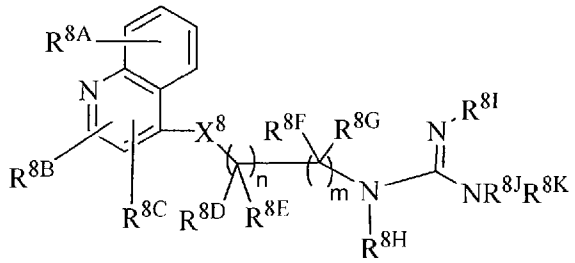
where R^{6J} is H or CH_3. Desirably, R^{6H} and R^{6I} combine to form an alkylene or alkenylene of from 2 to 4 carbon atoms, e.g., ring systems of 5, 6, and 7-membered rings. The guanylated nitrogen in formula V is identified herein as N". Exemplary compounds of formula VI include N-guanidyl derivatives (e.g., $-C(NH)NH_2$ derivatives) of anesthetic drugs, such as such as N"-guanidyl procaine, N"-guanidyl proparacaine, N"-guanidyl procainamide, N"-guanidyl metoclopramide, N"-guanidyl propoxycaine, N"-guanidyl chloroprocaine, N"-guanidyl tetracaine, N"-guanidyl benzocaine, and N"-guanidyl butamben. These derivatives can be prepared using methods analogous to those described in Schemes 2-5.

The synthesis of parent drugs of formulas III-VI are described in the literature. See, for example, U.S. Patent No. 812,554 (synthesis of procaine), Clinton et al., *J. Am. Chem. Soc.* 74:592 (1952) (synthesis of proparacaine), U.S. Patent No. 2,689,248 (synthesis of propoxycaine), Hadicke et al., *Pharm. Zentralh.* 94:384 (1955) (synthesis of chloroprocaine), U.S. Patent No. 1,889,645 (synthesis of tetracaine), Salkowski et al., *Ber.* 28:1921 (1895) (synthesis of benzocaine), Brill et al., *J. Am. Chem. Soc.* 43:1322 (1921) (synthesis of butamben), U.S. Patent No. 3,931,195 (synthesis of encainide), Yamazaki et al., *J. Pharm. Soc. Japan* 73:294 (1953) (synthesis of procainamide), U.S. Patent No. 3,177,252 (synthesis of metoclopramide), U.S. Patent No. 3,900,481 (synthesis of flecainide), and Fourneau et al., *Bull. Sci. Pharmacol.* 35:273 (1928) (synthesis of stovaine), each of which is hereby incorporated by reference.



(VII)

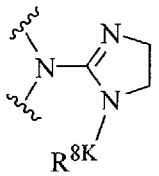
In formula VII, n = 0-3 and m = 0-3, with (n+m) = 0-6; each of R^{7A}, R^{7B}, and R^{7C} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, OR^{7L}, $NR^{7M}R^{7N}$, $NR^{7O}C(O)R^{7P}$, $S(O)R^{7Q}$, $SO_2R^{7R}R^{7S}$, $SO_2NR^{7T}R^{7U}$, SO_3R^{7V}, CO_2R^{7W}, $C(O)R^{7X}$, and $C(O)NR^{7Y}R^{7Z}$; and each of R^{7L},R^{7M}, R^{7N}, R^{7O}, R^{7P}, R^{7Q}, R^{7R}, R^{7S}, R^{7T}, R^{7U}, R^{7V}, R^{7W}, R^{7X}, R^{7Y}, and R^{7Z} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; X^7 is selected from $-CR^{7AA}R^{7AB}-$, $-NR^{7AC}C(O)-$, -OC(O)-, -SC(O)-, $-C(O)NR^{7AD}-$, $-CO_2-$, and -OC(S)-; and each of R^{7AA}, R^{7AB}, R^{7AC}, and R^{7AD} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; each of R^{7D}, R^{7E}, R^{7F}, and R^{7G} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, and C_{3-10} alkheterocyclyl; and each of R^{7H}, R^{7J}, and R^{7K} is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl. In a preferred embodiment, X^7 is -C(O)NH-. Exemplary compounds of formula VII include methylated quaternary ammonium derivatives of anesthetic drugs, such as N'-methyl dibucaine. These derivatives can be prepared using methods analogous to those described in Scheme 1.



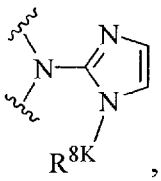
(VIII)

In formula VIII, n = 0-3 and m = 0-3, with (n+m) = 0-6; each of R^{8A}, R^{8B}, and R^{8C} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, OR^{8L}, $NR^{8M}R^{8N}$, $NR^{8O}C(O)R^{8P}$,

$S(O)R^{8Q}$, $SO_2R^{8R}R^{8S}$, $SO_2NR^{8T}R^{8U}$, SO_3R^{8V}, CO_2R^{8W}, $C(O)R^{8X}$, and $C(O)NR^{8Y}R^{8Z}$; and each of R^{8L}, R^{8M}, R^{8N}, R^{8O}, R^{8P}, R^{8Q}, R^{8R}, R^{8S}, R^{8T}, R^{8U}, R^{8V}, R^{8W}, R^{8X}, R^{8Y}, and R^{8Z} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; X^8 is selected from $-CR^{8AA}R^{8AB}-$, $-NR^{8AC}C(O)-$, $-OC(O)-$, $-SC(O)-$, $-C(O)NR^{8AD}-$, $-CO_2-$, and $-OC(S)-$; and each of R^{8AA}, R^{8AB}, R^{8AC}, and R^{8AD} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; each of R^{8D}, R^{8E}, R^{8F}, and R^{8G} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, and C_{3-10} alkheterocyclyl; R^{8H} is H or C_{1-4} alkyl; and each of R^{8I}, R^{8J}, and R^{8K} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; or R^{8I} and R^{8J} together complete a heterocyclic ring having two nitrogen atoms. Where R^{8I} and R^{8J} form a heterocyclic ring having two nitrogen atoms, the resulting guanidine group is, desirably, selected from

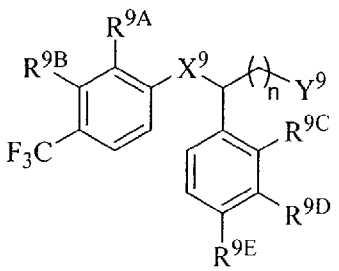


and



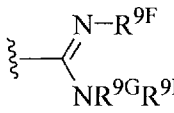
,

where R^{8K} is H or CH_3. Desirably, R^{8I} and R^{8J} combine to form an alkylene or alkenylene of from 2 to 4 carbon atoms, e.g., ring systems of 5, 6, and 7-membered rings. The guanylated nitrogen in formula V is identified herein as N'. In a preferred embodiment, X^8 is -C(O)NH-. Exemplary compounds of formula VIII include N-guanidyl derivatives (e.g., $-C(NH)NH_2$ derivatives) of anesthetic drugs, such as such as desethyl-N-guanidyl dibucaine. These derivatives can be prepared using methods analogous to those described in Schemes 2-5.



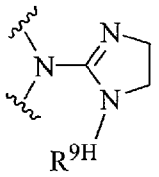
(IX)

In formula IX, n = 0-6; each of R^{9A}, R^{9B}, R^{9C}, R^{9D}, and R^{9E} is, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, OR^{9I}, $NR^{9J}R^{9K}$, $NR^{9L}C(O)R^{9M}$, $S(O)R^{9N}$, $SO_2R^{9O}R^{9P}$, $SO_2NR^{9Q}R^{9R}$, SO_3R^{9S}, CO_2R^{9T}, $C(O)R^{9U}$, and $C(O)NR^{9V}R^{9W}$; and each of R^{9I}, R^{9J}, R^{9K}, R^{9L}, R^{9M}, R^{9N}, R^{9O}, R^{9P}, R^{9Q}, R^{9R}, R^{9S}, R^{9T}, R^{9U}, R^{9V}, and R^{9W} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; X^9 is selected from $-CR^{9X}R^{9Y}-$, -O-, -S-, and $-NR^{9Z}-$; and each of R^{9X}, R^{9Y}, and R^{9Z} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl; Y^9 is $NR^{9AA}NR^{9AB}NR^{9AC}$ or $NR^{9AD}Z^9$; each of R^{9AA}, R^{9AB}, and R^{9AC} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl; R^{9AD} is H or C_{1-4} alkyl; Z^9 is

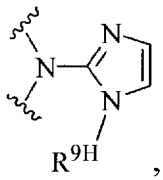


$NR^{9G}R^{9H}$; and

each of R^{9F}, R^{9G}, and R^{9H} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, or R^{9F} and R^{9G} together complete a heterocyclic ring having two nitrogen atoms. Where R^{9F} and R^{9G} form a heterocyclic ring having two nitrogen atoms, the resulting guanidine group is, desirably, selected from

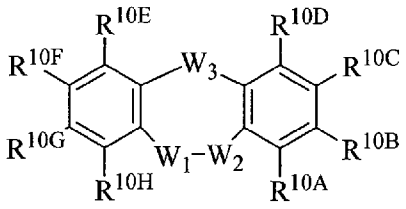


and



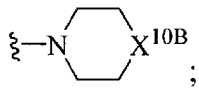
,

where R^{9H} is H or CH_3. Desirably, R^{9F} and R^{9G} combine to form an alkylene or alkenylene of from 2 to 4 carbon atoms, e.g., ring systems of 5, 6, and 7-membered rings. In a preferred embodiment, X^9 = -O-. Exemplary compounds of formula IX include N-guanidyl derivatives (e.g., $-C(NH)NH_2$ derivatives), such as N-guanidyl fluoxetine, and methylated quaternary ammonium derivatives, such as N,N-dimethyl fluoxetine. These derivatives can be prepared using methods analogous to those described in Schemes 1-5.



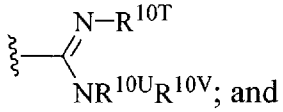
(X)

In formula X, W_3 is O, NH, NCH_2R^{10J}, $NC(O)CH_2R^{10J}$, $CHCH_2R^{10J}$, $C{=}CHR^{10J}$, or $C{=}CHR^{10K}$; W_1-W_2 is S, O, $OCHR^{10K}$, $SCHR^{10K}$, $N{=}CR^{10K}$, CHR^{10L}-CHR^{10K}, or $CR^{10L}{=}CR^{10K}$; each of R^{10A}, R^{10B}, R^{10C}, R^{10D}, R^{10E}, R^{10F}, R^{10G}, and R^{10H} is, independently, selected from H, OH, halide, C_{1-4} alkyl, and C_{2-4} heteroalkyl; R^{10J} is $CH_2CH_2X^{10A}$ or $CH(CH_3)CH_2X^{10A}$; R^{10L} is H or OH; R^{10K} is H, OH, or the group:



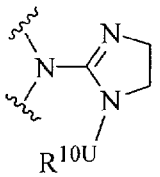
;

X^{10A} is $NR^{10M}R^{10N}R^{10P}$, or $NR^{10Q}X^{10C}$; X^{10B} is $NR^{10R}R^{10S}$, or NX^{10C}; each of R^{10M}, R^{10N}, R^{10P}, R^{10R}, and R^{10S} is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl, or R^{10R}, and R^{10S} together complete a heterocyclic ring having at least one nitrogen atom; R^{10Q} is H or C_{1-4} alkyl; X^{10C} is

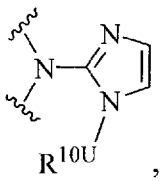


; and

each of R^{10T}, R^{10U}, and R^{10V} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl, or R^{10T} and R^{10V} together complete a heterocyclic ring having two nitrogen atoms. Where R^{10T} and R^{10V} form a heterocyclic ring having two nitrogen atoms, the resulting guanidine group is, desirably, selected from



and



,

where R^{10U} is H or CH_3. Desirably, R^{10T} and R^{10V} combine to form an alkylene or alkenylene of from 2 to 4 carbon atoms, e.g., ring systems of 5, 6, and 7-membered rings. Exemplary compounds of formula X include N-guanidyl derivatives (e.g., $-C(NH)NH_2$ derivatives) and methylated quaternary

ammonium derivatives. N-guanidyl derivatives of formula X include, without limitation, N-guanidyl amoxapine, desmethyl-N-guanidyl trimipramine, desmethyl-N-guanidyl dothiepin, desmethyl-N-guanidyl doxepin, desmethyl-N-guanidyl amitriptyline, N-guanidyl protriptyline, N-guanidyl desipramine, desmethyl-N-guanidyl clomipramine, desmethyl-N-guanidyl clozapine, desmethyl-N-guanidyl loxapine, N-guanidyl nortriptyline, desmethyl-N-guanidyl cyclobenzaprine, desmethyl-N-guanidyl cyproheptadine, desmethyl-N-guanidyl olopatadine, desmethyl-N-guanidyl promethazine, desmethyl-N-guanidyl trimeprazine, desmethyl-N-guanidyl chlorprothixene, desmethyl-N-guanidyl chlorpromazine, desmethyl-N-guanidyl propiomazine, desmethyl-N-guanidyl prochlorperazine, desmethyl-N-guanidyl thiethylperazine, desmethyl-N-guanidyl trifluoperazine, desethyl-N-guanidyl ethacizine, and desmethyl-N-guanidyl imipramine. Methylated quaternary ammonium derivatives of formula X include, without limitation, N,N-dimethyl amoxapine, N-methyl trimipramine, N-methyl dothiepin, N-methyl doxepin, N-methyl amitriptyline, N,N-dimethyl protriptyline, N,N-dimethyl desipramine, N-methyl clomipramine, N-methyl clozapine, N-methyl loxapine, N,N-dimethyl nortriptyline, N-methyl cyclobenzaprine, N-methyl cyproheptadine, N-methyl olopatadine, N-methyl promethazine, N-methyl trimeprazine, N-methyl chlorprothixene, N-methyl chlorpromazine, N-methyl propiomazine, N-methyl moricizine, N-methyl prochlorperazine, N-methyl thiethylperazine, N-methyl fluphenazine, N-methyl perphenazine, N-methyl flupenthixol, N-methyl acetophenazine, N-methyl trifluoperazine, N-methyl ethacizine, and N-methyl imipramine. These derivatives can be prepared using methods analogous to those described in Schemes 1-5.

Other ion channel blockers that can contain an amine nitrogen which can be guanylated or quaternized as described herein include, without limitation, orphenadrine, phenbenzamine, bepridil, pimozide, penfluridol, flunarizine, fluspirilene, propiverine, disopyramide, methadone, tolterodine, tridihexethyl salts, tripelennamine, mepyramine, brompheniramine, chlorpheniramine, dexchlorpheniramine, carbinoxamine, levomethadyl acetate, gallopamil,

verapamil, devapamil, tiapamil, emopamil, dyclonine, pramoxine, lamotrigine, fendiline, mibefradil, gabapentin, amiloride, diltiazem, nifedipine, nimodipine, nitrendipine, cocaine, mexiletine, propafenone, quinidine, oxethazaine, articaine, riluzole, bencyclane, lifarizine, and strychnine. Still other ion channel blockers can be modified to incorporate a nitrogen atom suitable for quaternization or guanylation. These ion channel blockers include, without limitation, fosphenytoin, ethotoin, phenytoin, carbamazepine, oxcarbazepine, topiramate, zonisamide, and salts of valproic acid.

Examples of these channel blockers, including still other derivatives that can be quaternized or guanylated according to the methods described herein are provided in Table 1.

Table 1

No.	Channel Blocker	Exemplary References
1	orphenadrine	U.S. Patent No. 2,567,351 (see, e.g., the compounds of Examples 1-6 and the formula described at col.1, lines 10-24). U.S. Patent No. 2,991,225 (see, e.g., the structure shown at col. 1, line 25).
2	phenbenzamine (RP-2339; Antergan®),	Passalacqua et al., "Structure and Classification of H_1-Antihistamines and Overview of Their Activities," in *Histamine and H1-antihistamines in Allergic Disease*, F.E.R. Simons, Ed., Informa Health Care (2002).
3	bepridil	U.S. Patent No. 3,962,238 (see, e.g., Formulas I-V and compounds 1-6 of Table 1). US RE30577
4	pimozide	See, e.g., Janssen et al., *Arzneimittel-Forsch.* 18:261, 279, 282 (1968), and *Journal of Neuroscience*, 22(2):396-403 (2002)
5	penfluridol	U.S. Patent No.3,575,990 (see, e.g., the compounds of Formula (I), claims 1-7, and Examples I-XXXIII).
6	flunarizine	U.S. Patent No. 3,773,939 (see, e.g., Formula (I) and the compound described at col. 5, line 40).

