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(54) Title: CHARGED ION CHANNEL BLOCKERS AND METHODS FOR USE

(57) Abstract: The invention provides compounds of Formula (I), or pharmaceutically acceptable salts thereof. The compounds, compositions, methods and kits of the invention are particularly useful for the treatment of itch and other dermal conditions.

WO 2021/183639 A1

CHARGED ION CHANNEL BLOCKERS AND METHODS FOR USE

RELATED APPLICATION

This application is a continuation-in-part of U.S. Application Serial No. 16/815,426 filed March 11, 2020. The entire contents of the above application are incorporated by reference herein.

TECHNICAL FIELD

The present invention relates generally to quaternary ammonium compounds, pharmaceutical compositions, and methods useful as selective inhibitors of pain, cough and itch sensing neurons (nociceptors, cough receptors and pruriceptors) and in the treatment of neurogenic inflammation.

BACKGROUND OF THE INVENTION

The invention features compounds, compositions and methods for the selective inhibition of sensory neurons and the treatment of itch and/or neurogenic inflammation by targeting nociceptors with a small molecule drug, while minimizing effects on non-nociceptive neurons or other types of cells. According to the method of the invention, small, cationic drug molecules gain access to the intracellular compartment of sensory neurons via entry through large pore receptor/ion channels that are present in itch-sensing neurons but to a lesser extent or not at all in other types of neurons or in other types of tissue.

Local anesthetics such as lidocaine, articaine and pramocaine act by inhibiting voltage-dependent sodium channels in neurons. These anesthetics block sodium channels and thereby the excitability of all neurons, not just pain-sensing neurons (nociceptors). Thus, while the goal of topical or regional anesthesia is to block transmission of signals in nociceptors to prevent pain, administration of local anesthetics also produces unwanted or deleterious effects such as general numbness from block of low threshold pressure and touch receptors, motor deficits and/or paralysis from block of motor axons and other complications from block of autonomic fibers. Local anesthetics are relatively hydrophobic molecules that gain access to their blocking site on the sodium channel by diffusing through the cell membrane. Charged derivatives of these compounds, which are not membrane-permeable, have no effect on neuronal sodium channels when applied to the external surface of the nerve membrane but can block sodium channels if somehow introduced inside the cell, for example by diffusion from a micropipette used for whole-cell electrophysiological recording from

isolated neurons. Pain-, cough-, and itch-sensing neurons differ from other types of neurons in expressing (in most cases) the TRPV1 receptor/channel, which is activated by painful heat or by capsaicin, the pungent ingredient in chili pepper. Other types of channels selectively expressed in various types of pain-sensing, cough-sensing and itch-sensing (pruriceptor) neurons include but are not limited to TRPV2-4, TRPA1, TRPM8, ASIC and P2X(2/3) channels. It is well established that some cationic small molecules such as QX-314 are able to enter a cell via passage through activated large pore channels such as TRPV1.

Neuropathic, inflammatory, and nociceptive pain differ in their etiology, pathophysiology, diagnosis, and treatment. Nociceptive pain occurs in response to the activation of a specific subset of high threshold peripheral sensory neurons, the nociceptors, by intense or noxious stimuli. It is generally acute, self-limiting and serves a protective biological function by acting as a warning of potential or on-going tissue damage. It is typically well-localized. Examples of nociceptive pain include, but are not limited to, traumatic or surgical pain, labor pain, sprains, bone fractures, burns, bumps, bruises, injections, dental procedures, skin biopsies, and obstructions.

Inflammatory pain is pain that occurs in the presence of tissue damage or inflammation including postoperative (i.e. pain associated with acute perioperative pain resulting from inflammation caused by tissue trauma (e.g., surgical incision, dissection, burns) or direct nerve injury (e.g., nerve transection, stretching, or compression)), post-traumatic pain, arthritic pain (rheumatoid; or osteoarthritis (i.e. joint pain and stiffness due to gradual deterioration of the joint cartilage; risk factors include aging, injury, and obesity; commonly affected joints are the hand, wrist, neck, knee, hip, and spine), pain and pain associated with damage to joints, muscle, and tendons as in axial low back pain (i.e. a prevalent, painful condition affecting the lower portion of the back; common causes include muscle strain, spine fracture, bulging or ruptured disc, and arthritis), severe nociceptive pain may transition to inflammatory pain if there is associated tissue injury.

Neuropathic pain is a common type of chronic, non-malignant pain, which is the result of an injury or malfunction in the peripheral or central nervous system and serves no protective biological function. It is estimated to affect more than 1.6 million people in the U.S. population. Neuropathic pain has many different etiologies, and may occur, for example, due to trauma, surgery, herniation of an intervertebral disk, spinal cord injury, diabetes, infection with herpes zoster (shingles), HIV/AIDS, late-stage cancer, amputation (including mastectomy), carpal tunnel syndrome, chronic alcohol use, exposure to radiation, and as an unintended side-effect of neurotoxic treatment agents, such as certain anti-HIV and

chemotherapeutic drugs. Peripheral neuropathy is caused by damages to the peripheral nerves from injury, trauma, prolonged pressure, or inflammation causing numbness and pain in corresponding areas of the body.

Neuropathic pain is frequently described as "burning," "electric," "tingling," or "shooting" in nature. It is often characterized by chronic dynamic allodynia (defined as pain resulting from a moving stimulus that does not ordinarily elicit a painful response, such as light touch) and hyperalgesia (defined as an increased sensitivity to a normally painful stimulus) and may persist for months or years beyond the apparent healing of any damaged tissues.

Pain may occur in patients with cancer, which may be due to multiple causes; inflammation, compression, invasion, metastatic spread into bone or other tissues.

There are some conditions where pain occurs in the absence of a noxious stimulus, tissue damage or a lesion to the nervous system, called dysfunctional pain and these include but are not limited to fibromyalgia, tension type headache, and irritable bowel disorders.

Migraine is a headache associated with the activation of sensory fibers innervating the meninges of the brain.

Itch (pruritus) is a dermatological condition that may be localized and generalized and can be associated with skin lesions (rash, atopic eczema, wheals). Itch accompanies many conditions including but not limited to stress, anxiety, UV radiation from the sun, metabolic and endocrine disorders (e.g., liver or kidney disease, hyperthyroidism), cancers (e.g., lymphoma), reactions to drugs or food, parasitic and fungal infections, allergic reactions, diseases of the blood (e.g., polycythemia vera), and dermatological conditions. Itch is mediated by a subset of small diameter primary sensory neurons, the pruriceptor, that share many features of nociceptor neurons, including but not limited to expression of TRPV1 channels and other large pore channels (e.g. TRPV2-4, TRPA1, TRPM8, ASIC and P2X(2/3). Certain itch mediators—such as eicosanoids, histamine, bradykinin, ATP, and various neurotrophins have endovanilloid functions. Topical capsaicin suppresses histamine-induced itch. Pruriceptors like nociceptors are therefore a suitable target for this method of delivering ion channel blockers.