No.	Channel Blocker	Exemplary References
7	fluspirilene	U.S. Patent No. 3,238,216 (see, e.g., the compounds recited in any of claims 1-34).
8	propiverine	DD 106643
9	disopyramide	U.S. Patent No. 3,225,054 (see, e.g., the compounds of Examples 1-15 and claims 1-3)
10	methadone	DE711069 U.S. Patent No. 2,983,757
11	tolterodine	U.S. Patent No. 5,382,600 (see, e.g., Formula (I), the compounds described at col.3, lines 20-39, in Table 1, and in claims 1-7)
12	tridihexethyl salts	U.S. Patent No. 2,913,494 (see, e.g., col. 1, lines 15-22)
13	tripelennamine	U.S. Patent No. 2,502,151 (see, e.g., Formula (I) and the compounds recited in claims 1-13)
14	mepyramine (pyrilamine)	U.S. Patent No. 2,502,151
15	brompheniramine	U.S. Patent No. 2,567,245 (see, e.g., the formula described at col. 1, lines 30-45, the compounds of Examples I-XXI, and the compounds recited in claims 1-15) U.S. Patent No. 2,676,964 (see, e.g., the formula described at col.1, lines 5-28, the compounds of Examples I-XLIV, and the compounds recited in claims 1-14) U.S. Patent No. 3,061,517 (see, e.g., the formula at col.1, lines 49-67, and the compounds described at col. 2, lines 17-19, col. 2, lines 40-43, col. 4, lines 2-7, and claims 1-6)
16	chlorpheniramine	U.S. Patent No. 2,567,245 (see, e.g., the

No.	Channel Blocker	Exemplary References
17	dexchlorpheniramine	formula described at col. 1, lines 30-45, the compounds of Examples I-XXI, and the compounds recited in claims 1-15) U.S. Patent No. 2,676,964 (see, e.g., the formula described at col.1, lines 5-28, the compounds of Examples I-XLIV, and the compounds recited in claims 1-14) U.S. Patent No. 3,061,517 (see, e.g., the formula at col.1, lines 49-67, and the compounds described at col. 2, lines 17-19, col. 2, lines 40-43, col. 4, lines 2-7, and claims 1-6)U.S. Patent No. 2,766,174 (see, e.g., the formula described at col. 1, lines 41-72)
18	carbinoxamine	U.S. Patent No. 2,606,195 (see, e.g., the formula described at col. 1, lines 7-24, Examples I-VIII, and in claims 1-3) U.S. Patent No. 2,800,485 GB 905993
19	levomethadyl acetate	Pohland et al., *J. Am. Chem. Soc.* 71:460 (1949)
20	gallopamil	U.S. Patent No. 3,261,859 (see, e.g., Formula (I), Examples 1-28, and claims 1-19) Theodore et al., *J. Org. Chem.* 52:1309 (1987)
21	verapamil	U.S. Patent No. 3,261,859 (see, e.g., Formulas (I) and (IV), Examples 1-28, and claims 1-19)
22	devapamil	Godfraind, *Calcium Channel Blockers*, Birkhauser Verlag (January 2004).
23	tiapamil	
24	emopamil	
25	dyclonine	Pofft, *Chem. Tech. (Berlin)* 4:241 (1952)
26	pramoxine	U.S. Patent No. 2,870,151 (see, e.g., the formula described at col.1, lines 18-25, and the compounds of Examples I-XII and claims 1-13).
27	lamotrigine	EP21121 U.S. Patent No. 4,602,017 (see, e.g., Formulas (I)-(III) and the compounds described at col. 2, line 63-col. 3, line 12, Examples 1-5, and claims 1-2)

No.	Channel Blocker	Exemplary References
28	mibefradil	U.S. Patent No. 4,808,605 (see, e.g., Formula I described at col.1, lines 10-33 and the compounds described at col. 3, line 58-col. 7, line 6, Examples 1-41, and claims 1-15).
29	gabapentin	U.S. Patent No. 4,024,175 (see, e.g., Formula (I) described at col.1, lines 5-17, Examples 1-12, and claims 1-11)
30	amiloride	U.S. Patent No. 3,313,813 (see, e.g., the compounds described at col. 1, line 13-col.2, line 55, Examples 1-205, and claims 1-31)
31	diltiazem	U.S. Patent No. 3,562,257 (see, e.g., Formula (I) described at col.1, lines 39-64, and the compounds described at col. 2, lines 15-30, Tables 1-3, and claims 1-43) U.S. Patent No. 4,552,695 (see, e.g., the compound of Formula (I))
32	nifedipine	U.S. Patent No. 3,485,847 (see, e.g., the Formula described at col. 1, line 40-col. 2, line 6, the compounds of Examples 1-6, and claims 1-27)
33	nimodipine	U.S. Patent No. 3,799,934 (see, e.g., the Formula described at col. 1, lines 39-69, the compounds described at col. 4, line 50-col. 5, line 16, Examples 1-53, and claims 1-13)
34	nitrendipine	
35	mexiletine	U.S. Patent No. 3,954,872 (see, e.g., Formula (I) described at col.1, lines 14-35, and the compounds of Examples 1-6 and claims 1-4)
36	propafenone	DE2001431 (see, e.g., claims 1-4)
37	quinidine	Turner et al., *The Alkaloids*, Vol. 3, 1-63 (1953) Mason et al., *Ann. N.Y. Acad. Sci.* 432:162-176 (1984)
38	oxethazaine	U.S. Patent No. 2,780,646 (see, e.g., the formula described at col. 1, lines 18-42, and the compounds of Examples 1-14 and claims 1-8)
39	articaine	Becker et al., *Anesth Prog.* 53(3): 98–109 (Fall 2006)

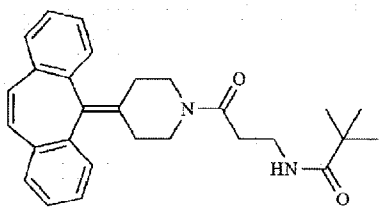
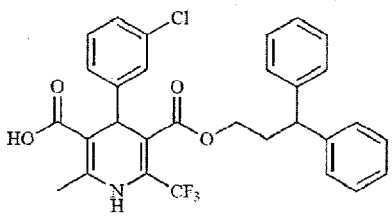
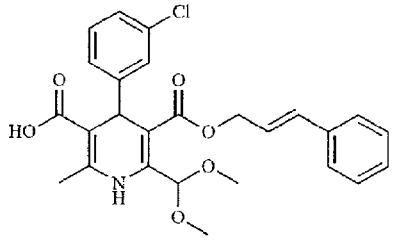
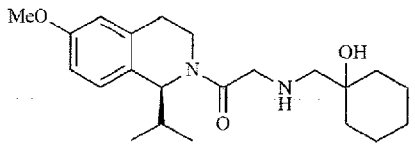
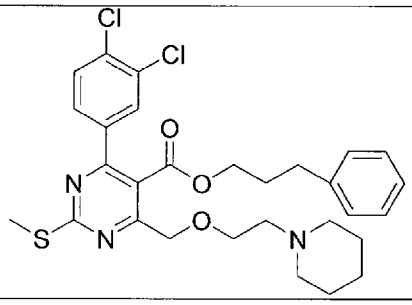
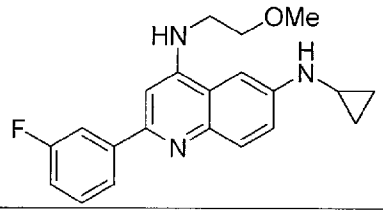
No.	Channel Blocker	Exemplary References
40	riluzole	U.S. Patent No. 4,370,338 (see, e.g., the compound described at col. 1, line 15)
41	bencyclane	HU 151865
42	lifarizine	Grauert et al., *J. Med. Chem.* 45(17):3755-3764 (2002)
43	strychnine	Makarevich et al., "Quaternary salts of alkaloids,"Vol. 42, pages 473-476, *Chemistry of Natural Compounds*, Springer New York: 2006.
44	fendiline	U.S. Patent No. 3,262,977 (see, e.g., Formula (I), Examples 1-9, and the compounds of claims 1-9)

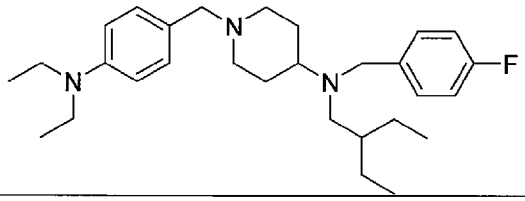
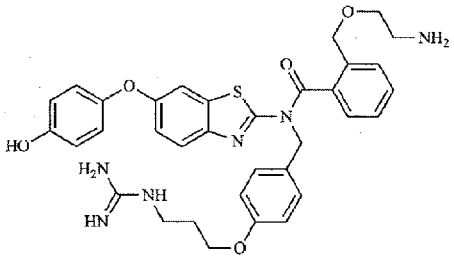
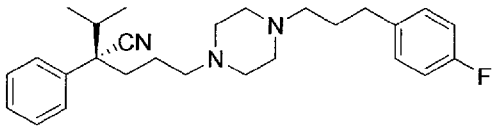
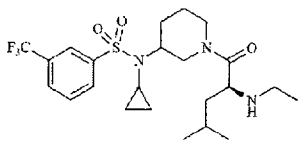
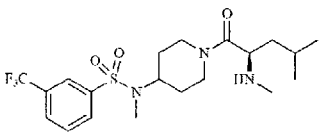
Calcium-Channel Blockers

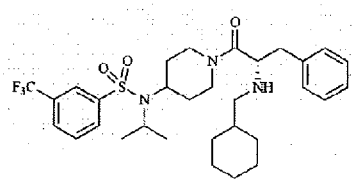
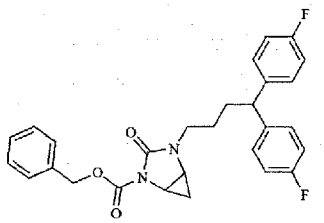
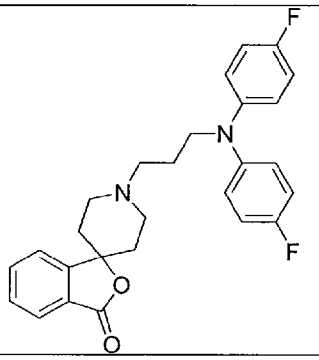
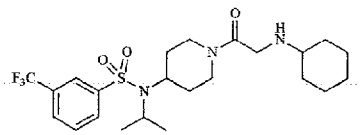
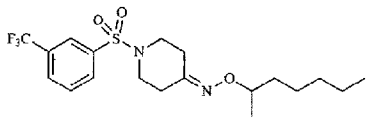
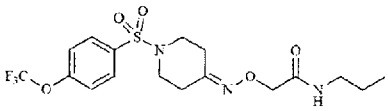
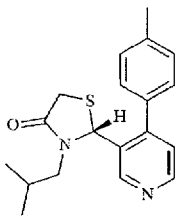
Exemplary cationic calcium channel blockers include D-890, CERM 11888, *N*-methyl-verapamil, *N*-methylgallopamil, *N*-methyl-devapamil, and dodecyltrimethylammonium. Other exemplary compounds include any charged derivative, e.g., a quarternary amine derivative, of verapamil, gallopamil, devapamil, diltiazem, fendiline, mibefradil, terpene compounds (e.g., sesquiterpenes) such as those described in Norman et al. *Agricultural and Biological Chemistry* 49(10):2893-8 (1985), and other inhibitors of calcium channels (see, for example, Triggle, *European Journal of Pharmacology*, 375:311-325 (1999), Eller et al., *British Journal of Pharmacology,* 130:669-677 (2000), and Yamamoto et al., *Current Topics in Medicinal Chemistry*, 9:377-395 (2009), which can be prepared according to the methods described herein.

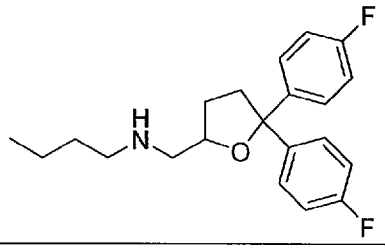
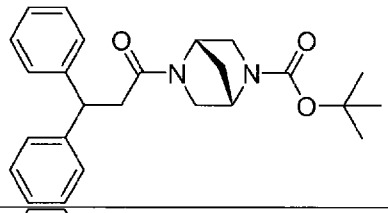
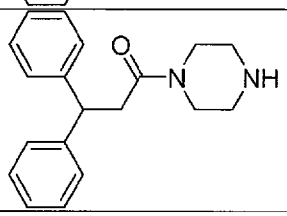
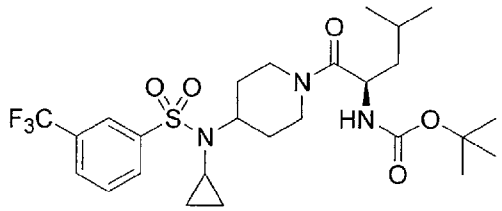
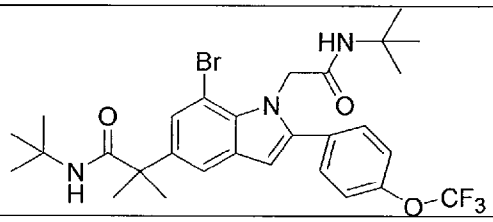
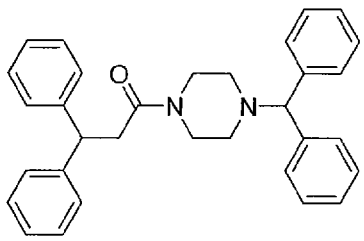
For example, Yamamoto et al. provides the following N-type calcium channel blockers (Table 2), which can be modified (e.g., quaternized or guanylated) according to the methods described herein.

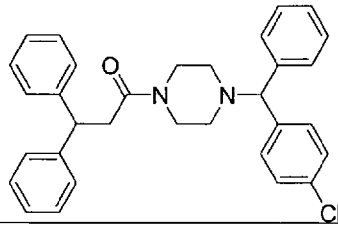
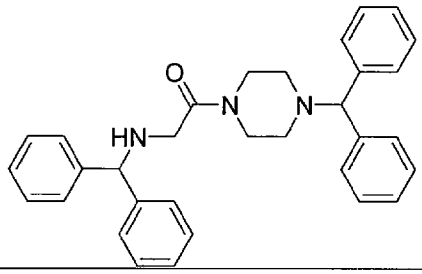
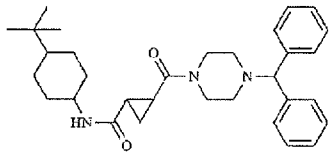
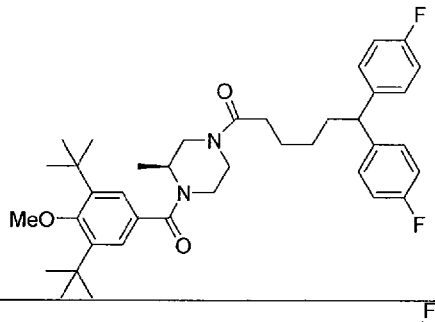
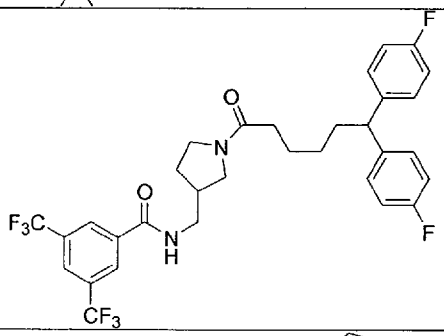
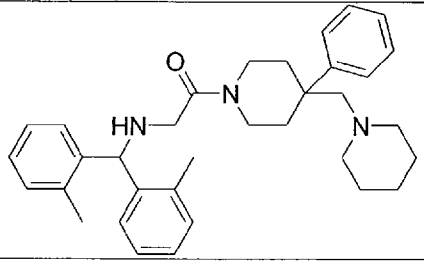
Table 2

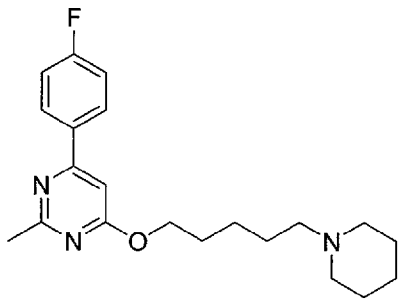
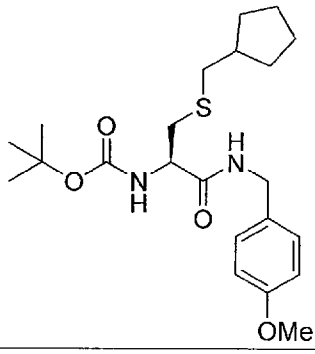
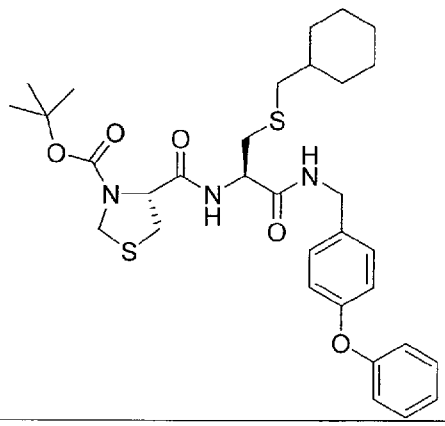
No.	Channel Blocker	Exemplary References
45		Yamamoto et al., *Bioorg. Med. Chem.* 14:5333-5339 (2006).
46		Yamamoto et al., *Bioorg. Med. Chem. Lett.* 16:798-802 (2006).
47		Yamamoto et al., *Bioorg. Med. Chem. Lett.* 18:4813-4815 (2008).
48		See, e.g., WO08143263and EP2149560 (e.g., Formula (I), the compounds of Tables 6-35, 43-110, 126-127, and the compounds of claims 1-6)
49		Miller et al., *Soc. Neurosci. Abstr.* 25(Part 2):896.3 (1999)
50		WO0236567 (see, e.g., formulas I-IV, the compounds of Table 2 (Examples 1-111), and claims 1-5)

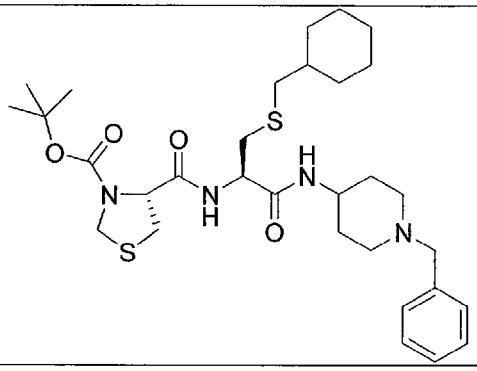
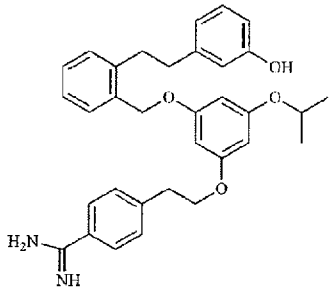
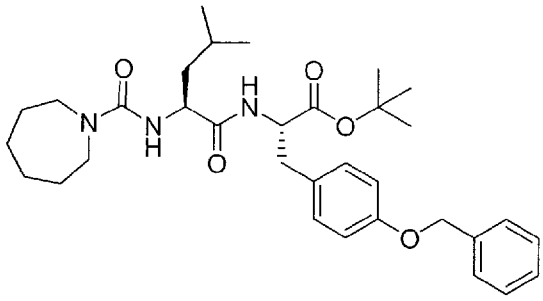
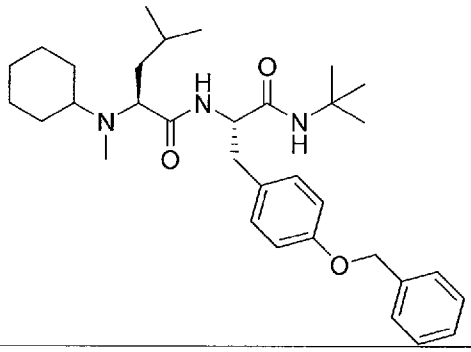
No.	Channel Blocker	Exemplary References
51		Zhang et al., *Eur. J. Pharmacol.* 587:24-47 (2008)
52		Baell et al., *Bioorg. Med. Chem.* 12:4025-4037 (2004)
53		Yamamoto et al., *22nd National Meeting of American Chemical Society*, American Chemical Scoiety: Washington, DC: Chicago, IL 2001; Kaneda et al, *Soc. Neurosci. Abstr.* 27:332.15 (2001); Niidome et al., *Soc. Neurosci. Abstr.* 27:332.14 (2001); and Suzuki et al., *Bioorg. Med. Chem. Lett.* 13:919-922 (2003).
54	E-2051	Kaneda, *Soc. Neurosci. Abstr.* 28:490.1 (2002)
55		WO07110449 (see, e.g., Formulas I-XIII, the compounds described at Paragraphs [0181]-[0183] and Examples 1-14, and claims 1-72)
56		WO06040181 (see, e.g., Formulas I-X, the compounds described at Paragraphs [0105]-[0109] and Examples 1-37, and in claims 1-56)

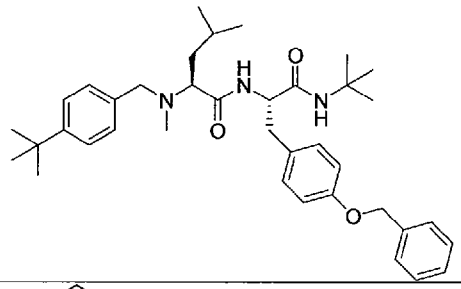
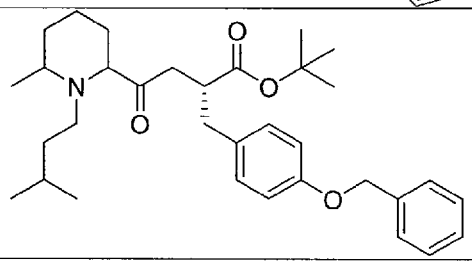
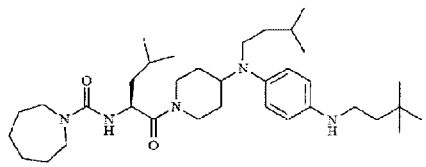
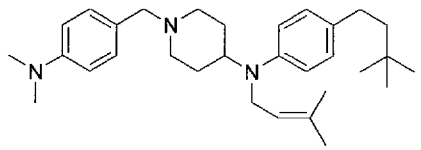
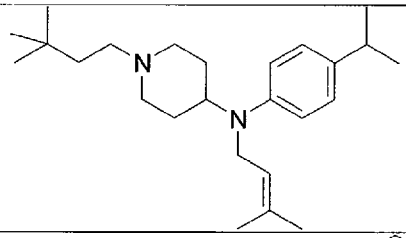
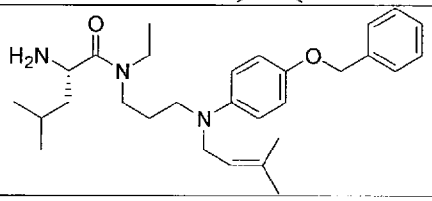
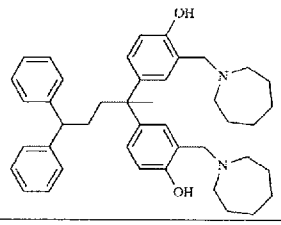
No.	Channel Blocker	Exemplary References
57		WO07118853 (see, e.g., Formulas I-XIII, the compounds described at Paragraph [0320] and Examples 1-19, and the compounds of claims 1-165)
58		WO07085357 (see, e.g., Formulas I-VII, the compounds described at Paragraphs [0065]-[0067], Examples 1-6, and claims 1-16)
59		WO07028638 (see, e.g., Formulas I-XXVI, the compounds described at Paragraphs [0119]-[0123], Examples 1-24, and claims 1-2(
60		WO07118854 (see, e.g., Formulas I-VII and the compounds of Examples 1-11 and claims 1-36)
61		WO08008398 (see, e.g., Formulas I, I', I", II, and II'; Examples 1-377, and claims 1-7)
62		WO08150447 (see, e.g., Formulas I, I', I", and the compounds of Examples 1-135 and claims 1-5
63		Knutsen et al., *Bioorg. Med. Chem. Lett.* 17: 662-667 (2007)

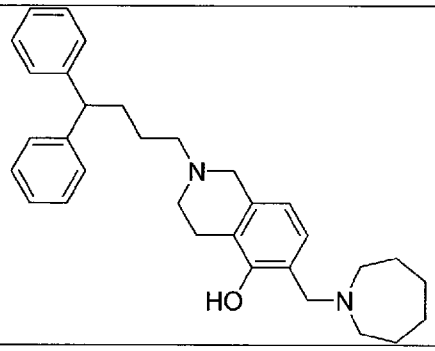
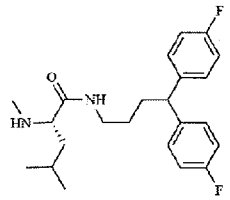
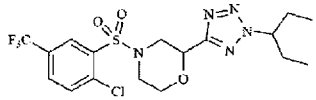
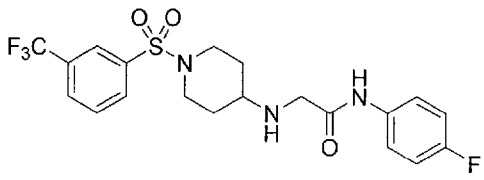
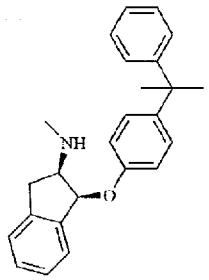
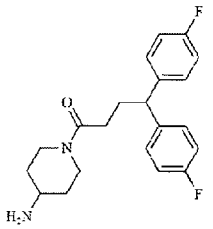
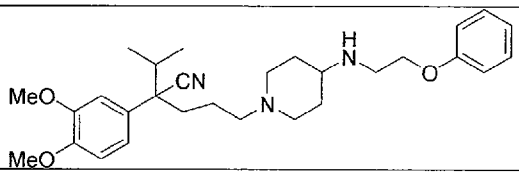
No.	Channel Blocker	Exemplary References
64		O'Neill, *Brain Res.* 888:138-149 (2001); Hicks et al., *Eur. J. Pharmacol.* 408:241-248 (2000)
65		WO07084394 (see, e.g., the compounds of Formulas I and Ia-Ig, and the compounds of Examples 1-11 and claims 1 and 2)
66		WO08066803 (see, e.g., Formulas I and II, the compound of Example 1, and claims 1-11)
67		WO07075524 (see, e.g., Formulas (I), (Ia)-(Ie), the compounds of Examples 1-184, and claims 1-16)
68		WO08133867 (see, e.g., Formulas (I) and (II), the compounds of Examples 1-163, and claims 1-16)
69		WO01045709 (see, e.g., Formula (1), the compounds of Example 4, and claims 24-38) WO06105670 (see, e.g., Formula (1), the compounds described at Paragraphs [0065] and [0066], and claims 1-13)

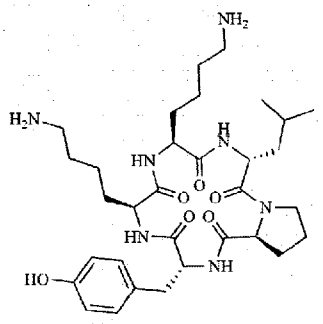
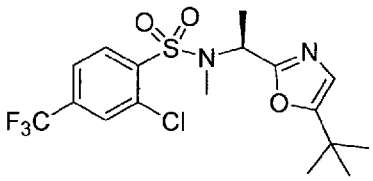
No.	Channel Blocker	Exemplary References
70		WO04089377 (see, e.g., Formula (1), Examples 1-5, original claims 1-13, and amended claims 1-17)
71		WO07071035 (see, e.g., Formula (1), the compounds of Examples 1-18, and claims 20-35)
72		WO08043183 (see, e.g., Formulas (1) and (2), the compounds of Examples 1-16, and claims 16-28)
73		WO04089922 (see, e.g., Formulas (1)-(4), the compounds of Examples 1-9, claims 1-17, and the compounds of Figure 1)
74		WO04105750 (see, e.g., Formulas (1)-(8), the compounds of Examples 1-10, claims 1-23, and Figure 1)
75		WO08031227 (see, e.g., Formulas (1) and (2), the compounds of Examples 1-20, and claims 21-37)

No.	Channel Blocker	Exemplary References
76		Tatsumi et al., *Jpn. J. Pharmacol.* 73:193 (1997); Aoki et al., *Brain Res.* 890:162-169 (2001); Katsumata et al., *Brain Res.* 969:168-174 (2003); Tamura et al., *Brain Res.* 890:170-176 (2001); Shi et al., *J. Thorac. Cardiovasc. Surg.* 129:364-371 (2005); Small, *IDrugs*, 3:460-465 (2000); Suma et al., *Jpn. J. Pharmacol.* 73: 193 (1997); Shimidzu et al., *Naunyn Schmiedebergs Arch. Pharamcol.* 355:601-608 (1997); and Suma et al., *Eur. J. Pharmacol.* 336:283-290 (1997).
77		Seko et al, *Bioorg. Med. Chem. Lett.* 11:2067-2070 (2001)
78		Seko et al., *Bioorg. Med. Chem.* 11:1901-1913 (2003). Seko et al., *Bioorg. Med. Chem. Lett.* 12:915-918 (2002)

No.	Channel Blocker	Exemplary References
79		Seko et al., *Bioorg. Med. Chem. Lett.* 12:2267-2269 (2002)
80		Menzler et al., *Bioorg. Med. Chem. Lett.* 10:345-347 (2000)
81		Malone et al., *217th National Meeting of the American Chemical Society,* American Chemical Society: Washington DC: Anaheim CA 1999; Hu et al., *J. Med. Chem.* 42:4239-4249 (1999)
82		Hu et al., *Bioorg. Med. Chem. Lett.* 9:907-912 (1999)

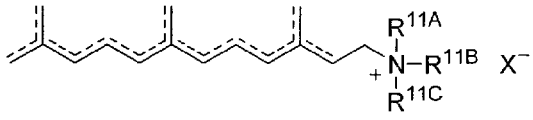
No.	Channel Blocker	Exemplary References
83		Hu et al., *Bioorg. Med. Chem. Lett.* 9:2151-2156 (1999) Ryder et al., *Bioorg. Med. Chem. Lett.* 9:1813-1818 (1999)
84		Hu et al., *Bioorg. Med. Chem. Lett.* 9:1121-1126 (1999)
85		Bennett et al., *Pain* 33:87-107 (1988)
86		Hu et al., *Bioorg. Med. Chem.* 8:1203-1212 (2000)
87		Hu et al., *Bioorg. Med. Chem.* 8:1203-1212 (2000)
88		Hu et al., *J. Med. Chem.* 42:4239-4249 (1999)
89		Schelkun et al., *Bioorg. Med. Chem. Lett.* 9:2447-2452 (1999).

No.	Channel Blocker	Exemplary References
90		Yuen et al., *Bioorg. Med. Chem. Lett.* 8:2415-2418 (1998)
91		Song et al., *J. Med. Chem.* 43:3474-3477 (2000)
92		WO07125398 (see, e.g., Formula (I), the compounds of Examples 1-29, and claims 1-9)
93		WO08124118 (see, e.g., Formula I-VI, the compounds of Paragraphs [0129] and Examples 1-5, and claims 1-42)
94		Campbell et al., *Eur. J. Pharmacol.* 401:419-428 (2000)
95		Teodori et al., *J. Med. Chem.* 47:6070-6081 (2004)
96		Teodori et al., *J. Med. Chem.* 47:6070-6081 (2004)

No.	Channel Blocker	Exemplary References
97		Schroeder et al., *Mol. Divers.* 8:127-134 (2004).
98		WO06030211 (see, e.g., Formula (I), the compounds described at page 9, line 17-page 15, line 12, Examples 1-99, and claims 1-12)

Farnesyl Amine Compounds

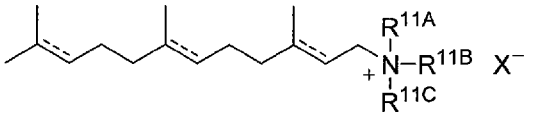
Compounds having a structure according to Formula (XI) can also be used in the invention as calcium channel blockers.



(XI),

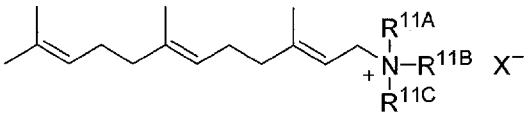
where each R^{11A}, R^{11B}, and R^{11C} is selected, independently, from H or C_{1-4} alkyl, and where 0, 1, 2, or 3 of the dashed bonds represents a carbon-carbon double bond (i.e., compounds of Formula (XI) can include 0, 1, 2, or 3 double bonds), provided that when 2 or 3 carbon-carbon double bonds are present, the double bonds are not adjacent to one another. Compounds that include 0, 1, or 2 double bonds can be prepared according to methods known in the literature, e.g., partial or total hydrogenation of the parent triene.

In some embodiments, compounds of Formula (XI) can be represented by the following formula (XI-A),



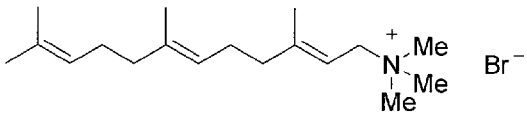
(XI-A), where each R^{11A}, R^{11B}, R^{11C}, and X is according to Formula (XI), and where each dashed bond represents an optional carbon-carbon double bond.

Still other farnesyl amine compounds can include those compounds that have a structure according to Formula (XI-B),



(XI-B), where each R^{11A}, R^{11B}, R^{11C}, and X is according to Formula (XI).

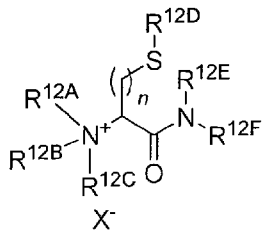
Exemplary compounds of Formula (XI) include



(99).

Cysteine-Derived Compounds

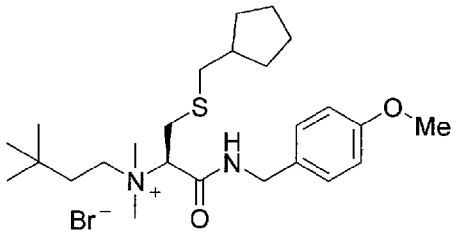
Amino acid derivatives, e.g., those described in U.S. Patent No. 7,166,590 or in Seko et al., *Bioorg. Med. Chem. Lett.* 11(16):2067-2070 (2001), each of which is herein incorporated by reference, can also be used in the invention. For example, compounds having a structure according to Formula (XII) can be N-type calcium channel blockers.



(XII), wherein each of R^{12A}, R^{12B}, R^{12C}, and R^{12D} is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; or R^{12A} and R^{12B} together complete a heterocyclic ring having at least one nitrogen atom, n is an integer between 1-5, each of R^{12E} and R^{12F} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14}

alkaryl, C_{3-10} alkcycloalkyl, or C_{3-10} alkheterocyclyl, and X is any pharmaceutically acceptable anion.