Cough is a defensive reflex designed to protect the airway from foreign bodies and to aid in the clearance of luminal debris. This reflex, however, can became aberrant in a number of diseases leading to a non-productive dry cough where hyper- or allo-tussive states exist. Hyper- and allo-tussive states are often chronic in nature lasting greater than three months and can be manifested in many airway diseases states including asthma, COPD, asthma-

COPD overlap syndrome (ACOS), interstitial pulmonary fibrosis (IPF) and lung cancer. In addition, inappropriate cough reflexes can be manifested acutely and chronically following viral infection. Furthermore, chronic cough can be idiopathic in nature with unknown etiology.

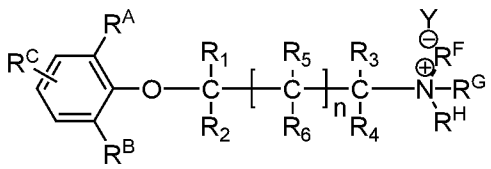
Neurogenic inflammation is a mode of inflammation mediated by the efferent (motor) functions of sensory neurons, in which pro-inflammatory mediator molecules released in the periphery by pain-sensing neurons (nociceptors) both activate a variety of inflammatory pathways in immune cells, and also act 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, allergy, exposure to irritants in a variety of tissues, and is thought to play an important role in the pathogenesis of numerous disorders (e.g. allergic inflammation, inflammatory bowel disease, interstitial cystitis, atopic dermatitis, asthma, conjunctivitis, arthritis, colitis, contact dermatitis, diabetes, eczema, cystitis, gastritis, migraine headache, psoriasis, rhinitis, rosacea, sunburn, pancreatitis, chronic cough, chronic rhinosinusitis, traumatic brain injury, polymicrobial sepsis, tendinopathies, chronic urticaria, rheumatic disease, acute lung injury, exposure to irritants, inhalation of irritants, pollutants, or chemical warfare agents). 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 mediators.

Despite the development of a variety of therapies for pain, itch, and neurogenic inflammation, there is a need for additional agents.

SUMMARY OF THE INVENTION

The present invention provides compounds represented by Formula (**I**) that can be used to treat or prevent itch, pain, cough, and neurogenic inflammation:



(**I**),

wherein:

Y^- is a pharmaceutically acceptable anion;

R^A, R^B, and R^C are each independently selected from H, D, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, OR^I, CN, CF_3, NR^JR^K, $NR^LC(O)R^M$, $S(O)R^N$, $S(O)_2R^N$, $SO_2R^OR^P$, $SO_2NR^QR^R$, SO_3R^S, CO_2R^T; $C(O)R^U$, and $C(O)NR^VR^W$;

each of R^I, R^J, R^K, R^L, R^M, R^N, R^O, R^P, R^Q, R^R, R^S, R^T, R^U, R^V, and R^W is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl; or R^J and R^K or R^V and R^W or R^Q and R^R can also be taken together with the nitrogen to which they are attached to form a substituted or unsubstituted 5, 6, 7, or 8 membered ring;

R^A, R^B, and/or R^C can be taken together with the phenyl ring to which they are attached can form a fused bicyclic or tricyclic ring system, such as naphthyl, dihydroindenyl, tetrahydronaphthyl, quinolinyl, indolyl, and the like;

R_1, R_2, R_3, R_4, R_5, and R_6 are independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, cycloalkyl, aryl or heteroaryl, preferably hydrogen, methyl or ethyl;

n is 0, 1, 2, 3, 4 and 5;

or R_1, R_2, R_3, R_4, R_5, and/or R_6 together with the carbon(s) to which they are attached form a substituted or unsubstituted cycloalkyl (such as a C_3-C_6 cycloalkyl) or a substituted or unsubstituted heterocyclic (such as a 3- to 15-membered heterocyclic ring);

R^F and R^G together with the N^+ form an optionally substituted heterocyclic ring having, zero, one or more heteroatoms in addition to the N^+, including but not limited to, a heteroaryl ring; for example, two of R^E, R^F, and R^G are taken together with the N^+ to form a heterocyclic ring having, zero, one or more heteroatoms in addition to the N^+;

R^H is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, such as -CH_2-cycloalkyl, -C_2H_4-cycloalkyl, substituted or unsubstituted –CH_2-C_5-C_{10} aryl, substituted or unsubstituted –C_2H_4-C_5-C_{10} aryl, substituted or unsubstituted –CH_2-C_5-C_{10} heteroaryl, substituted or unsubstituted –C_2H_4-C_5-C_{10} heteroaryl, -CH_2 $OC(O)R^T$, -CH_2 CO_2R^T, -$CH_2C(O)NR^VR^W$, -$C_2H_4OCOR^T$, -$C_2H_4OR^I$or

R^F, R^G and R^H together with the N^+ form substituted or unsubstituted heteroaryl ring (such as pyridinyl or phenyl-pyridinyl) or bridged heterocyclic ring.

The invention includes the surprising finding that the compounds are particularly active for the treatment of itch. The compounds have surprising high potency and superior topical localization, making the compounds surprisingly suitable for dermal applications.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A, 1B and 1C show that representative compounds significantly reduce chloroquine-induced itch up to 8 hours following topical administration.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds represented by Formula **(I)** as described above, or pharmaceutically acceptable salts, stereoisomers, solvates, hydrates or combinations thereof. The invention also provides compositions comprising compounds having Formula (**I**) or a pharmaceutically acceptable salts thereof, for example, a composition comprising an effective amount of a compound of Formula (**I**) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. The compositions of the invention may further comprise compounds of the invention and a biologically active agent. The compositions can be formulated for oral, intravenous, intramuscular, rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, inhalation, vaginal, intrathecal, epidural, or ocular administration. However, preferred compositions can be formulated for topical or dermal administration.

The invention further provides methods for treating itch, pruritis, psoriasis or atopic dermatitis, in a patient, including administering to the patient a composition comprising a compound having Formula (**I**).

As used herein, the words “a” and “an” are meant to include one or more unless otherwise specified.

By “biologically active” is meant that a molecule, including biological molecules, such as nucleic acids, peptides, polypeptides, and proteins, exerts a biological, physical or chemical effect activity on a protein, enzyme, receptor, ligand, antigen, itself or other molecule. For example, a “biologically active” molecule may possess, e.g., enzymatic activity, protein binding activity, or pharmacological activities.

Biologically active agents that can be used in the methods and kits described herein include, without limitation, TRPA1 receptor agonists, TRPV1-4 receptor agonists, ASIC agonists, TRPM8 agonists, P2X receptor agonists, NSAIDs, glucocorticoids, narcotics, anti-proliferative and immune modulatory agents, an antibody or antibody fragment, an

antibiotic, a polynucleotide, a polypeptide, a protein, an anti-cancer agent, a growth factor, and a vaccine.

The term "itch" is used herein in the broadest sense and refers to itching and stinging sensations localized and generalized, acute intermittent and persistent. The itch may be idiopathic, allergic, metabolic, infectious, drug-induced, due to liver, kidney disease, or cancer. "Pruritus" is severe itching.

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. Dermal inflammation is preferred.

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

The term "pain" is used herein in the broadest sense and refers to all types of pain, including acute and chronic pain, such as nociceptive pain, e.g., somatic pain and visceral pain; inflammatory pain, dysfunctional pain, idiopathic pain, neuropathic pain, e.g., centrally generated pain and peripherally generated pain, migraine, and cancer pain. Dermal pain is preferred.