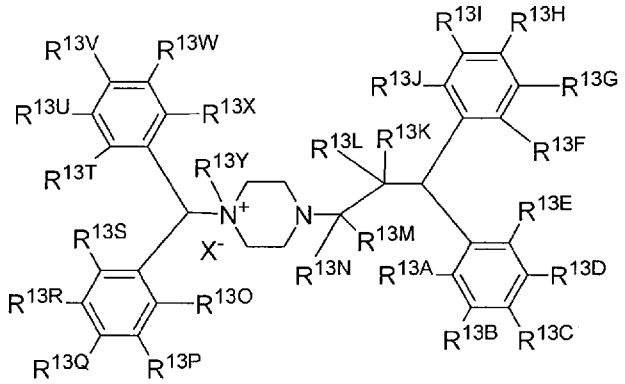
Exemplary compounds of Formula (XII) include



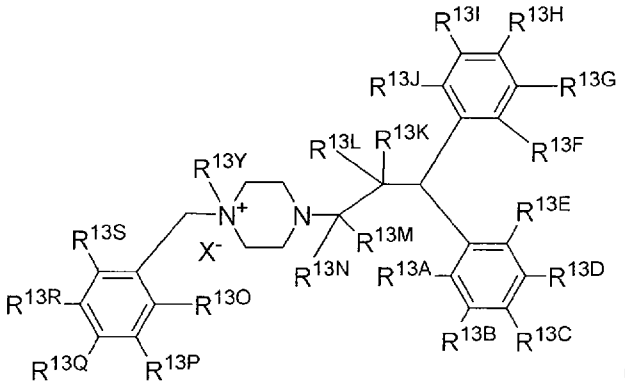
(100).

Flunarizine and Related Compounds

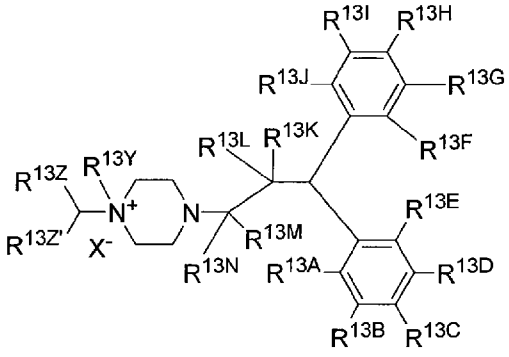
Still other compounds that can be used in the invention are charged derivatives of flunarizine and related compounds (see, e.g., U.S. Patent Nos. 2,883,271 and 3,773,939, as well as Zamponi et al., *Bioorg. Med. Chem. Lett.* 19: 6467 (2009)), each of which is hereby incorporated by reference. For example, compounds according to Formulas (XIII-A), (XIII-B), and (XIII-C) can be prepared according to, e.g., Zamponi et al., and used in the invention,



(XIII-A),



(XIII-B), and



(XIII-C),

where each R^{13A}-R^{13J} and R^{13O}-R^{13T} is selected, independently, from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl, OR^{13AA}, $NR^{13AB}R^{13AC}$, $NR^{13AD}C(O)R^{13AE}$, $S(O)R^{13AF}$, $SO_2R^{13AG}R^{13AH}$, $SO_2NR^{13AI}R^{13AJ}$, SO_3R^{13AK}, CO_2R^{13AL}, $C(O)R^{13AM}$, and $C(O)NR^{13AN}R^{13AO}$; and each of R^{13AA}-R^{13AO} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

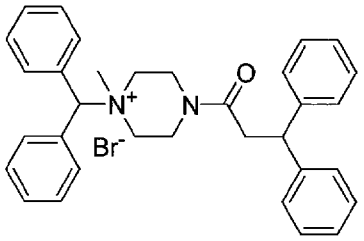
each R^{13K}, R^{13L}, R^{13M}, and R^{13N} is, independently, H or C_{1-4} alkyl, or R^{13K} and R^{13L}, or R^{13M} and R^{13N}, combine to form C=O, or R^{13K} and R^{13M} combine to form C=C;

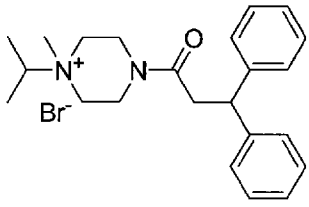
R^{13Y} is H or C_{1-4} alkyl;

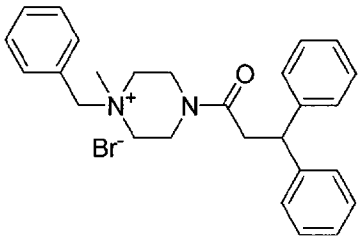
R^{13Z} and $R^{13Z'}$ are, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; and

X^- is any pharmaceutically acceptable anion.

Exemplary compounds according to Formulas (XIII-A)-(XIII-C) include

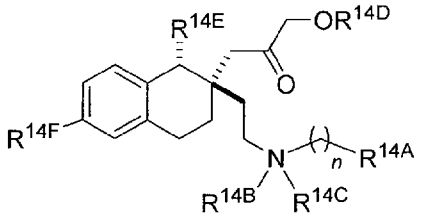

(101),


(102), and


(103).

Mibefradil Derivatives

Derivatives of mibrefradil, such as those described in U.S. Patent No. 4,808,605, hereby incorporated by reference can also be used. Exemplary mibrefadil derivatives include compounds of Formula (XIV),


(XIV), where

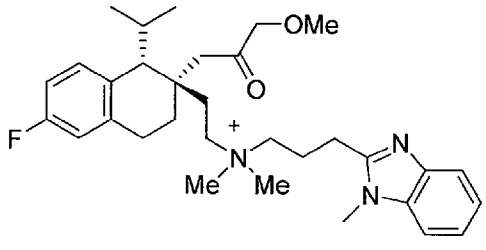
n is an integer between 0-5;

R^{14A} is heterocyclyl (e.g., a heteroaryl such as benzimidazole),

each of R^{14B}, R^{14C}, R^{14D}, and $R1^{4E}$ is, independently, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; and

R^{14F} is selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl, OR^{14G}, $NR^{14H}R^{141}$, $NR^{14J}C(O)R^{14K}$, $S(O)R^{14L}$, $SO_2R^{14M}R^{14N}$, $SO_2NR^{14O}R^{14P}$, SO_3R^{14Q}, CO_2R^{14R}, $C(O)R^{14S}$, and $C(O)NR^{14T}R^{14V}$; and each of R^{14G}-R^{13AO} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl.

An exemplary compound of Formula (XIV) is



(104).

4-Piperidinylaniline Compounds

Charged derivatives of 4-piperidinylaniline compounds (e.g., Compounds (86)-(88) of Table 2) can be prepared according to methods known in the literature and described herein. For example, charged N-alkyl derivatives (e.g., N-methyl) of Compounds (86)-(88) can be prepared and used in the compositions, methods, and kits described herein.

Still other channel blockers that can be quaternized or guanylated according to the methods described herein are described, for example, in PCT Publication No. WO 2004/093813 (see, e.g., Tables 5, 6, and 8), which is herein incorporated by reference. For example, the channel blockers shown in Table 3 can be quaternized or guanylated as described herein.

Table 3

No.	Channel Blocker	Exemplary References
105	Isradipine	
106	Nickel Chloride	
107	A-53930A	JP 08208690
108	AE-0047 Watanidipine dihydrochloride	EP 00424901
109	AGN-190604	*Inflammation*, 19(2):261-275 (1995)
110	AGN-190744	EP372940
111	AH-1058	*European Journal of Pharmacology*, 398(1):107-112 (2000)
112	AHR 5360C	*European Journal of Pharmacology* 146(2-3): 215-22 (1988)

No.	Channel Blocker	Exemplary References
113	AHR 12234	*Archives Internationales de Pharamcodynamie et de Therapie* 301:131-50 (1989)
114	AHR-12742	ZA 08604522
115	AHR-16303B	*Journal of Cardiovascular Pharmacology* 17(1):134-44 (1991)
116	AHR-16462B	*Drug Development Research*, 22(3): 259-271 (1991)
117	AIT 110	
118	AIT 111	
119	AJ 2615	WO 8601203 A1
120	AJ-3941	*Arzneimittel Forschung* 46(6):567-71 (1996)
121	(+)-alismol	JP 04077420 A2
122	AM-336 (synthetic version of CVID marine cone snail venom)	WO9954350
123	AM 543	
124	amlodipine	US 4572902
125	S-(-)amlodipine	GB 2233974 A1
126	AN 132	EP 196648
127	animpamil LU 42668	EP 64158 A1
128	antioquine (alkaloid from stem bark)	*Journal of natural Products* 55(9):1281-6 (1992)
129	AP-1067	IDDB 268934
130	AQ-AH-208	CH 645628 A
131	AR 12456 (derivative of trapidil)	BE 902218 A1 *Cardiovascular Drug Reviews* 9(4):385-397 (1991)
132	aranidipine	US 4446325
133	atosiban	EP 00112809
134	azenidipine CS 905	EP 88266922
135	B 84439	EP 240828
136	barnidipine (derivative of nicardipine)	US 4220649 DE 02904552
137	BAY-E-6927	DE 2117571
138	BAY-K-9320	EP 9206
139	BAY-T-7207	
140	BBR-2160	EP 28204 A2
141	BDF 8784	EP 25111
142	belfosdil/BMY 21891/SR7037	EP 173041 A1
143	Bencylcalne/EGYT-201	FR 151193
144	benipidine/KW3049/Nakadipine	US 4448964
145	bepridil	US 3962238

No.	Channel Blocker	Exemplary References
146	bisaramil/RGH 2957	WO 9622096
147	BK 129	*Methods and Findings in Experimental and Clinical Pharamcology* 14(3):175-81 (1992)
148	BMS-181102	EP 559569
149	BMS-188107	US 5070088
150	BMY 20014	DE 3512995 A1
151	BMY 20064	DE 3512995 A1
152	BMY-43011	*Bioorganic and Medicinal Chemistry Letters*, 3(12):2817-2820 (1993)
153	BN 50149	WO 9323082
154	BN 50175	WO 9323082
155	BN 50394	WO 9323082
156	BR 1022	*Current Science* 83(4):426-431 (2002)
157	BRL 3287A	WO 9323082
158	BRL-32872	WO 09323024
159	buflomedil	US 4326083
160	butoprozine	DE 2707048
161	CAF 603	*Organic and Bioorganic Chemistry*, 22:3349:52 (1994)
162	calciseptine (venom polypeptide)	WO 2000 069900
163	calcium antagonists	WO 9205165
164	calcium channel antagonists	WO 00236586 WO 0236567
165	calcium channel blocker (L-type)	*Journal of Medicinal Chemistry*, 39(15):2922-2938 (1996)
166	calcium channel blockers	EP 400665 A2 US 4965356
167	calcium channel blockers	WO 9526325
168	carvedilol	US 4503067
169	caryachine	*British Journal of Pharmacology*, 116(8):3211-8 (1995)
170	CD-349	EP 92936 A1
171	CD-832	EP 00370821
172	CER-2 metabolite of furnipidine	WO 9919302
173	cerebrocrast	DE 3534385
174	CERM 11956	EP 138684
175	CERM-12816	IDDB 283075
176	CGP 22442	WO 9323082

No.	Channel Blocker	Exemplary References
177	CGP 26797	WO 9323082
178	CGP 28727	WO 9323082
179	CGP 32413	WO 9323082
180	changrolin	*Sci. Sin. (Engl. Ed.)* 22(10):1220-8 (1979)
181	CHF-1521 (combination of delapril and manidipine)	
182	cilnidipine	US 4672068
183	cinnarizine	US 3799934
184	civamide	WO 9640079 US 5840762
185	clentiazem/TA3090	EP 00127882 US 4567175
186	clevidipine	WO 9512578
187	CNS-1067	IDdb 211675
188	CNS-1237	*Annals of the New York Academy of Sciences,* 765 (Neuroprotective Agents):210-29 (1995)
189	CNS-2103 (from spider venom)	WO 9214709 A2
190	COR 28-22	WO 9323082
191	COR 2707C	WO 9323082
192	COR 3752C	WO 9323082
193	CP-060S	WO 9500471 A1
194	CPC-301	IDdb 231888
195	CPC 304	IDdb 185705
196	CPC-317	IDdb 185700
197	CPU 23	*Yaoxue Xuebao*, 25(11): 815-23 (1990) CAN 114:143097
198	CPU-86017	EP 00538844
199	CRE 202	WO 9323082
200	CRE 204	WO 9323082
201	CRE 1005	WO 9323082
202	CRL-42752	WO 00003987
203	cronidipine (LF 2-0254)	EP 240398 A1
204	CV 159	FR 2511370 A1
205	D-2024 (verapamil(S))	WO 09509150
206	D 2603	WO 9323082
207	dagapamil	WO 9323082 EP 64158 A1
208	darodipine PY108068	EP 00000150
209	dauricine NSC 36413	*Acta Pharmacologica Sinica* 7(6): 543-7 (1986)

No.	Channel Blocker	Exemplary References
210	desmethyl verapamil	
211	DHM 9	WO 8604581 A1
212	DHP 218/PAK 9	EP 00121117
213	diclofurime	DE 79-29227999
214	dihydropyridine calcium channel blockers	*Journal of Medicinal Chemistry* 41(4):509-514 (1998)
215	diltiazem	US 3562257
216	diperdipine	EP 00218996
217	dipfluzine	DE 3318577 A1
218	diproteverine BRL 40015	BE 866208
219	dopropidil	EP 00031771
220	dotarizine/FI 6026	US 4883797
221	DTZ-323	*Molecular Pharmacology*, 51(2):262-268 (1997)
222	E-2050	JP 2001199949 A2
223	E 4080	EP 344577 A2
224	efonidipine hydrochloride	US 4885284
225	EG 1088	EP 56637 A1
226	EGIS 3966	DE 4027052 A1
227	eglodipine	DE 3825962 A1
228	emopamil (racemic) SZ 45	DE 3344755 A1
229	(S)-emopamil	DE 3344755 A1
230	enalapril_nitrendipine, Vita-Inveest	EP 00884054
231	etafenonee LG 11457	DE 1265758
232	ethosuximide	
233	eugenodilol	JP 11255719 A2
234	evodiamine	JP 52077098
235	F-0401	EP 00320984
236	falipamil AQA 39	*Journal of Medicinal Chemistry*, 33(5):1496-504 (1990)
237	fantofarone SR 33557	EP 235111 A1 US 4957925
238	fasudil (iv formulation), Asahi	US 4678783
239	FCE-24265	EP 373645 A1
240	FCE-26262	
241	FCE-27335	
242	FCE-27892	
243	FCE-28718	EP 00755931
244	fedopamil	
245	felodipine	US 4264611
246	felodipine+ramipril (Astra/Aventis)	WO 09607400

No.	Channel Blocker	Exemplary References
247	fendiline	US 3262977
248	feniline	
249	flezelastine, D 18024	EP 590551 A2
250	flordipine	
251	fluodipine	US 3773939
252	fluphenazine, S94 SQ 4918 Triflumethazine Vespazine	*Journal of Medicinal Chemistry*, 19(6):850-2 (1976)
253	fostedil KB944	EP 10120
254	FPL 62129	EP 125803 A2
255	FR 46171	
256	FR-172516	JP 09040647
257	FRC 9411	
258	FRG 8653	
259	FRG-8701	
260	furaldipine	
261	furnidipine (CRE 319)	*Journal of Medicinal Chemistry*, 38(15):2830-41 (1995)
262	GOE 5057	
263	GOE 5584 A	EP 173933 A1
264	GOE 93007	
265	GR 60139	
266	GR 55234A (R-enantiomer of telupidine)	*Haemotalogica*, 79(4):328-33 (1994)
267	GR 55235A (L-enantiomer of telupidine)	*Haemotalogica*, 79(4):328-33 (1994)
268	GS-386	
269	GYKI 46544	
270	H32438	
271	HA 22	US 5240947
272	HA 23	US 5240947
273	HA 1004	
274	GA 1077	
275	HE 30346	
276	HNS 32	JP 08311007 A2
277	HOE 166	*Molecular Pharmacology* 33(4):363-9 (1988)
278	HOE 263	
279	HP 406	US 4521537
280	ICI 206970	EP 293170 A1 19881130

No.	Channel Blocker	Exemplary References
281	iganidipine	JP 63225355 A2 19880920
282	IHC 72	*Acta Pharmaceutica Sinica*, 27(6):407-11 (1992)
283	ipenoxazone	
284	isradipine	US 4466972
285	JTV-519	WO 09212148
286	KB 2796	
287	KP-840	*Yakubutsu, Seishin, Kodo*, 12(6):353 (1992)
288	KP 873	
289	KT-362	*Archiv Der Pharmazie*, 328(4):313-6 (1995)
290	KT 2230	*General Pharmacology*, 22(3):443-8 (1991)
291	KW 3049 (see benipidine)	
292	L-366682	EP 00444898
293	L-651582	
294	L 735821	WO 9514471 A1 19950601 *British Journal of Pharmacology*, 132(1):101-110 (2001)
295	lacidipine GR 43659 Sn305	US 4801599 DE 03529997
296	LAS 30356	
297	LAS 30398	
298	LAS 30538	*Journal of Pharmacy and Pharmacology*, 44(10:830-5 (1992)
299	LAS Z077	
300	LCB-2514	
301	lemildipine	P 59152373 A2
302	lercanidipine	US 4705797
303	leualacin	EP 00358418
304	levosemotiadil SA 3212	WO 08700838
305	lidoflazine R7904	US 3267104
306	lifarizine RS 87476	US 0435417
307	LOE-908	
308	lomerizine KB 2796	US 4663325 EP 00158566
309	LU 49700 (main metabolite of gallopamil)	DE 3642331 A1
310	LU 49938	