The term "nociceptive pain" is used to include all pain caused by noxious stimuli that threaten to or actually injure body tissues, including, without limitation, by a cut, bruise, bone fracture, crush injury, burn, and the like. Pain receptors for tissue injury (nociceptors) are located mostly in the skin, musculoskeletal system, or internal organs, preferably the skin or dermis.

The term "somatic pain" is used to refer to pain arising from bone, joint, muscle, skin, or connective tissue, preferably the skin and tissues adjacent to the skin. This type of pain is typically well localized.

The term "visceral pain" is used herein to refer to pain arising from visceral organs, such as the respiratory, gastrointestinal tract and pancreas, the urinary tract and reproductive organs. Visceral pain includes pain caused by tumor involvement of the organ capsule. Another type of visceral pain, which is typically caused by obstruction of hollow viscus, is characterized by intermittent cramping and poorly localized pain. Visceral pain may be associated with inflammation as in cystitis or reflux esophagitis.

The term "inflammatory pain" includes pain associates with active inflammation that may be caused by trauma, surgery, infection and autoimmune diseases.

The term “neuropathic pain” is used herein to refer to pain originating from abnormal processing of sensory input by the peripheral or central nervous system consequent on a lesion to these systems.

The term “procedural pain” refers to pain arising from a medical, dental or surgical procedure wherein the procedure is usually planned or associated with acute trauma.

By “patient” is meant any animal. In one embodiment, the patient is a human. Other animals that can be treated using the methods, compositions, 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.

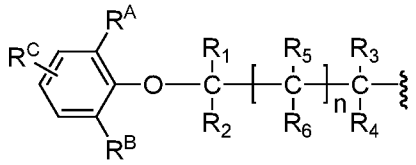
The term “pharmaceutically acceptable anion” as used herein, refers to the conjugate base of a pharmaceutically acceptable acid. Such acids are described in Stahl, P.H. and Wermuth, C.G. (eds.), Handbook of Pharmaceutical Salts: Properties, Selection and Use, Wiley VCH (2008). Pharmaceutically acceptable acids include, but are not limited to, acetic acid, dichloroacetic acid, adipic acid, alginic acid, L-ascorbic acid, L-aspartic acid, benzenesulfonic acid, 4-acetamidobenzoic acid, benzoic acid, p-bromophenylsulfonic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, sulfuric acid, boric acid, citric acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxoglutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicyclic acid, 4-aminosalicyclic acid, sebacic acid, stearic acid, succinic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, and undecylenic acid. Pharmaceutically acceptable anions include the conjugate base of any the acids set forth above.

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. 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, camphorsulfonate, 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.

"D" is deuterium.

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-*} alkyl" is meant a branched, unbranched or cyclic hydrocarbon group having from 1 to * carbon atoms, where * is an integer, such as 2, 3, 4, 5, 6, 7, 8, 10, 12, or more. An alkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide (F, Cl, Br or I), hydroxyl, fluoroalkyl, perfluoralkyl, oxo, amino, alkylamino, disubstituted amino, quaternary amino, amido, ester, alkylcarboxy, alkoxycarbonyl, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxyl, alkylcarbonyl, arylcarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, aryl, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. In certain aspects, the alkyl is a C_1-C_6 alkyl. C_{1-6} alkyls include, without limitation, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, cyclopentyl,

hexyl and cyclohexyl. Another specific example of a substituted alkyl is a moiety which will form a homodimer or heterodimer, such as:



Another example of a substituted alkyl is a heteroalkyl. By "heteroalkyl" is meant a branched or unbranched alkyl, cycloalkyl, alkenyl, or alkynyl group having from 1 to 7 or more carbon atoms in addition to 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O, S, and P. Heteroalkyls can 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 alkyl, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide (F, Cl, Br or I), hydroxyl, fluoroalkyl, perfluoralkyl, oxo, amino, alkylamino, disubstituted amino, quaternary amino, amido, ester, alkylcarboxy, alkoxycarbonyl, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxyl, alkylcarbonyl, arylcarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, aryl, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Examples of C_{1-7} heteroalkyls include, without limitation, methoxymethyl and ethoxyethyl.

An alkenyl is a branched or unbranched hydrocarbon group containing one or more double bonds. For example, by "C_{2-6} alkenyl" or "C_2-C_6 alkenyl" is meant a branched or unbranched hydrocarbon group containing one or more double bonds and having from 2 to 6 carbon atoms. An alkenyl may optionally include monocyclic or polycyclic rings, in which each ring desirably has from three to six members. The alkenyl group may be substituted or unsubstituted. Exemplary substituents include those described above for alkyl, and specifically include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, alkylamino, disubstituted amino, quaternary amino, alkylcarboxy, and carboxyl groups. C_{2-6} 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.

An alkynyl is a branched or unbranched hydrocarbon group containing one or more triple bonds. For example, by "C_{2-6} alkynyl" or "C_2-C_6 alkynyl" is meant a branched or unbranched hydrocarbon group containing one or more triple bonds and having from 2 to 6 carbon atoms. An alkynyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has five or six members. The alkynyl group may be substituted or unsubstituted. Exemplary substituents those described above for alkyl, and specifically include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, alkylamino, disubstituted amino, quaternary amino, alkylcarboxy, and carboxyl groups. C_{2-6} alkynyls include, without limitation, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

By "heterocyclyl," "heterocyclic," or "heterocycloalkyl" is meant a stable monocyclic or a polycyclic (including a bicyclic or a tricyclic) heterocyclic ring which is saturated, partially unsaturated or unsaturated (including heteroaryl or aromatic), and which consists of 2 or more carbon atoms and 1, 2, 3 4 or more heteroatoms independently selected from P, N, O, and S and including any bicyclic or polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, heteroaryl, cycloalkyl or heterocycloalkyl. In certain aspects, the heterocyclyl is a 3- to 15-membered ring system, a 3- to 12- membered ring system, or a 3- to 9-membered ring system. The heterocyclyl (incuding heteroaryl groups) may be substituted or unsubstituted. Exemplary substituents include substituted or unsubstituted alkyl, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide (F, Cl, Br or I), hydroxyl, fluoroalkyl, perfluoralkyl, oxo, amino, alkylamino, disubstituted amino, quaternary amino, amido, ester, alkylcarboxy, alkoxycarbonyl, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxyl, alkylcarbonyl, arylcarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, aryl, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be covalently attached via a 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 or phosphorus atom in the heterocycle can 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, , β-lactam, γ-lactam and δ-lactam. 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, quinolinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, piperazinyl, piperidinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and tetrazolyl. Preferred substituents include phenyl, methyl, ethyl, propyl, butyl, oxo, chloro, bromo, fluoro and iodo.