No.	Channel Blocker	Exemplary References
311	LY-042826	*European Journal of Pharmacology*, 408(3):241-248 (2000)
312	LY-393615	*European Journal of Pharmacology*, 408(3):241-248 (2000)
313	manidipine/CV 4093/franidipine	US 4892875 EP 00094159
314	MCI 176 (MY7674)	EP 169537 A2
315	McN 5691 (see RWJ 26240)	
316	McN-6186	
317	MCN 6497	
318	MD 260792	
319	MDL 143	
320	MDL 12330A	
321	MDL 16582A	WO 9323082
322	MDL 72567	GB 2137622 A1 19841010 CAN 102:95548
323	MEM 1003/nimopidine analog/BAY Z 4406	
324	mepirodipine	
325	mesudipine	
326	mibefradil	EP 00268148 US 4808605
327	minodipine	
328	mioflazine	
329	MJ 14712	
330	monatepil maleate (AD 2615)	WO 08601203 US 4749703
331	MPC 1304	
332	MPC 2101	FR 2514761 A1
333	MR-14134	*Pharmacology*, 51(2):84-95 (1995)
334	N-3601	EP 254322 A1
335	N 20776	
336	N-allyl secoboldine	
337	naltiazem Ro 23-6152	US 4652561
338	NB 818	
339	NC 1100	
340	NC O 700	
341	NCC 09-0026	
342	nexopamil	EP 00271013
343	NH 2250	

No.	Channel Blocker	Exemplary References
344	NH 2716	
345	nicainoprol RU 42924	DE 2934609
346	nicardipine (nifelan)	US 3985847
347	nictiazem	
348	nifedipine	US 3485847
349	nigulipine	WO 8807525 A1
350	niludipine	
351	nilvadipine FK 235	US 4338322 DE 02940833
352	nimodipine	US 3842096
353	misoldipine Bay y 5552	US 4154839
354	nitrendipine Bay k 5009	US 3799934
355	NMDA/calcium channel antagonists, Allelix	WO 09745115
356	NKY 722	
357	NMED 126 (MC-34D)	WO 0145709 A1 US 6387897
358	NMED 427	WO 0145709 A1 US 6387897
359	NMED 724	WO 0145709 A1 US 6387897
360	NMED 826	WO 0145709 A1 US 6387897
361	NMED JM-G-10	WO 0145709 A1 US 6387897
362	NMED 157 39-1B4	WO 0145709 A1 US 6387897
363	NMED 160 39-45-3	WO 0145709 A1 US 6387897
364	NNC-09-0026	WO 9201672
365	NP 252	*Life Sciences*, 48(2):183-8 (1991)
366	NS 626	
367	NS-638	US 5314903 EP 545845 A1
368	NS-649	EP 520200 A2
369	NS-696	
370	NS-7	WO 09607641
371	NS 3034	
372	NZ 105	
373	olradipine S 11568	FR 2602231 A1
374	ONO-2921	WO 0000470 A1
375	OPC 13340	
376	OPC 88117	EP 236140 A2

No.	Channel Blocker	Exemplary References
377	ORG 13020	
378	Org-13061	*Fundamental & Clinical Pharmacology*, 11(5):416-426 (1997)
379	OSAT (nifedipine)	
380	osthole	JP 47000430
381	oxodipine IQB 837V	ES 531033 A1
382	P 0825	
383	P 1268	
384	palonidipine hydrochloride	Ep 128010 A2
385	PCA-50922	
386	PCA-50938	*Brain Research* 772(1,2):57-62 (1997)
387	PCA-50941	
388	PCA 50982	
389	PD-0204318	WO 9943658 A1
390	PD-029361	IDdb 300520
391	PD 122860	Ep 206747 A2
392	PD 151307	US 6423689 *J. Med. Chem.* 43:3472 (2000)
393	PD-157667	US 5767129
394	PD-158143	WO 9705125 A1
395	PD 173212	
396	PD 175069	WO 9854123 A1
397	PD 176078	WO 9955688 *J. Med. Chem.* 43:3474 (2000)
398	PD 181283	*Bioorganic & Medicinal Chemistry Letters*, 9(16):2453-2458 (1999)
399	pelanserin	
400	perhexiline	GB 1025578
401	petrosynol	*Tetrahedron*, 49(45):10435-8 (1993)
402	PF 244	
403	PFS 1144 (EO 122)	DE 2802208
404	pirmenol	US 4112103
405	pirprofurol	
406		
407	PN 200110	
408	PNU 156654E	WO 9705102 A1
409	pranidipine	EP 00145434
410	prenylamine	
411	propiverine	DD 106643

No.	Channel Blocker	Exemplary References
412	ptilomycalin AM	
413	QM 96233	
414	QM 96159	
415	QM 96127	
416	QX-314	*Biophysical Journal*, 27(1):39-55 (1979)
417	R 56865	EP 184257 A1
418	R 59494	Ep 184257 A1
419	R 71811	
420	Rec 152288	
421	Rec 152375, Rec 15/375	
422	RGH-2716 (TDN 345)	EP 414421 A2
423	RGH 2970	
424	riodipine	
425	Ro-11-2933	EP 00523493
426	Ro 18-3981	
427	Ro 40-5967	
428	RO 445912 dithiane derivatives of tiapamil	*Biochemical Pharmacology*, 50(2):187-96 (1995)
429	ronipamil	
430	RS-5773	EP 00353032
431	RS 93007	
432	RS 93522	US 4595690
433	RU-43945	WO 9323082 A1
434	RWJ-22108	US 04845225
435	RWJ-22726	US 04845225
436	RWJ 26240 McN 5691	EP 146721 A2
437	RWJ 26899	EP 237191 A1
438	RJW-26902	
439	RWJ-29009	EP 00493048
440	RWJ-37868	WO 0048584
441	ryanodine	
442	S-(-)-amlodipine	
443	S 11568	
444	S 12967	ZA 9000231 A
445	S-12968	EP 00406502
446	S-2150	Ep 00615971
447	S-312-d	JP 03052890
448	S 830327	
449	SA 2572	JP 63104969 A2
450	SA 2995	
451	SA 3212	
452	sabeluzole	Ep 184257 A1

No.	Channel Blocker	Exemplary References
453	safinamide	EP 400495 A1
454	sagandipine	
455	salicylaldoxime	*Clinical and Experimental Pharmacology and Physiology* 26(12):964-9 (1999)
456	SANK-71996	
457	SB-201823A	WO 09202502
458	SB-206284A	
459	SB 221420A	WO 9002494 A1
460	SB-237376	WO 0209761 A2
461	SB 262470	WO 0183546 A1
462	SC 30552	
463	SDZ-249482	
464	selodipine	
465	semotiadil (SD 3211)	US 4786635 JP 09012576
466	SIM 6080	Ep 293925 A2
467	sipatrigine	EP 372934 A2
468	sinomenine (active from a Chinese medicinal plant)	WO 0269971 A1
469	siratiazem	WO 09117153
470	SKF-45675	
471	SKF-96365	*European Journal of Pharmacology* 188(6):417-21 (1990)
472	SKT-M-26	
473	SL-34.0829	WO 0209761 A2
474	SL 651708	
475	SL 851016	
476	SL-870495	
477	SM-6586	EP 00177965
478	SNX-124	
479	SNX 185	WO 9310145 A1
480	SNX-236	WO 09313128
481	SNX-239	*Pain*, 60(1):83-90 (1995)
482	SNX-483 (peptides from tarantula venom)	WO 9805780 A2
483	sornidipine	
484	SQ 31486	EP 205334 A2
485	SQ 31727	
486	SQ 31765	
487	SQ 32321	
488	SQ 32324	

No.	Channel Blocker	Exemplary References
489	SQ 32547	EP 400665 A2
490	SQ 32926	EP 400665 A2
491	SQ-33351	WO 09006118
492	SQ 33537	
493	SQ 34399	
494	SR-33805	EP 576347 A1
495	SUN 5647	
496	SUN 6087	
497	SUN-N8075	WO 9923072 A2
498	T-477	EP 00441539
499	TA-993	JP 01050872
500	taludipine	
501	tamolarizine	EP 00354068
502	TDN-345	
503	Teczem	
504	temiverine	CAN 131:193592
505	terflavoxate	EP 72620 A1
506	terodiline TD 758	US 3371014
507	tetrandrine	*Clinical and Experimental Pharmacology and Physiology*, 23(8):715-753 (1996)
508	TH-1177	
509	TH-9229	WO 09607415
510	thapsigargin	*British Journal of Pharmacology*, 95(3):705-712 (1985)
511	tiapamil	
512	tinctormine	*Chemical & Pharmaceutical Bulletin* 40(12):3355-7 (1992)
513	TJN 220 (O-ethylfangchinoline)	JP 63179878 A2
514	TMB 8	*Journal of Cell Science* 79:151-160 (1985)
515	TN-871	*European Journal of Pharmacology* 342 (2/3):167-175 (1998)
516	TR 2957	
517	trapidil	
518	trimetazidine	US 3262852
519	TY-10835	*Pharmacometrics*, 1998, 54:3 (153)
520	U-88999	WO 9204338
521	U-92032	WO 09204338
522	U-92798	WO 9204338 A1

No.	Channel Blocker	Exemplary References
523	UK 1745	EP 653426 A1
524	UK-51656	EP 00089167
525	UK 52831	JP 59118782 A2
526	UK 55444	EP 00132375
527	UK 56593	
528	UK-84149	EP 404359 A1
529	ULAH 99	*European Journal of Pharmacology*, 229(1):55-62 (1992)
530	vantanipidine	EP 257616 A2
531	verapamil, verelan	US 3261859
532	S-verapamil, D-2024, levoverapamil	WO 09509150
533	vexibinol Sophoraflavanone G	*Chemical and Pharmaceutical Bulletin* 38(4):1039-44 (1990)
534	vinigrol	
535	vintoperol RGH 2981 RT 303	WO 9207851
536	vingrol	
537	vintoperol/RGH 2981/RT 303	WO 9207851
538	VUF-8929	EP 467435 A2
539	VULM 993	
540	vantanipidine	Ep 257616 A2
541	W 787	
542	WAS 4206	
543	WK 269	
544	WY 27569	
545	WY 44644	
546	WY 44705	
547	WY 46622	
548	WY 47324	
549	xanthonolol	US 5495005
550	Y 19638	
551	Y-22516	WO 9323082
552	Y 208835	
553	YC 114	
554	YH-334	EP 00366548
555	YM 15430-1 (see YM 430)	
556	YM-16151-4 (YM 151)	EP 00167371
557	YM-430 (YM 15430)	WO 0209761 A2
558	YS 035	BE 897244
559	YS 161	
560	Z-6568	*Journal of Mass Spectrometry*, 31(1):37-46 (1996)

No.	Channel Blocker	Exemplary References
561	ziconotiide omega conotoxin/MVIIA/SNX-111	WO 9107980
562	ZM-224832	EP 00343865
563	zonisamide	US 4172896

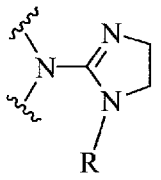
Synthesis

The synthesis of charge-modified ion channel blockers may involve the selective protection and deprotection of alcohols, amines, ketones, sulfhydryls or carboxyl functional groups of the parent ion channel blocker, the linker, the bulky group, and/or the charged group. For example, commonly used protecting groups for amines include carbamates, such as *tert*-butyl, benzyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 9-fluorenylmethyl, allyl, and m-nitrophenyl. Other commonly used protecting groups for amines include amides, such as formamides, acetamides, trifluoroacetamides, sulfonamides, trifluoromethanesulfonyl amides, trimethylsilylethanesulfonamides, and *tert*-butylsulfonyl amides. Examples of commonly used protecting groups for carboxyls include esters, such as methyl, ethyl, *tert*-butyl, 9-fluorenylmethyl, 2-(trimethylsilyl)ethoxy methyl, benzyl, diphenylmethyl, O-nitrobenzyl, ortho-esters, and halo-esters. Examples of commonly used protecting groups for alcohols include ethers, such as methyl, methoxymethyl, methoxyethoxymethyl, methylthiomethyl, benzyloxymethyl, tetrahydropyranyl, ethoxyethyl, benzyl, 2-napthylmethyl, O-nitrobenzyl, P-nitrobenzyl, P-methoxybenzyl, 9-phenylxanthyl, trityl (including methoxy-trityls), and silyl ethers. Examples of commonly used protecting groups for sulfhydryls include many of the same protecting groups used for hydroxyls. In addition, sulfhydryls can be protected in a reduced form (e.g., as disulfides) or an oxidized form (e.g., as sulfonic acids, sulfonic esters, or sulfonic amides). Protecting groups can be chosen such that selective conditions (e.g., acidic conditions, basic conditions, catalysis by a nucleophile, catalysis by a Lewis acid, or hydrogenation) are required to remove each, exclusive of other protecting groups in a molecule. The conditions required for the addition of protecting groups to amine, alcohol,

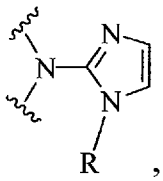
sulfhydryl, and carboxyl functionalities and the conditions required for their removal are provided in detail in T.W. Green and P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd Ed.), John Wiley & Sons, 1991 and P.J. Kocienski, Protecting Groups, Georg Thieme Verlag, 1994.

Charge-modified ion channel blockers can be prepared using techniques familiar to those skilled in the art. The modifications can be made, for example, by alkylation of the parent ion channel blocker using the techniques described by J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, John Wiley & Sons, Inc., 1992, page 617. The conversion of amino groups to guanidine groups can be accomplished using standard synthetic protocols. For example, Mosher has described a general method for preparing mono-substituted guanidines by reaction of aminoiminomethanesulfonic acid with amines (Kim et al., *Tetrahedron Lett.* 29:3183 (1988)). A more convenient method for guanylation of primary and secondary amines was developed by Bernatowicz employing *1*H-pyrazole-1-carboxamidine hydrochloride; 1-H-pyrazole-1-(N,N'-*bis*(*ter*t-butoxycarbonyl)carboxamidine; or 1-II-pyrazole-1-(N,N'-*bis*(benzyloxycarbonyl)carboxamidine. These reagents react with amines to give mono-substituted guanidines (see Bernatowicz et al., *J. Org. Chem.* 57:2497 (1992); and Bernatowicz et al., *Tetrahedron Lett.* 34:3389 (1993)). In addition, thioureas and S-alkyl-isothioureas have been shown to be useful intermediates in the syntheses of substituted guanidines (Poss et al., *Tetrahedron Lett.* 33:5933 (1992)). In certain embodiments, the guanidine is part of a heterocyclic ring having two nitrogen atoms (see, for example, the structures below).

The ring system can include an alkylene or



and



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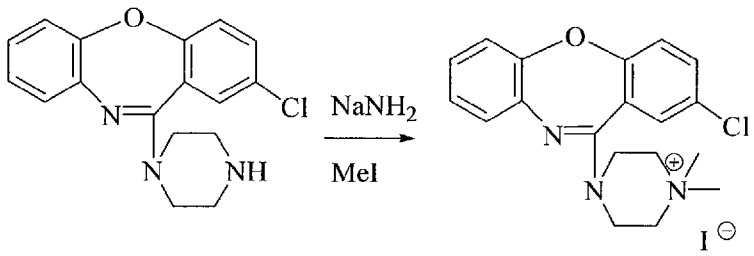
alkenylene of from 2 to 4 carbon atoms, e.g., ring systems of 5, 6, and 7-membered rings. Such ring systems can be prepared, for example, using the methods disclosed by Schlama et al., *J. Org. Chem.* 62:4200 (1997).

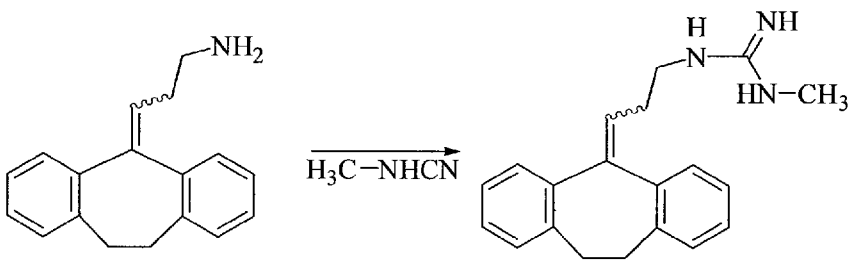
Charge-modified ion channel blockers can be prepared by alkylation of an amine nitrogen in the parent compound as shown in Scheme 1.

Scheme 1

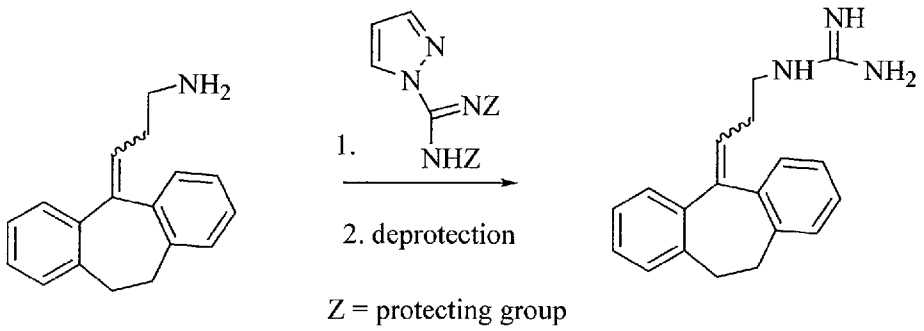


Alternatively, charge-modified ion channel blockers can be prepared by introduction of a guanidine group. The parent compound can be reacted with a cynamide, e.g., methylcyanamide, as shown in Scheme 2 or pyrazole-1-carboxamidine derivatives as shown in Scheme 3 where Z is H or a suitable protecting group. Alternatively, the parent compound can be reacted with cyanogens bromide followed by reaction with methylchloroaluminum amide as shown in Scheme 4. Reagents such as 2-(methylthio)-2-imidazoline can also be used to prepare suitably functionalized derivatives (Scheme 5).