By "aryl" is meant an aromatic group having a ring system comprised of carbon atoms with conjugated π electrons (e.g., phenyl). A "C_6-C_{12} aryl" or "C_6-C_{10} aryl" is an aryl group has from 6 to 12 carbon atoms or 6 to 10 carbon atoms, respectively. Aryl groups may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has

five or six members. Ring systems can be fused (e.g., naphthyl) or not (biphenyl). The aryl group may be substituted or unsubstituted. Exemplary substituents include substituted or unsubstituted alkyl, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide (F, Cl, Br or I), hydroxyl, fluoroalkyl, perfluoralkyl, oxo, amino, alkylamino, disubstituted amino, quaternary amino, amido, ester, alkylcarboxy, alkoxycarbonyl, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxyl, alkylcarbonyl, arylcarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, aryl, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

By "aralkyl" is meant a substituted or unsubstituted alkyl that is substituted by a substituted or unsubstituted aryl (including, for example, (e.g., benzyl, phenethyl, or 3,4-dichlorophenethyl)). By "heteroaralkyl" is meant a substituted or unsubstituted alkyl that is substituted by or heteroaryl group.

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

By "fluoroalkyl" is meant an alkyl group that is substituted with one or more fluorine atoms, such as a perfluoroalkyl group. Trifluoromethyl, difluoromethyl, fluoromethyl and heptafluoroethyl are examples.

By "alkoxy" is meant a chemical moiety with the formula -O-R, wherein R is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl.

By "alkylcarboxy" is meant a chemical moiety with the formula —(R)—COOH, wherein R is selected from alkyl (e.g., C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl), heterocyclyl, aryl, heteroaryl, aralkyl, heterocycloalkyl, or heteroalkyl, each optionally substituted.

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.

By "therapeutically effective amount" or "effective amount" means an amount sufficient to produce a desired result, for example, the reduction or elimination of pain, cough, itch, or 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. allergic inflammation, inflammatory bowel disease, interstitial cystitis, atopic dermatitis, asthma, conjunctivitis, arthritis, colitis, contact dermatitis, diabetes, eczema,

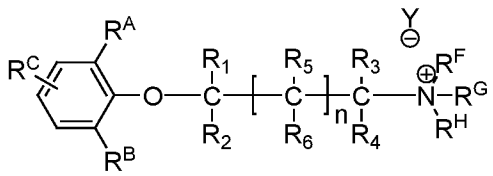
cystitis, gastritis, migraine headache, psoriasis, rhinitis, rosacea, sunburn, pancreatitis, chronic cough, chronic rhinosinusistis, traumatic brain injury, polymicrobial sepsis, tendinopathies, chronic urticaria, rheumatic disease, acute lung injury, exposure to irritants, inhalation of irritants, pollutants, or chemical warfare agents).

"Solvates" means solvent addition forms that contain either stoichiometric or nonstoichiometric amounts of solvent.

The compounds of the present invention, including salts of the compounds, can exist in unsolvated forms as well as solvated forms, including hydrated forms and unhydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Nonlimiting examples of hydrates include monohydrates, dihydrates, hemihydrates, etc. In certain aspects, the compound is a hemihydrate. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

The compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for uses contemplated by the present invention and are intended to be within the scope of the invention.

Compounds having Formula (**I**) are preferred:



(**I**),

wherein:

Y^- is a pharmaceutically acceptable anion;

R^A, R^B, and R^C are each independently selected from H, D, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, OR^I, CN, CF_3, NR^JR^K, $NR^LC(O)R^M$, $S(O)R^N$, $S(O)_2R^N$, $SO_2R^OR^P$, $SO_2NR^QR^R$, SO_3R^S, CO_2R^T; $C(O)R^U$, and $C(O)NR^VR^W$;

each of R^I, R^J, R^K, R^L, R^M, R^N, R^O, R^P, R^Q, R^R, R^S, R^T,R^U, R^V, and R^W is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl; R^J and R^K or R^V and R^W or R^Q and R^R can also be taken

together with the nitrogen to which they are attached to form a substituted or unsubstituted 5, 6, 7, or 8 membered ring;

R^A, R^B, and/or R^C can be taken together with the phenyl ring to which they are attached can form a fused bicyclic or tricyclic ring system, such as naphthyl, dihydroindenyl, tetrahydronaphthyl, quinolinyl, indolyl, and the like.

Preferred R^A is selected from H, methyl, halo (such as F, Cl or Br), CF_3, CN, CO_2R^T, or OR^I, more preferably methyl, F, CF_3 or CN, most preferably methyl.

Preferred R^B is selected from H and methyl, most preferably methyl.

Preferred R^C is selected from H, methyl, halo (such as F, Cl or Br), CF_3, CN, CO_2R^T, or OR^I, more preferably H or OR^I, most preferably H.

R_1, R_2, R_3, R_4, R_5, and R_6 are independently selected from hydrogen, C_1-C_4 alkyl, cycloalkyl, C_1-C_4 heteroalkyl, aryl or heteroaryl, preferably hydrogen, methyl or ethyl;

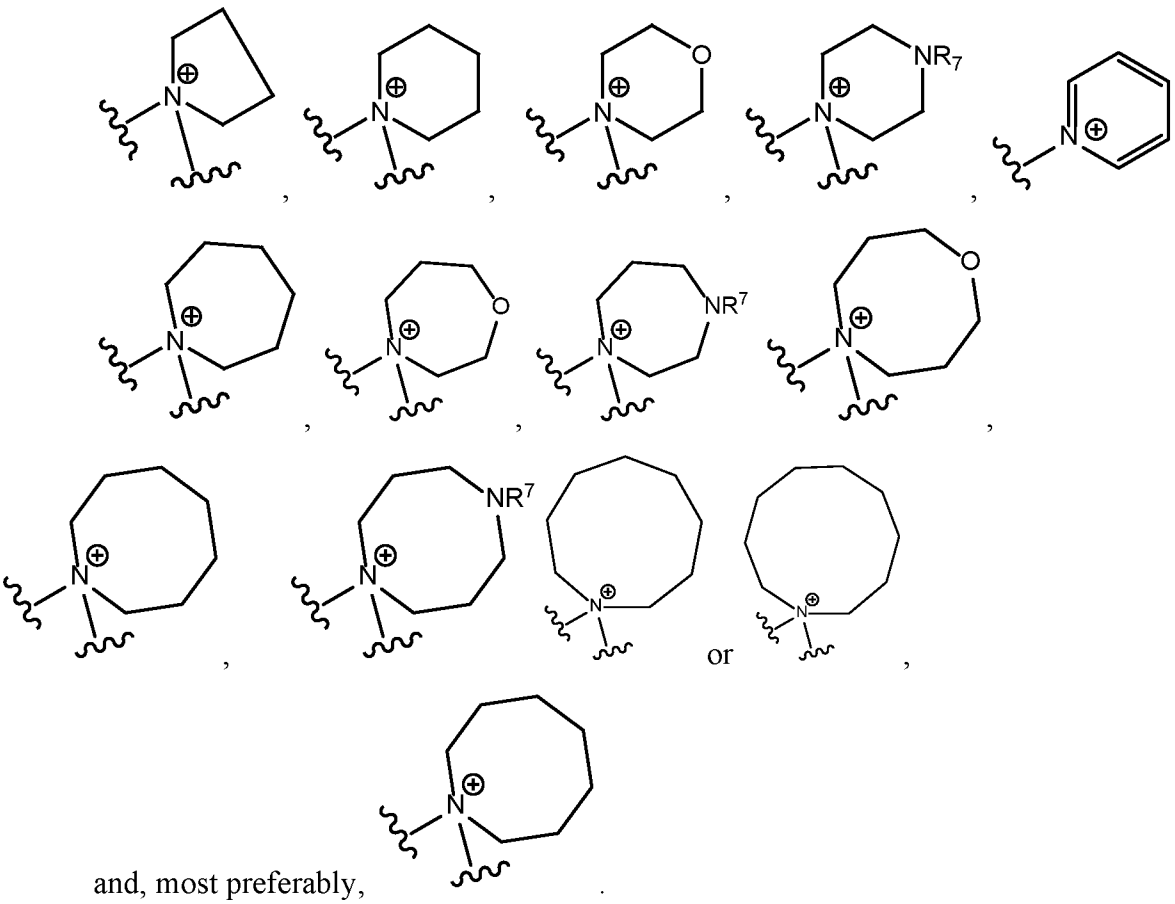
n is 0, 1, 2, 3, 4 and 5;

or R_1, R_2, R_3, R_4, R_5, and/or R_6 together with the carbon(s) to which they are attached form a substituted or unsubstituted cycloalkyl (such as a C_3-C_6 cycloalkyl) or a substituted or unsubstituted heterocyclic (such as a 3- to 15-membered heterocyclic ring).

It will be understood that an optionally substituted alkylenyl linker of 2 to 7 carbons is formed between the ether oxygen and the quaternary nitrogen. In preferred compounds, each R_1, R_2, R_3, R_4, R_5, and/or R_6 are hydrogen (e.g., forming a straight chain alkylenyl, such as ethylenyl, propylenyl, butylenyl or pentylenyl). In preferred compounds, each of R_5 and R_6 are hydrogen. In other compounds, the R_1 and/or R_2 are both hydrogen. In other compounds, the R_3 and R_4 are both hydrogen. Alternatively, R_1 is methyl or ethyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen. Alternatively, R_3 is methyl or ethyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen.

R^F and R^G together with the N^+ form an optionally substituted heterocyclic ring having, zero, one or more heteroatoms in addition to the N^+. The ring can have 5, 6, 7, 8, or 9 ring members. 7 and 8-membered rings are preferred. Thus, examples of preferred heterocyclic rings include:

As will be understood, the N^+-containing ring of Formula (I) includes:



and, most preferably,

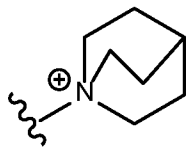
The heterocyclic ring can be optionally substituted, as described above. For example, R_7 can be hydrogen or a substituted or unsubstituted alkyl. Preferred substituents include alkyl, CF3, halogen, OH and OR^I.

R^H is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, such as -CH_2-cycloalkyl, -C_2H_4-cycloalkyl, substituted or unsubstituted –CH_2-C_5-C_{10} aryl, substituted or unsubstituted –C_2H_4-C_5-C_{10} aryl, substituted or unsubstituted –CH_2-C_5-C_{10} heteroaryl, substituted or unsubstituted –C_2H_4-C_5-C_{10} heteroaryl, -CH_2 $OC(O)R^T$, -CH_2 CO_2R^T, -$CH_2C(O)NR^VR^W$, -$C_2H_4OCOR^T$, -$C_2H_4OR^I$ or

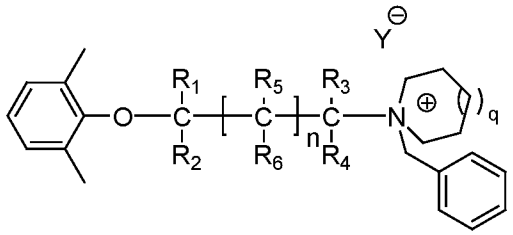
Preferably, R^H is benzyl or substituted benzyl. Alternatively, R^H is an unsubstituted alkyl, alkenyl or alkynyl, such as a C_3, C_4, C_5, C_6, C_7 or C_8 alkyl. The alkyl can be a straight or branched chain alkyl. Examples of branched chain alkyls include sec-butyl. The cycloalkyl can preferably a 3 to 6 carbon cycloalkyl, preferably cyclopentyl or cyclohexyl.

Alternatively, R^F, R^G and R^H together with the N^+ form heteroaryl ring or bridged heterocyclic ring. Examples of heteroaryl groups include substituted or unsubstituted

pyridinyl (e.g., a phenyl-pyridinyl). A preferred example of a bridged heterocycle includes



Preferred compounds that can be used in the compositions, kits, and methods of the invention include compounds having Formula (**II**):



(**II**),

wherein:

Y^- is a pharmaceutically acceptable anion;

R_1, R_2, R_3, R_4, R_5, and R_6 are independently selected from hydrogen, methyl, or ethyl

q is 0, 1, 2, 3, 4 or 5; and

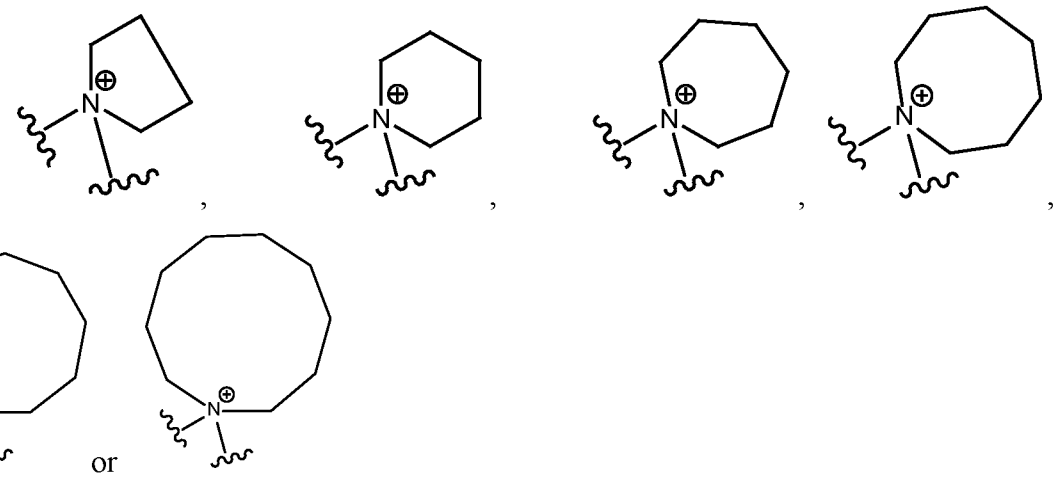
n is 0, 1, 2, 3, 4, or 5.

Preferably, Y^- is a halide anion, a carboxylate, or a sulfonate. Y^- can, for example, be a halide ion, a substituted or unsubstituted alkylsulfonate, a substituted or unsubstituted arylsulfonate, a substituted or unsubstituted alkyl or aliphatic carboxylate, a substituted or unsubstituted aryl carboxylate, or a substituted or unsubstituted heterocyclyl carboxylate.