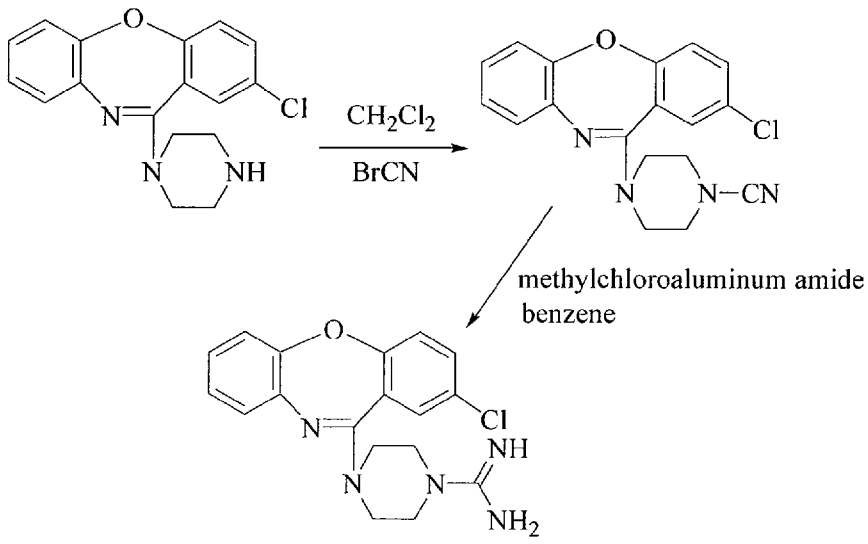
Scheme 2



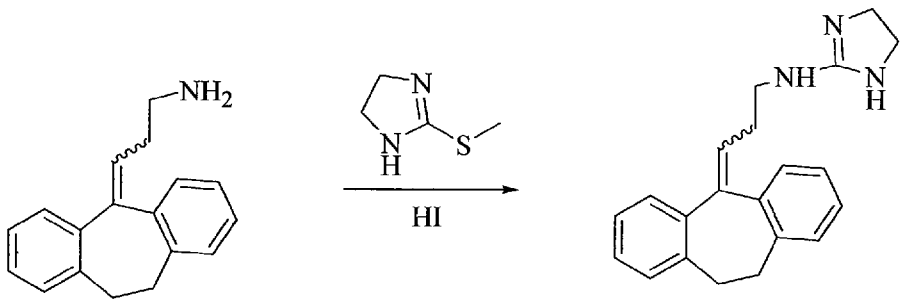
Scheme 3



Scheme 4



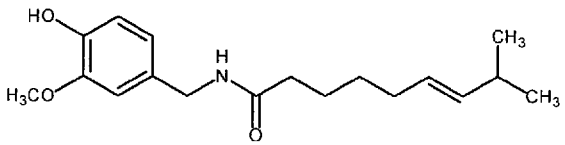
Scheme 5



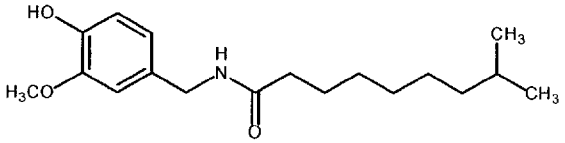
Any ion channel blocker containing an amine nitrogen atom (e.g., a compound selected from Compounds (1)-(563) or a compound according to Formulas (I)-(XIV)) can be modified as shown in Schemes 1-5.

TRPV1 Agonists

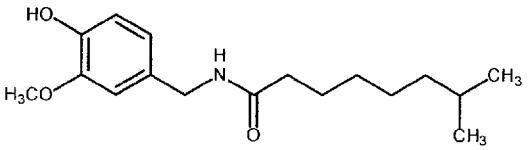
TRPV1 agonists that can be employed in the methods and kits of the invention include but are not limited to any that activates TRPV1 receptors on nociceptors and allows for entry of at least one inhibitor of voltage-gated ion channels. A suitable TRPV1 agonist is capsaicin or another capsaicinoids, which are members of the vanilloid family of molecules. Naturally occurring capsaicinoids are capsaicin itself, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, and nonivamide, whose structures are provided below.



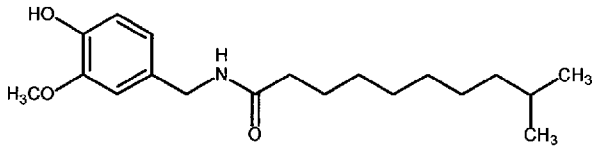
capsaicin



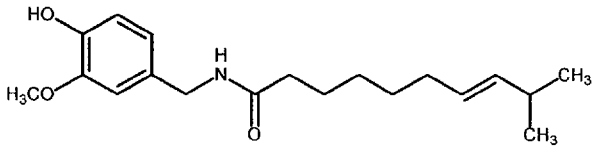
dihydrocapsaicin



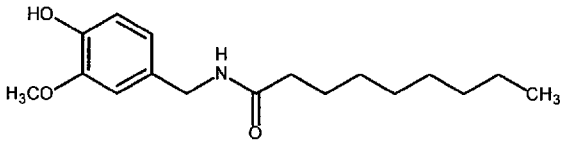
nordihydrocapsaicin



homodihydrocapsaicin



homocapsaicin



nonivamide

Other suitable capsaicinoids and capsaicinoid analogs and derivatives for use in the compositions and methods of the present invention include naturally occurring and synthetic capsaicin derivatives and analogs including, e.g., vanilloids (e.g., N-vanillyl-alkanedienamides, N-vanillyl-alkanedienyls, and N-vanillyl-cis-monounsaturated alkenamides), capsiate, dihydrocapsiate, nordihydrocapsiate and other capsinoids, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, resiniferatoxin, tinyatoxin, civamide, N-phenylmethylalkenamide capsaicin derivatives, olvanil, N-[(4-(2-aminoethoxy)-3-methoxyphenyl)methyl]-9Z-octa-decanamide, N-oleyl-homovanillamide, triprenyl phenols (e.g., scutigeral), gingerols, piperines, shogaols, guaiacol, eugenol, zingerone, nuvanil, NE-19550, NE-21610, and NE-28345. Additional capsaicinoids, their structures, and methods of their manufacture are described in U.S. Patent Nos. 7,446,226 and 7,429,673, which are hereby incorporated by reference.

Additional suitable TRPV1 agonists include but are not limited to eugenol, arvanil (N-arachidonoylvanillamine), anandamide, 2-aminoethoxydiphenyl borate (2APB), AM404, resiniferatoxin, phorbol 12-phenylacetate 13-acetate 20-homovanillate (PPAHV), olvanil (NE 19550), OLDA (*N*-oleoyldopamine), *N*-arachidonyldopamine (NADA), 6'-iodoresiniferatoxin (6'-IRTX), C18 N-acylethanolamines, lipoxygenase derivatives such as 12-hydroperoxycicosatctraenoic acid, inhibitor cysteine

knot (ICK) peptides (vanillotoxins), piperine, MSK195 (N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-2-[4-(2-aminoethoxy)-3-methoxyphenyl]acetamide), JYL79 (N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N′-(4-hydroxy-3-methoxybenzyl)thiourea), hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 10-shogaol, oleylgingerol, oleylshogaol, and SU200 (N-(4-tert-butylbenzyl)-N′-(4-hydroxy-3-methoxybenzyl)thiourea).

Still other TRPV1 agonists include amylocaine, articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine (novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), and trimecaine.

TRP1A Agonists

TRP1A agonists that can be employed in the methods and kits of the invention include any that activates TRP1A receptors on nociceptors or pruriceptors and allows for entry of at least one inhibitor of voltage-gated ion channels. Suitable TRP1A agonists include but are not limited to cinnamaldehyde, allyl-isothiocynanate, diallyl disulfide, icilin, cinnamon oil, wintergreen oil, clove oil, acrolein, hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 4-hydroxynonenal, methyl p-hydroxybenzoate, mustard oil, and 3'-carbamoylbiphenyl-3-yl cyclohexylcarbamate (URB597). Still other agonists include amylocaine, articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine (novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), and trimecaine.

P2X Agonists

P2X agonists that can be employed in the methods and kits of the invention include any that activates P2X receptors on nociceptors or pruriceptors and allows for entry of at least one inhibitor of voltage-gated ion channels. Suitable P2X agonists include but are not limited to 2-methylthio-ATP, 2' and 3'-*O*-(4-benzoylbenzoyl)-ATP, and ATP5'-*O*-(3-thiotriphosphate).

TRPM8 Agonists

TRPM8 agonists that can be employed in the methods and kits of the invention include any that activates TRPM8 receptors on nociceptors or pruriceptors and allows for entry of at least one inhibitor of voltage-gated ion channels. Suitable TRPM8 agonists include but are not limited to menthol, iciclin, eucalyptol, linalool, geraniol, and hydroxycitronellal.

Additional Agents

If desired, one or more additional biologically active agents typically used to treat neurogenic inflammation may be used in combination with a composition of the invention described herein. The biologically active agents include, but are not limited to, acetaminophen, NSAIDs, glucocorticoids, narcotics (e.g. opioids), tricyclic antidepressants, amine transporter inhibitors, anticonvulsants, antiproliferative agents, and immune modulators. The biologically active agents can be administered prior to, concurrent with, or following administration of a composition of the invention, using any formulation, dosing, or administration known in the art that is therapeutically effective.

Non-steroidal anti-inflammatory drugs (NSAIDs) that can be administered to a patient (e.g., a human) suffering from neurogenic inflammation in combination with a composition of the invention include, but are not limited to, acetylsalicylic acid, amoxiprin, benorylate, benorilate, choline magnesium salicylate, diflunisal, ethenzamide, faislamine, methyl salicylate, magnesium salicylate, salicyl salicylate, salicylamide, diclofenac,

aceclofenac, acemethacin, alclofenac, bromfenac, etodolac, indometacin, nabumetone, oxametacin, proglumetacin, sulindac, tolmetin, ibuprofen, alminoprofen, benoxaprofen, carprofen, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuproxam, indoprofen, ketoprofen, ketorolac, loxoprofen, naproxen, oxaprozin, pirprofen,suprofen, tiaprofenic acid, mefenamic acid, flufenamic acid, meclofenamic acid, tolfenamic acid, phenylbutazone, ampyrone, azapropazone, clofezone, kebuzone, metamizole, mofebutazone, oxyphenbutazone, phenazone, sulfinpyrazone, piroxicam, droxicam, lornoxicam, meloxicam, tenoxicam, and the COX-2 inhibitors celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib, and pharmaceutically acceptable salts thereof.

Glucocorticoids that can be administered to a patient (e.g., a human) suffering from neurogenic inflammation in combination with a composition of the invention include, but are not limited to, hydrocortisone, cortisone acetate, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisones acetate, deoxycorticosterone acetate, aldosterone, and pharmaceutically acceptable salts thereof.

Narcotics that can be administered to a patient (e.g., a human) suffering from neurogenic inflammation in combination with a composition of the invention include, but are not limited, to tramadol, hydrocodone, oxycodone, morphine, and pharmaceutically acceptable salts thereof.

Antiproliferative and immune modulatory agents that can be administered to a patient (e.g., a human) suffering from neurogenic inflammation in combination with a composition of the invention include, but are not limited to, alkylating agents, platinum agents, antimetabolites, topoisomerase inhibitors, dihydrofolate reductase inhibitors, antitumor antibiotics, antimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase inhibitors, ribonucleoside reductase inhibitors, TNF-alpha agonists, TNF-alpha antagonists or scavengers, interleukin 1 (IL-1) antagonists or scavengers,

endothelin A receptor antagonists, retinoic acid receptor agonists, hormonal agents, antihormonal agents, photodynamic agents, and tyrosine kinase inhibitors.

Formulation of Compositions

The administration of a combination of the invention may be by any suitable means that results in the reduction of inflammation at the target region (e.g., any inflamed tissue or mucosal surface). The inhibitor(s) of voltage-gated ion channels may be contained in any appropriate amount in any suitable carrier substance, and are generally 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, sublingual, nasal, vaginal, intravesicular, intraurethral, intrathecal, epidural, aural, or ocular administration, or by injection, inhalation, or direct contact with the nasal, genitourinary, gastrointesitnal, reproductive or oral mucosa.

Thus, the composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, 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 (see, e.g., Remington: The Science and Practice of Pharmacy, 20th edition, 2000, ed. A.R. Gennaro, Lippincott Williams & Wilkins, Philadelphia, and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

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. Desirably, the first and second agents are formulated together for the simultaneous or near simultaneous administration of the agents.

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.

Controlled Release Formulations

Each compound of the invention, alone or in combination with one or more of the biologically active agents as described herein, can be formulated for controlled release (e.g., sustained or measured) administration, as described in U.S. Patent Application Publication Nos. 2003/0152637 and 2005/0025765, each incorporated herein by reference. For example, a compound of the invention, alone or in combination with one or more of the biologically active agents as described herein, can be incorporated into a capsule or tablet, that is administered to the site of inflammation.

Any pharmaceutically acceptable vehicle or formulation suitable for local infiltration or injection into a site to be treated (e.g., a painful surgical incision, wound, or joint), that is able to provide a sustained release of compound of the invention, alone or in combination with one or more of the biologically active agents as described herein, may be employed to provide for

prolonged elimination or alleviation of inflammation, as needed. Slow release formulations known in the art include specially coated pellets, polymer formulations or matrices for surgical insertion or as sustained release microparticles, e.g., microspheres or microcapsules, for implantation, insertion, infusion or injection, wherein the slow release of the active medicament is brought about through sustained or controlled diffusion out of the matrix and/or selective breakdown of the coating of the preparation or selective breakdown of a polymer matrix. Other formulations or vehicles for sustained or immediate delivery of an agent to a preferred localized site in a patient include, e.g., suspensions, emulsions, gels, liposomes and any other suitable art known delivery vehicle or formulation acceptable for subcutaneous or intramuscular administration.

A wide variety of biocompatible materials may be utilized as a controlled release carrier to provide the controlled release of a compound of the invention, alone or in combination with one or more biologically active agents, as described herein. Any pharmaceutically acceptable biocompatible polymer known to those skilled in the art may be utilized. It is preferred that the biocompatible controlled release material degrade *in vivo* within about one year, preferably within about 3 months, more preferably within about two months. More preferably, the controlled release material will degrade significantly within one to three months, with at least 50% of the material degrading into non-toxic residues, which are removed by the body, and 100% of the compound of the invention being released within a time period within about two weeks, preferably within about 2 days to about 7 days. A degradable controlled release material should preferably degrade by hydrolysis, either by surface erosion or bulk erosion, so that release is not only sustained but also provides desirable release rates. However, the pharmacokinetic release profile of these formulations may be first order, zero order, bi- or multi-phasic, to provide the desired reversible local anesthetic effect over the desired time period.

Suitable biocompatible polymers can be utilized as the controlled release material. The polymeric material may comprise biocompatible, biodegradable polymers, and in certain preferred embodiments is preferably a copolymer of lactic and glycolic acid. Preferred controlled release materials which are useful in the formulations of the invention include the polyanhydrides, polyesters, co-polymers of lactic acid and glycolic acid (preferably wherein the weight ratio of lactic acid to glycolic acid is no more than 4:1 i.e., 80% or less lactic acid to 20% or more glycolic acid by weight)) and polyorthoesters containing a catalyst or degradation enhancing compound, for example, containing at least 1% by weight anhydride catalyst such as maleic anhydride. Examples of polyesters include polylactic acid, polyglycolic acid and polylactic acid-polyglycolic acid copolymers. Other useful polymers include protein polymers such as collagen, gelatin, fibrin and fibrinogen and polysaccharides such as hyaluronic acid.

The polymeric material may be prepared by any method known to those skilled in the art. For example, where the polymeric material is comprised of a copolymer of lactic and glycolic acid, this copolymer may be prepared by the procedure set forth in U.S. Patent No. 4,293,539, incorporated herein by reference. Alternatively, copolymers of lactic and glycolic acid may be prepared by any other procedure known to those skilled in the art. Other useful polymers include polylactides, polyglycolides, polyanhydrides, polyorthoesters, polycaprolactones, polyphosphazenes, polyphosphoesters, polysaccharides, proteinaceous polymers, soluble derivatives of polysaccharides, soluble derivatives of proteinaceous polymers, polypeptides, polyesters, and polyorthoesters or mixtures or blends of any of these. Pharmaceutically acceptable polyanhydrides which are useful in the present invention have a water-labile anhydride linkage. The rate of drug release can be controlled by the particular polyanhydride polymer utilized and its molecular weight. The polysaccharides may be poly-1,4-glucans, e.g., starch glycogen, amylose, amylopectin, and mixtures thereof. The biodegradable hydrophilic or hydrophobic polymer may be a water-soluble derivative of a poly-1,4-glucan,

including hydrolyzed amylopectin, hydroxyalkyl derivatives of hydrolyzed amylopectin such as hydroxyethyl starch (HES), hydroxyethyl amylose, dialdehyde starch, and the like. The polyanhydride polymer may be branched or linear. Examples of polymers which are useful in the present invention include (in addition to homopolymers and copolymers of poly(lactic acid) and/or poly(glycolic acid)) poly[bis(p-carboxyphenoxy) propane anhydride] (PCPP), poly[bis(p-carboxy)methane anhydride] (PCPM), polyanhydrides of oligomerized unsaturated aliphatic acids, polyanhydride polymers prepared from amino acids which are modified to include an additional carboxylic acid, aromatic polyanhydride compositions, and co-polymers of polyanhydrides with other substances, such as fatty acid terminated polyanhydrides, e.g., polyanhydrides polymerized from monomers of dimers and/or trimers of unsaturated fatty acids or unsaturated aliphatic acids. Polyanhydrides may be prepared in accordance with the methods set forth in U.S. Patent No. 4,757,128, incorporated herein by reference. Polyorthoester polymers may be prepared, e.g., as set forth in U.S. Patent No. 4,070,347, incorporated herein by reference. Polyphosphoesters may be prepared and used as set forth in U.S. Patent Nos. 6,008,318, 6,153,212, 5,952,451, 6,051,576, 6,103,255, 5,176,907 and 5,194,581, each of which is incorporated herein by reference.