In certain embodiments, Y^- is selected from the group consisting of trifluoroacetate, sulfate, phosphate, acetate, fumarate, formate, carbonate, maleate, citrate, pyruvate, succinate, oxalate, a sulfonate, (for example, methanesulfonate, trifluoromethanesulfonate, toluenesulfonate such as p-toluenesulfonate, benzenesulfonate, ethanesulfonate, camphorsulfonate, 2-mesitylenesulfonate, or naphthalenesulfonate such as 2-naphthalenesulfonate), bisulfate, malonate, xinafoate, ascorbate, oleate, nicotinate, saccharinate, adipate, formate, glycolate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, 2-furoate, 3-furoate, napadisylate (naphthalene-1,5-disulfonate or naphthalene-1-(sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isethionate (2-hydroxyethylsulfonate), D-mandelate, L-mandelate, propionate, tartarate, phthalate, hydrochlorate, hydrobromate, and nitrate.

In one embodiment, Y^- is halide anion. In a preferred embodiment, Y^- is selected from the halide ions bromide, chloride, or iodide.

As will be understood, when q is 0, 1, 2, or 3, the N^+-containing ring of Formula (II) is:



respectively. Preferably, q is 3. Another preferred embodiment, q is 2. Alternatively, q is 0 or 1.

In Formula II, R_1, R_2, R_3, R_4, R_5, and/or R_6 can each be hydrogen (e.g., forming a straight chain alkylenyl, such as ethylenyl, propylenyl, butylenyl or pentylenyl). In preferred compounds, each of R_5 and R_6 are hydrogen. In other compounds, the R_1 and/or R_2 are both hydrogen. In other compounds, the R_3 and R_4 are both hydrogen. Alternatively, R_1 is methyl or ethyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen. Alternatively, R_3 is methyl or ethyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen.

For example, q is 0 and R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
q is 0 and R_1 is methyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
q is 0 and R_3 is methyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen; or
q is 1 and R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
q is 1 and R_1 is methyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
q is 1 and R_3 is methyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen; or
q is 2 and R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
q is 2 and R_1 is methyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
q is 2 and R_3 is methyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen; or
q is 3 and R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
q is 3 and R_1 is methyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
q is 3 and R_3 is methyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen.

For example, n is 0 and R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
n is 0 and R_1 is methyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen; or
n is 0 and R_3 is methyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen; or

n is 1 and R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen; or

n is 1 and R_1 is methyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen; or

n is 1 and R_3 is methyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen; or

n is 2 and R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen; or

n is 2 and R_1 is methyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen; or

n is 2 and R_3 is methyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen; or

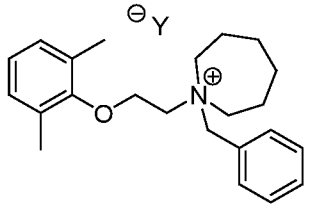
n is 3 and R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen; or

n is 3 and R_1 is methyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen; or

n is 3 and R_3 is methyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen.

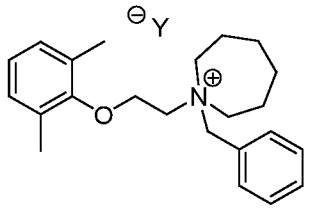
Each preferred group stated above can be taken in combination with one, any or all other preferred groups.

A preferred compound is:



Wherein Y is a pharmaceutically acceptable anion, such as bromine.

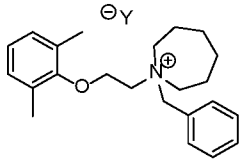
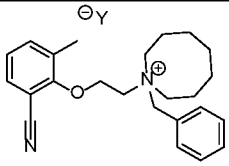
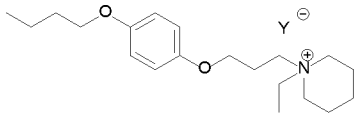
In other embodiments, the compound is not:

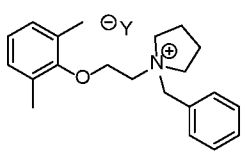
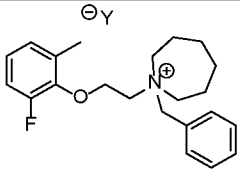
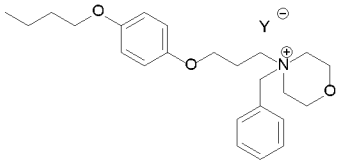
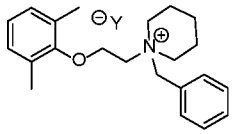
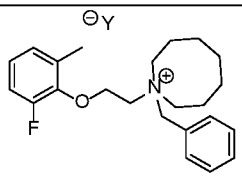
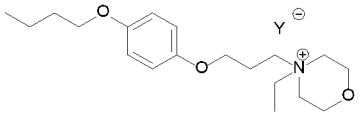
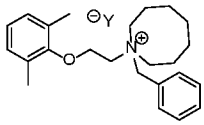
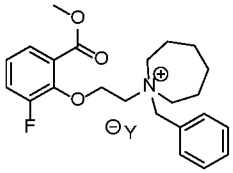
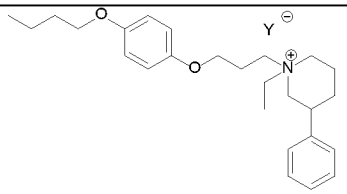
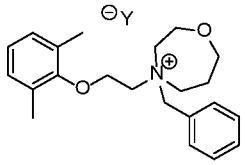
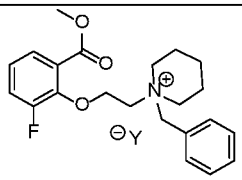
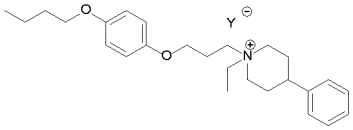
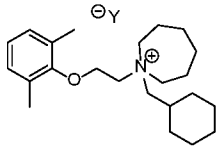
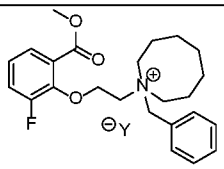
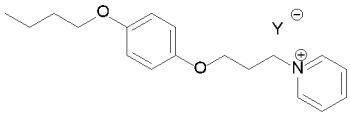
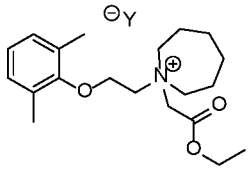
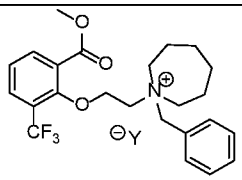
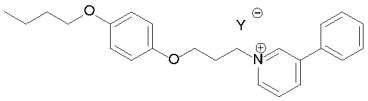
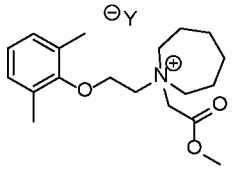
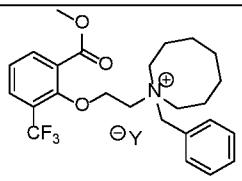
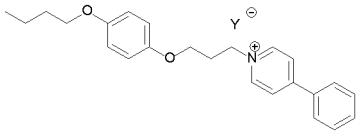
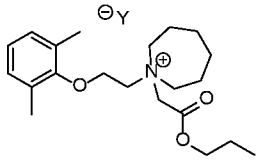
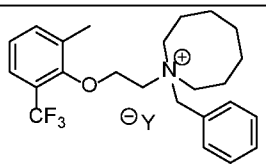
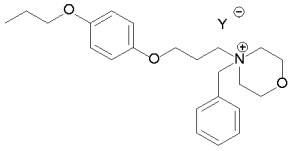
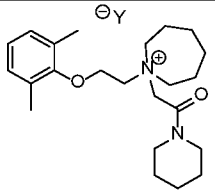
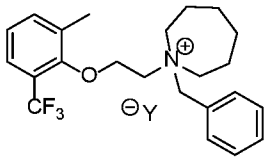
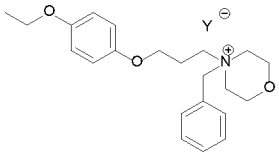


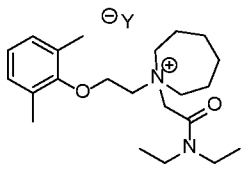
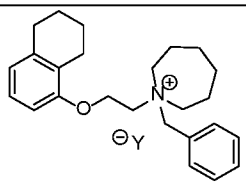
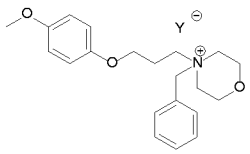
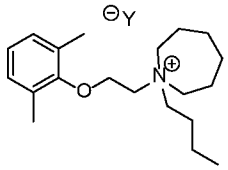
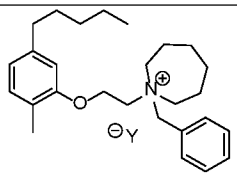
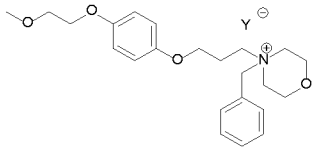
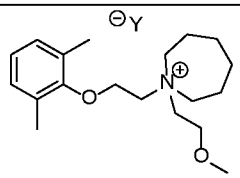
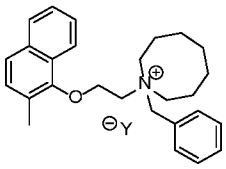
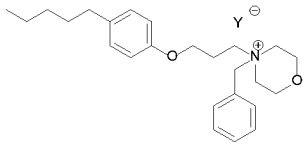
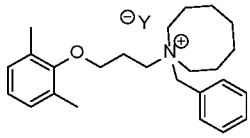
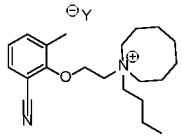
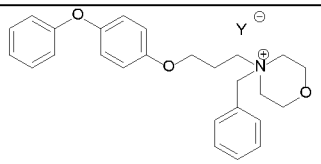
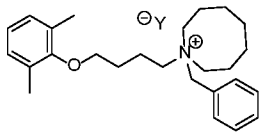
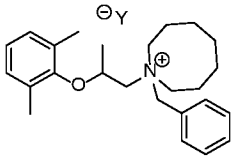
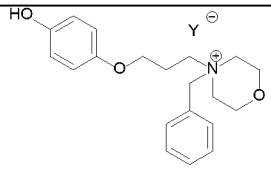
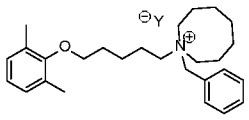
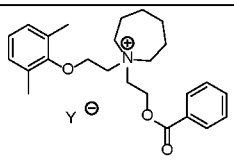
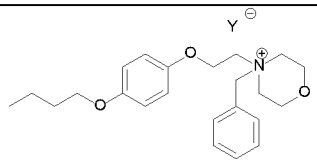
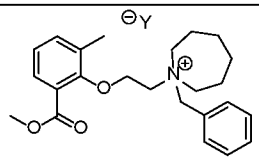
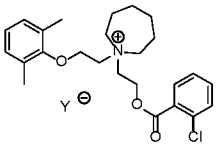
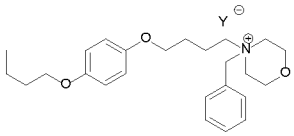
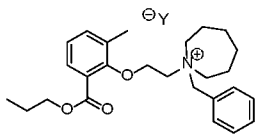
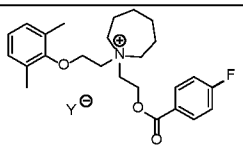
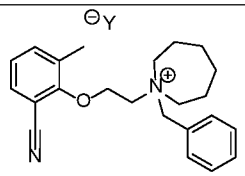
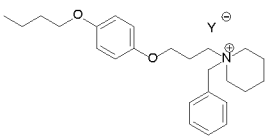
Wherein Y is a pharmaceutically acceptable anion, such as bromine.

In yet an additional aspect, the compound is selected from Table A below, or a pharmaceutically acceptable salt thereof, wherein Y^- is a pharmaceutically acceptable anion.

TABLE A

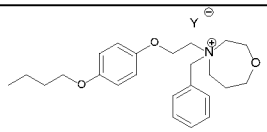
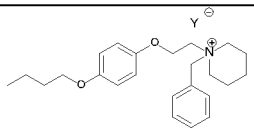
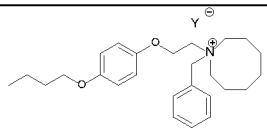
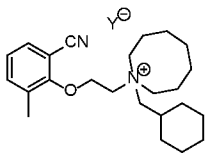
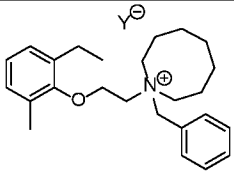
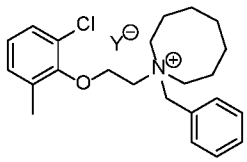
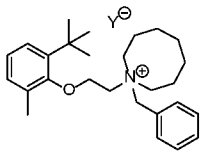
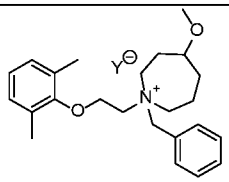
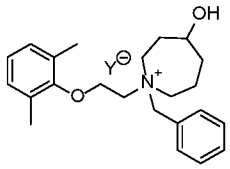
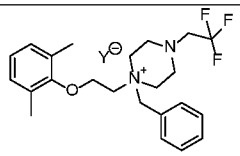
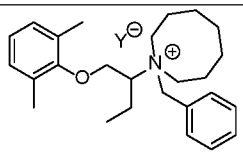
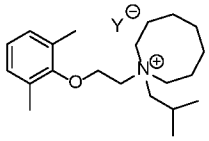
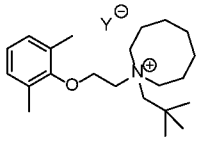
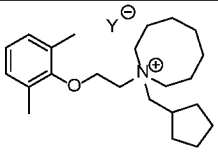
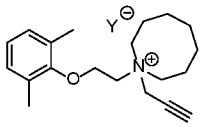
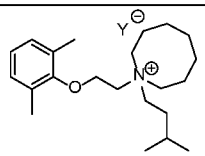
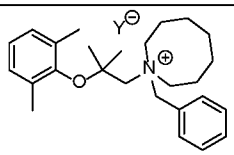
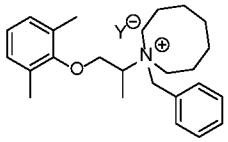
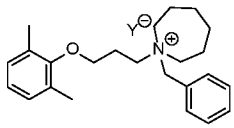
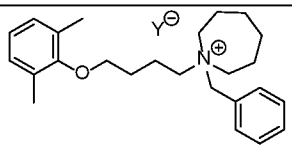
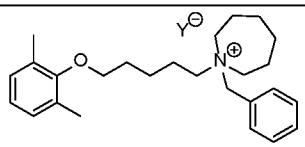
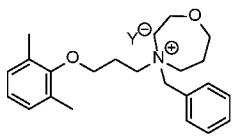
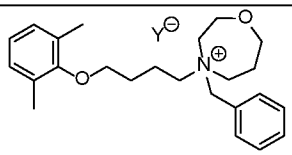
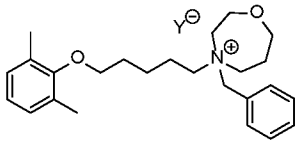
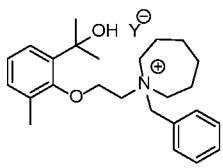
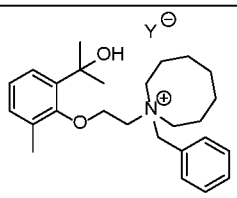
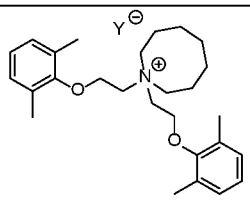
No.	Structure	No.	Structure	No.	Structure
1		20		39	