Proteinaceous polymers may also be used. Proteinaceous polymers and their soluble derivatives include gelation biodegradable synthetic polypeptides, elastin, alkylated collagen, alkylated elastin, and the like. Biodegradable synthetic polypeptides include poly-(N-hydroxyalkyl)-L-asparagine, poly-(N-hydroxyalkyl)-L-glutamine, copolymers of N-hydroxyalkyl-L-asparagine and N-hydroxyalkyl-L-glutamine with other amino acids. Suggested amino acids include L-alanine, L-lysine, L-phenylalanine, L-valine, L-tyrosine, and the like.

In additional embodiments, the controlled release material, which in effect acts as a carrier for a compound of the invention, alone or in combination with one or more biologically active agents as described herein, can further include a bioadhesive polymer such as pectins (polygalacturonic acid), mucopolysaccharides (hyaluronic acid, mucin) or non-toxic lectins or the

polymer itself may be bioadhesive, e.g., polyanhydride or polysaccharides such as chitosan.

In embodiments where the biodegradable polymer comprises a gel, one such useful polymer is a thermally gelling polymer, e.g., polyethylene oxide, polypropylene oxide (PEO-PPO) block copolymer such as Pluronic™ F127 from BASF Wyandotte. In such cases, the local anesthetic formulation may be injected via syringe as a free-flowing liquid, which gels rapidly above 30°C. (e.g., when injected into a patient). The gel system then releases a steady dose of a compound of the invention, alone or in combination with one or more biologically active agents as described herein, at the site of administration.

Solid Dosage Forms for Oral Use

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.

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 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.

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 (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 bed apparatus or a spray drying equipment.

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., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-hydroxymethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol 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.

The liquid forms in which the compounds and compositions of the present 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.

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.

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 will be indicated in many cases.

Topical Formulations

A composition of the invention, alone or in combination with one or more of the biologically active agents described herein, can also be adapted for topical use with a topical vehicle containing from between 0.0001% and 25% (w/w) or more of active ingredient(s).

In a preferred combination, the active ingredients are preferably each from between 0.0001% to 10% (w/w), more preferably from between 0.0005% to 4% (w/w) active agent. The cream can be applied one to four times daily, or as needed.

Performing the methods described herein, the topical vehicle containing the composition of the invention, or a combination therapy containing a composition of the invention is preferably applied to the site of inflammation on the patient. For example, a cream may be applied to the hands of a patient suffering from arthritic fingers.

Formulations for Nasal and Inhalation Administration

The pharmaceutical compositions of the invention can be formulated for nasal or intranasal administration. Formulations suitable for nasal

administration, when the carrier is a solid, include a coarse powder having a particle size, for example, in the range of approximately 20 to 500 microns which is administered by rapid inhalation through the nasal passage. When the carrier is a liquid, for example, a nasal spray or as nasal drops, one or more of the formulations can be admixed in an aqueous or oily solution, and inhaled or sprayed into the nasal passage.

For administration by inhalation, the active ingredient can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount, Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Examples

The following example is intended to illustrate the invention, and is not intended to limit it.

Example 1: Treatment of Neurogenic Inflammation with Intravenous Injection of QX-314.

Figure 1 is a graph showing the effect of intravenous QX-314 (0.4 mg/kg) on the edema elicited by injection of complete Freund's adjuvant (CFA) in the rat hindpaw determined by measuring the total volume of the hindpaw by plethysmography. The degree of swelling produced by injection of CFA is reduced by administration of QX-314 reflecting reduction in neurogenic edema resulting from the blockade of nociceptors by QX314. QX-314 by itself has no effect different from administration of saline.

Example 2: Entry of N-methyl-verapamil into Dorsal Root Ganglion Neurons Through Capsaicin-Activated TRPV1 Channels

N-methyl-verapamil, a charged derivative of the known calcium channel blocker verapamil and structurally related to D-890, can be loaded into dorsal root ganglion neurons through activation of TRPV1 channels by capsaicin. The internally-loaded N-methyl-verapamil then produces long-lasting inhibition of the voltage-dependent calcium channels in the neurons. Entry of the drug into the cell, and its blocking action, depends on applying the drug in the presence of capsaicin to activate the TRPV1 channels present in the neuronal membrane.

As shown in Figure 2, the inhibition of voltage-dependent calcium channel current in a DRG neuron by N-methyl-verapamil applied in the presence of capsaicin to open TRPV1 channels. The traces show currents through voltage-activated calcium channels in a dissociated rat dorsal root ganglion neuron, recorded in whole-cell mode. Current was carried by 2 mM Ba^{2+} on a background of 155 mM N-methyl-D-glucamine (to eliminate Na current), with an internal CsCl-based solution. Calcium channels were opened by a voltage step from -80 mV to -20 mV. When channels are opened, inward-going current is carried by Ba^{2+} ions flowing into the cell.

Each panel shows calcium channel currents before and 3 minutes after exposure of the cell to either 1 μM capsaicin alone (top panel), 300 μM N-methyl-verapamil alone (middle panel), or 300 μM N-methyl-verapamil applied in the presence of 1 μM capsaicin to open TRPV1 channels (bottom panel). Control experiments using either capsaicin alone or N-methyl-verapamil alone each produce weak, transient effects that are rapidly reversed when the agents are washed away. The combination, however, produces an inhibition of calcium channel currents that persists after washout of the agents, consistent with N-methyl-verapamil having entered through TRPV1 channels and remaining trapped inside the cells, blocking the calcium channels from the inside.

Other Embodiments

Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific desired embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the fields of medicine, immunology, pharmacology, endocrinology, or related fields are intended to be within the scope of the invention.

All publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication was specifically and individually incorporated by reference.

What is claimed is:

Claims

1. A method for treating neurogenic inflammation in a patient, said method comprising administering to said patient a therapeutically effective amount of a compound that is capable of (i) entering a nociceptor through a channel-forming receptor present in said nociceptor when said receptor is activated and (ii) inhibiting a voltage-gated ion channel present in said nociceptor, wherein said compound does not substantially inhibit said channel when applied to the extracellular face of said channel and when said receptor is not activated.

2. The method of claim 1, wherein said compound inhibits voltage-gated sodium channels.

3. The method of claim 2, wherein said compound is QX-314, N-methyl-procaine, QX-222, N-octyl-guanidine, 9-aminoacridine, pancuronium, or another low molecular weight, charged molecule that inhibits voltage-gated sodium channels when present inside of said nociceptor.

4. The method of claim 1, wherein said compound is a quarternary amine derivative or other charged derivative of a compound selected from the group consisting of riluzole, mexilitine, phenytoin, carbamazepine, procaine, tocainide, prilocaine, articaine, bupivicaine, mepivicine, diisopyramide, bencyclane, quinidine, bretylium, lifarizine, lamotrigine, flunarizine, and fluspirilene.

5. The method of claim 1, wherein said compound inhibits calcium channels.

6. The method of claim 5, wherein said compound is selected from

D-890, CERM 11888, *N*-methyl-verapamil, *N*-methylgallopamil, *N*-methyl-devapamil, and dodecyltrimethylammonium;

a quarternary amine derivative of verapamil, gallopamil, devapamil, diltiazem, fendiline, mibefradil, or farnesyl amine;

a compound according to any of Formulas (XI), (XII), (XIII-A), (XIII-B), (XIII-C), and (XIV); and

a quarternary amine derivative or other charged derivative of any of compounds (45)-(563).

7. The method of claim 1, wherein said compound is a quarternary amine derivative or other charged derivative of any of compounds (1)-(563).

8. The method of any of claims 1-7, wherein said channel-forming receptor has been activated prior to said administering of said compound.

9. The method of any of claims 1-8, further comprising administering a second compound that activates said channel-forming receptor.

10. The method of claim 9, wherein said second compound activates a channel-forming receptor selected from TRPV1, P2X(2/3), TRPA1, and TRPM8.

11. The method of claim 10, wherein said second compound is an activator of TRPV1 receptors, said activator selected from capsaicin, a capsaicinoid, eugenol, arvanil (N-arachidonoylvanillamine), anandamide, 2-aminoethoxydiphenyl borate (2APB), AM404, resiniferatoxin, phorbol 12-phenylacetate 13-acetate 20-homovanillate (PPAHV), olvanil (NE 19550), OLDA (*N*-oleoyldopamine), *N*-arachidonyldopamine (NADA), 6'-iodoresiniferatoxin (6'-IRTX), C18 N-acylethanolamines, lipoxygenase derivatives such as 12-hydroperoxyeicosatetraenoic acid, inhibitor cysteine knot (ICK) peptides

(vanillotoxins), piperine, MSK195 (N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-2-[4-(2-aminoethoxy)-3-methoxyphenyl]acetamide), JYL79 (N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N'-(4-hydroxy-3-methoxybenzyl)thiourea), hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 10-shogaol, oleylgingerol, oleylshogaol, SU200 (N-(4-tert-butylbenzyl)-N'-(4-hydroxy-3-methoxybenzyl)thiourea), articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine (novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), or trimecaine.

12. The method of claim 10, wherein said second compound is an activator of TRPA1 receptors, said activator selected from cinnamaldehyde, allyl-isothiocynanate, diallyl disulfide, icilin, cinnamon oil, wintergreen oil, clove oil, acrolein, hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 4-hydroxynonenal, methyl p-hydroxybenzoate, mustard oil, and 3'-carbamoylbiphenyl-3-yl cyclohexylcarbamate (URB597), articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine (novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), or trimecaine.

13. The method of claim 10, wherein said second compound is an activator of P2X receptors, said activator selected from ATP, 2-methylthio-ATP, 2' and 3'-O-(4-benzoylbenzoyl)-ATP, and ATP5'-O-(3-thiotriphosphate).

14. The method of claim 10, wherein said second compound is an activator of TRPM8 receptors, said activator selected from menthol, iciclin, eucalyptol, linalool, geraniol, and hydroxycitronellal.

15. The method of any of claims 1-14, further comprising administering one or more acetaminophens, NSAIDs, glucocorticoids, narcotics, tricyclic antidepressants, amine transporter inhibitors, anticonvulsants, antiproliferative agents, or immune modulators.

16. The method of any of claims 1-14, wherein said method is used to treat asthma, conjunctivitis, sepsis, sinusisitis, cough, arthritis, colitis, contact dermatitis, eczema, gastritis, cystitis, urethritis, migraine headache, psoriasis, rhinitis, rosacea, sunburn, traumatic brain injury, acute lung injury, chemical warfare agents, inhaled tear gases, or inhaled pollutants.

17. The method of any of claims 1-14, wherein said administering comprises intraarticular, surgical, intravenous, intramuscular, oral, rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, vaginal, intraurethral, intravesicular, intrathecal, epidural, mucosal, aural, or ocular administration by injection, inhalation, or direct contact.

18. The method any of claims 1-14, wherein said composition is formulated for controlled or sustained release over time.

19 A kit comprising:

a) a compound that is capable of (i) entering a nociceptor through a channel-forming receptor present in said nociceptor when said receptor is activated and (ii) inhibiting a voltage-gated ion channel present in said nociceptor, wherein

said compound does not substantially inhibit said channel when applied to the extracellular face of said channel and when said receptor is not activated; and

b) instructions for administering said compound to a patient to treat neurogenic inflammation.

20. The kit of claim 19, wherein said compound inhibits voltage-gated sodium channels.

21. The kit of claim 20, wherein said compound is QX-314, N-methyl-procaine, QX-222, N-octyl-guanidine, 9-aminoacridine, pancuronium, or another low molecular weight, charged molecule that inhibits voltage-gated sodium channels when present inside of said nociceptor.

22. The kit of claim 19, wherein said compound is a quarternary amine derivative or other charged derivative of a compound selected from the group consisting of riluzole, mexilitine, phenytoin, carbamazepine, procaine, tocainide, prilocaine, articaine, bupivicaine, mepivicine, diisopyramide, bencyclane, quinidine, bretylium, lifarizine, lamotrigine, flunarizine, and fluspirilene.

23. The kit of claim 19, wherein said compound inhibits calcium channels.

24. The kit of claim 19, wherein said compound is selected from

D-890, CERM 11888, *N*-methyl-verapamil, *N*-methylgallopamil, *N*-methyl-devapamil, and dodecyltrimethylammonium;

a quarternary amine derivative, of verapamil, gallopamil, devapamil, diltiazem, fendiline, mibefradil, or farnesyl amine;

a compound according to any of Formulas(XI), (XII), (XIII-A), (XIII-B), (XIII-C), and (XIV); and

a quarternary amine derivative or other charged derivative of any of compounds (1)-(563).

25. The kit of any of claims 19-24, further comprising:

c) a second compound that activates said channel-forming receptor.

26. The kit of claim 25, wherein said second compound activates a channel-forming receptor selected from TRPV1, P2X(2/3), TRPA1, and TRPM8.

27. The kit of claim 26, wherein said second compound is an activator of TRPV1 receptors, said activator selected from capsaicin, a capsaicinoid, eugenol, arvanil (N-arachidonoylvanillamine), anandamide, 2-aminoethoxydiphenyl borate (2APB), AM404, resiniferatoxin, phorbol 12-phenylacetate 13-acetate 20-homovanillate (PPAHV), olvanil (NE 19550), OLDA (*N*-oleoyldopamine), *N*-arachidonyldopamine (NADA), 6'-iodoresiniferatoxin (6'-IRTX), C18 N-acylethanolamines, lipoxygenase derivatives such as 12-hydroperoxyeicosatetraenoic acid, inhibitor cysteine knot (ICK) peptides (vanillotoxins), piperine, MSK195 (N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-2-[4-(2-aminoethoxy)-3-methoxyphenyl]acetamide), JYL79 (N-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-N'-(4-hydroxy-3-methoxybenzyl)thiourea), hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 10-shogaol, oleylgingerol, oleylshogaol, and SU200 (N-(4-tert-butylbenzyl)-N'-(4-hydroxy-3-methoxybenzyl)thiourea), articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine (novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), or trimecaine.

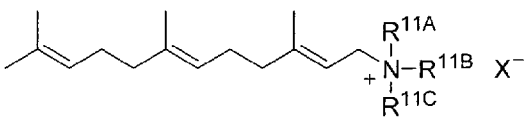
28. The kit of claim 26, wherein said second compound is an activator of TRPA1 receptors, said activator selected from cinnamaldehyde, allyl-isothiocynanate, diallyl disulfide, icilin, cinnamon oil, wintergreen oil, clove oil, acrolein, hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 4-hydroxynonenal, methyl p-hydroxybenzoate, mustard oil, and 3'-carbamoylbiphenyl-3-yl cyclohexylcarbamate (URB597), articaine, benzocaine, bupivacaine, carbocaine, carticaine, chloroprocaine, cyclomethycaine, dibucaine (cinchocaine), dimethocaine (larocaine), etidocaine, hexylcaine, levobupivacaine, lidocaine, mepivacaine, meprylcaine (oracaine), metabutoxycaine, piperocaine, prilocaine, procaine (novacaine), proparacaine, propoxycaine, risocaine, ropivacaine, tetracaine (amethocaine), or trimecaine.

29. The kit of claim 26, wherein said second compound is an activator of P2X receptors, said activator selected from ATP, 2-methylthio-ATP, 2' and 3'-O-(4-benzoylbenzoyl)-ATP, and ATP5'-O-(3-thiotriphosphate).

30. The kit of claim 26, wherein said second compound is an activator of TRPM8 receptors, said activator selected from menthol, iciclin, eucalyptol, linalool, geraniol, and hydroxycitronellal.

31. The kit of any one of claims 19-30, further comprising one or more acetaminophens, NSAIDs, glucocorticoids, narcotics, tricyclic antidepressants, amine transporter inhibitors, anticonvulsants, antiproliferative agents, or immune modulators.

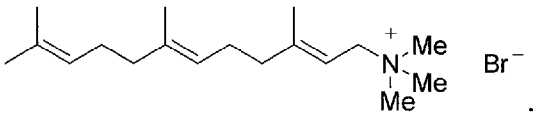
32. A compound according to Formula (XI):



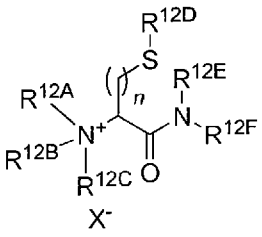
(XI), wherein

each R^{11A}, R^{11B}, and R^{11C} is selected, independently, from H or C_{1-4} alkyl, and X^- is any pharmaceutically acceptable anion.

33. The compound of claim 32, wherein said compound has the following structure:



34. A compound according to Formula (XII),



(XII), wherein

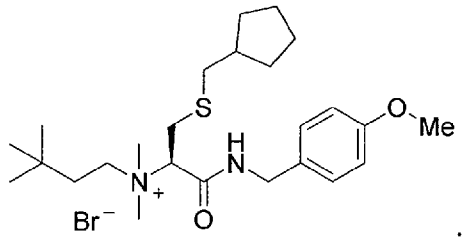
each of R^{12A}, R^{12B}, R^{12C}, and R^{12D} is, independently, selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; or R^{12A} and R^{12B} together complete a heterocyclic ring having at least one nitrogen atom;

n is an integer between 1-5;

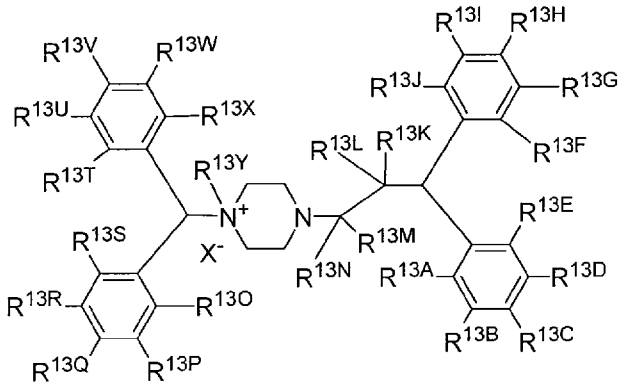
each of R^{12E} and R^{12F} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, or C_{3-10} alkheterocyclyl; and

X is any pharmaceutically acceptable anion.

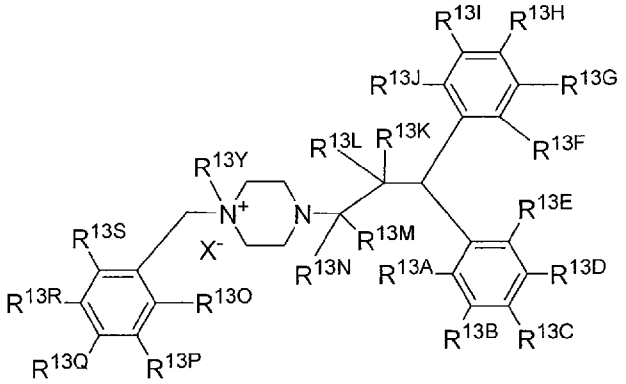
35. The compound of claim 34, wherein said compound has the following structure:



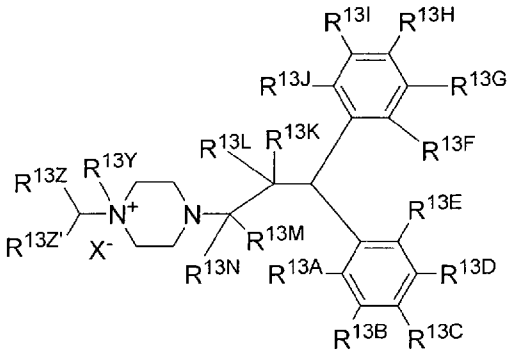
36. A compound having a structure according to:



(XIII-A),



(XIII-B), or



(XIII-C),

wherein

each R^{13A}-R^{13J} and R^{13O}-R^{13T} is selected, independently, from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl, OR^{13AA}, $NR^{13AB}R^{13AC}$, $NR^{13AD}C(O)R^{13AE}$, $S(O)R^{13AF}$, $SO_2R^{13AG}R^{13AH}$, $SO_2NR^{13AI}R^{13AJ}$, SO_3R^{13AK}, CO_2R^{13AL}, $C(O)R^{13AM}$, and $C(O)NR^{13AN}R^{13AO}$;

each of R^{13AA}-R^{13AO} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl;

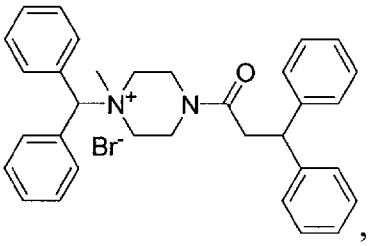
each R^{13K}, R^{13L}, R^{13M}, and R^{13N} is, independently, H or C_{1-4} alkyl, or R^{13K} and R^{13L}, or R^{13M} and R^{13N}, combine to form C=O, or R^{13K} and R^{13M} combine to form C=C;

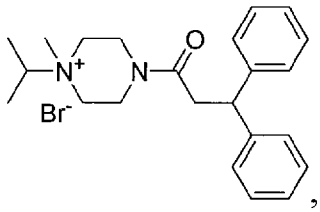
R^{13Y} is H or C_{1-4} alkyl;

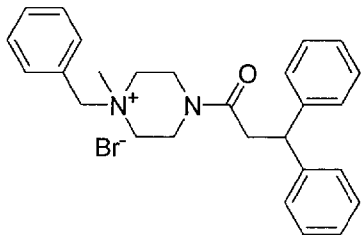
R^{13Z} and $R^{13Z'}$ are, independently, selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; and

X^- is any pharmaceutically acceptable anion.

37. The compound of claim 36, wherein said compound is selected from the group consisting of:

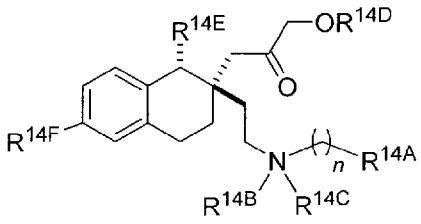


,


, and


.

38. A compound having a structure according to



(XIV), wherein

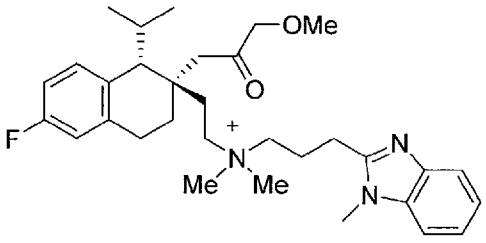
n is an integer between 0-5;

R^{14A} is heterocyclyl,

each of R^{14B}, R^{14C}, R^{14D}, and $R1^{4E}$ is, independently, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl; and

R^{14F} is selected from H, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-4} heteroalkyl, C_{7-14} alkaryl, C_{3-10} alkcycloalkyl, and C_{3-10} alkheterocyclyl, OR^{14G}, $NR^{14H}R^{141}$, $NR^{14J}C(O)R^{14K}$, $S(O)R^{14L}$, $SO_2R^{14M}R^{14N}$, $SO_2NR^{14O}R^{14P}$, SO_3R^{14Q}, CO_2R^{14R}, $C(O)R^{14S}$, and $C(O)NR^{14T}R^{14V}$; and each of R^{14G}-R^{13AO} is, independently, selected from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{2-4} heteroalkyl.

39. The compound of claim 37, wherein said compound is



X^-, where X is a pharmaceutically acceptable anion.

40. A pharmaceutical composition, comprising the compound of any of claims 32-39 and a pharmaceutically acceptable excipient.

41. A pharmaceutical composition, comprising a quarternary amine derivative or other charged derivative of any of compounds (1)-(563).

42. The pharmaceutical composition of claim 40 or 41, wherein said composition is formulated for oral administration.

43. The pharmaceutical composition of claim 40 or 41, wherein said composition is formulation for nasal administration.

44. The pharmaceutical composition of claim 40 or 41, wherein said composition is formulation for inhalation administration.

Figure 1

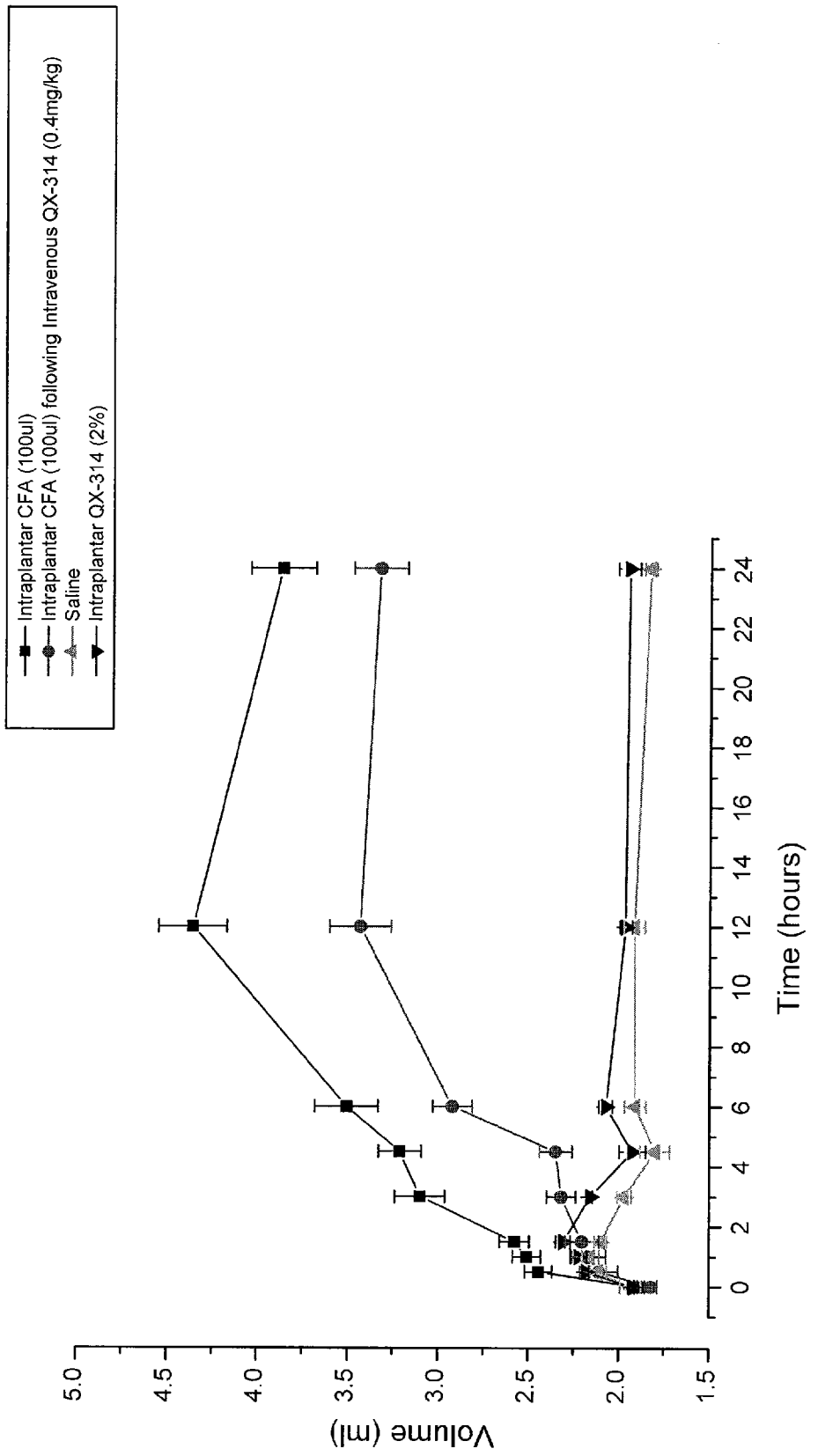
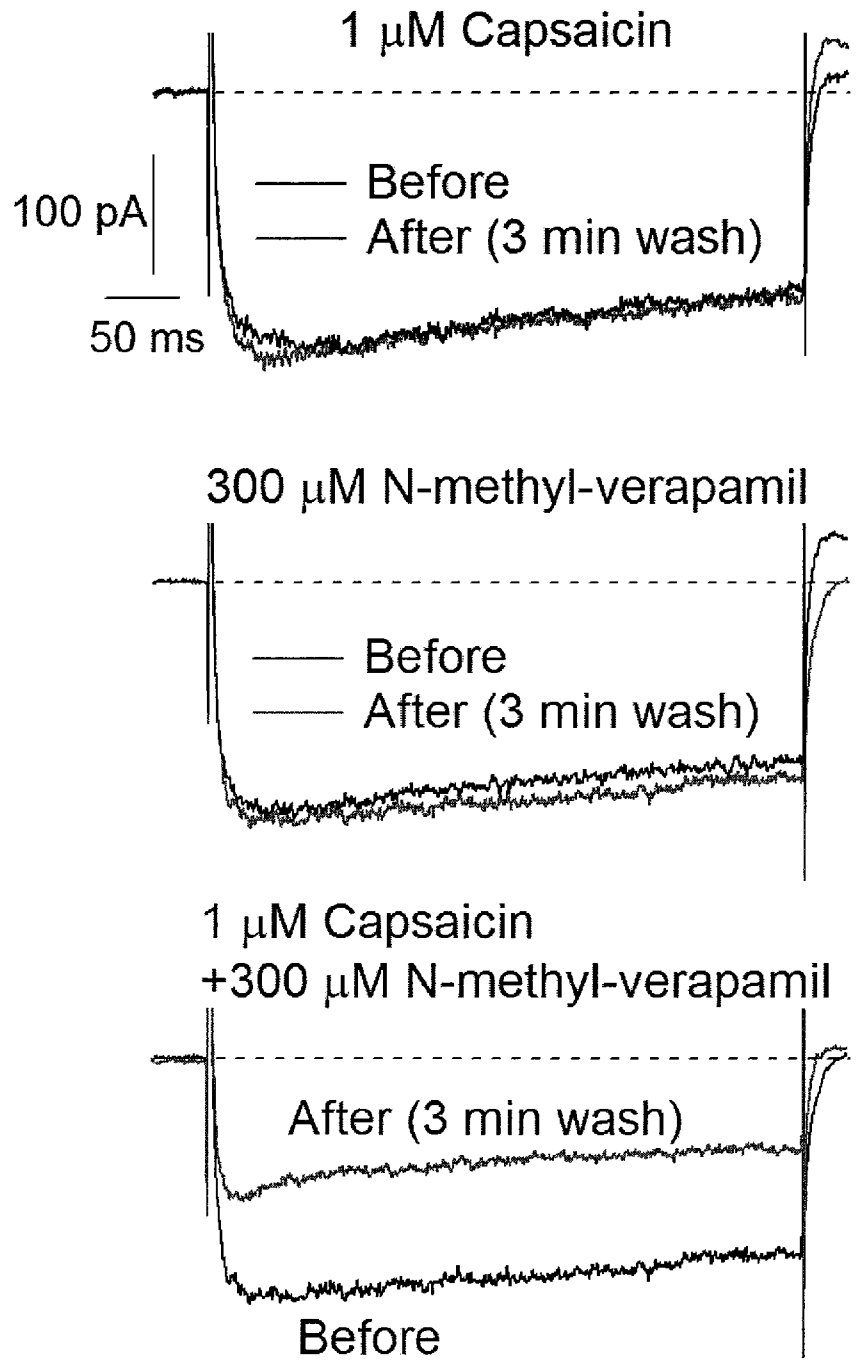

Intraplantar CFA (100ul)
Intraplantar CFA (100ul) following Intravenous QX-314 (0.4mg/kg)
Saline
Intraplantar QX-314 (2%)
Volume (ml)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hours)

Figure 2


1 μM Capsaicin
100 pA
Before
After (3 min wash)
50 ms
300 μM N-methyl-verapamil
Before
After (3 min wash)
1 μM Capsaicin
+300 μM N-methyl-verapamil
After (3 min wash)
Before

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/41537

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12N 5/16 (2010.01)
USPC - 435/7.1, 334
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 435/7.1, 334

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/1, 304, 626-627, 643 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Patentscope
neuropath$, neurolog$, pain, inflammation, ion channel, sodium channel, calcium channel, inhibit$, block$, modulat$, nociceptor, transducer, capsaicin$, QX-314, QX-222, N-methylprocaine, "N-octyl guanidine", riluzole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/063603 A2 (BEAN et al.) 29 May 2008 (29.05.2008) pg 4, para 1 to pg 7, para 1; pg 8, para 1; pg 41, para 1; pg 41, para 4 to pg 42, para 2	1-8, 19-30

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document 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
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2010 (13.10.2010)	18 OCT 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/41537

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☒ Claims Nos.: 9-18, 31 and 42-44
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:
see extra sheet

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-8 and 19-30

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/41537

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-8 and 19-30, drawn to methods for treating neurogenic inflammation in a patient, said method comprising administering to said patient a therapeutically effective amount of a compound that is capable of (i) entering a nociceptor through a channel-forming receptor present in said nociceptor when said receptor is activated and (ii) inhibiting a voltage-gated ion channel present in said nociceptor, wherein said compound does not substantially inhibit said channel when applied to the extracellular face of said channel and when said receptor is not activated, and related kits, etc.

Group II: claims 32-33, and 40-41 (in part), drawn to compounds according to formula XI, etc.

Group III: claims 34-35, and 40-41 (in part), drawn to compounds according to formula XII, etc.

Group IV: claims 36-37, and 40-41 (in part), drawn to compounds according to formula XIII, etc.

Group V: claims 38-39, and 40-41 (in part), drawn to compounds according to formula XIV, etc.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The claims of the various groups as defined above do not share any special technical feature. The compounds of formulae XI, XII, XIII, and XIV of the claims of groups II-V, respectively, do not share any significant special technical feature, as the compounds of said formulae, respectively, would be expected to exhibit different physical, chemical, biological and pharmacological properties. In addition, the methods (and related kits) of the claims of group I do not share any special technical feature with the claims of groups II-V, as there is no requirement therein that the compounds of formula XI-XIV of the claims of groups II-V be used in the methods of the claims of group I.

Thus, the inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

In this case the first named invention species that will be searched without additional fees is Group I represented by claims 1-8 and 19-30.

Claims 9-18, 31 and 42-44 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).