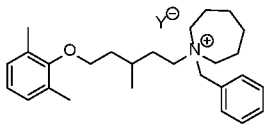
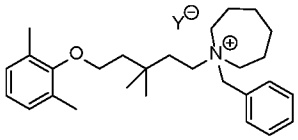
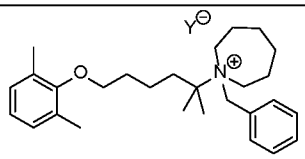
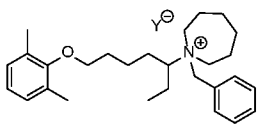
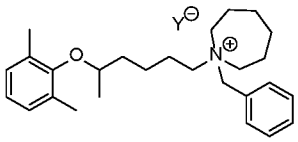
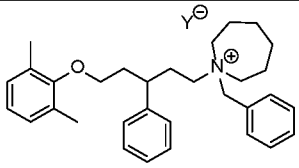
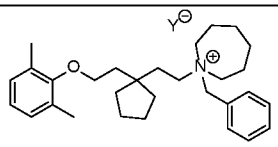
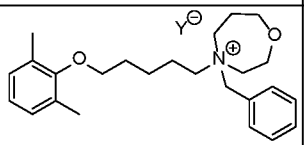
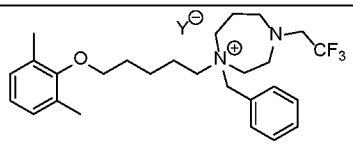
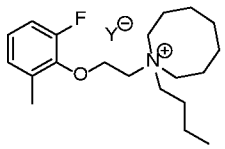
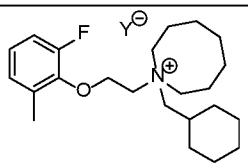
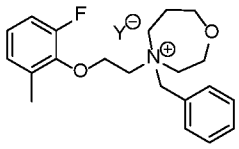
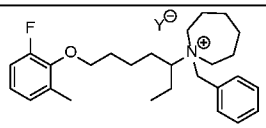
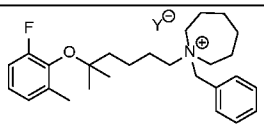
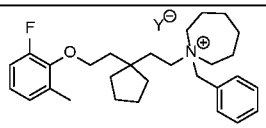
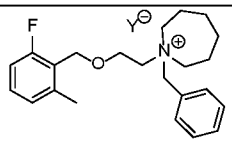
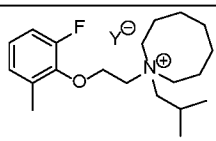
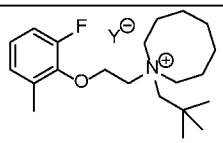
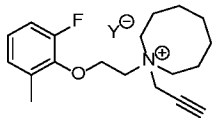
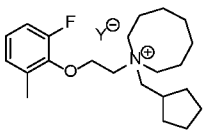
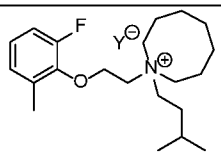
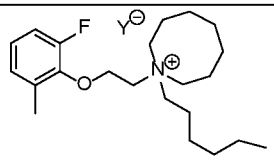
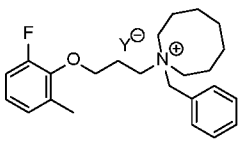
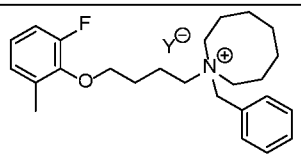
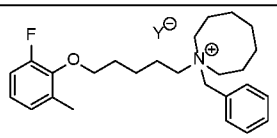
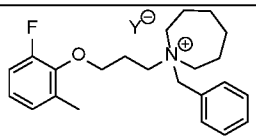
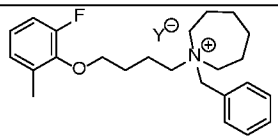
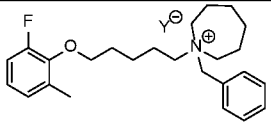
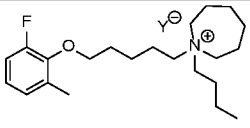
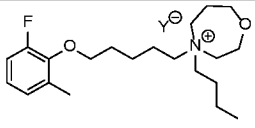
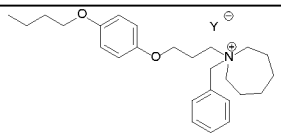
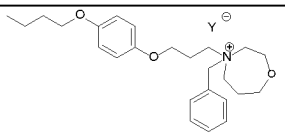
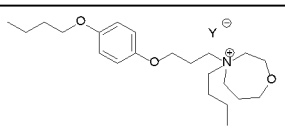
2		21		40	
3		22		41	
4		23		42	
5		24		43	
6		25		44	
7		26		45	
8		27		46	
9		28		47	
10		29		48	

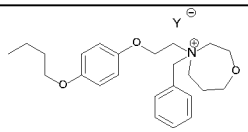
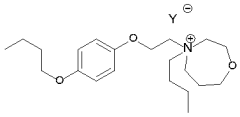
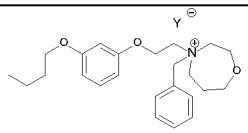
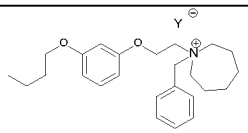
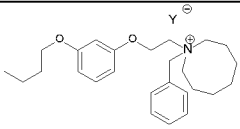
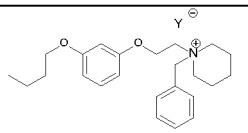
11		30		49	
12		31		50	
13		32		51	
14		33		52	
15		34		53	
16		35		54	
17		36		55	
18		37			
19		38			

In additional preferred aspects, the compound is selected from Table B below, or a pharmaceutically acceptable salt thereof:

TABLE B

No.	Structure	No.	Structure	No.	Structure
56		78		100	
57		79		101	
58		80		102	
59		81		103	
60		82		104	
61		83		105	
62		84		106	
63		85		107	
64		86		108	

65		87		109	
66		88		110	
67		89		111	
68		90		112	
69		91		113	
70		92		114	
71		93		115	
72		94		116	
73		95		117	
74		96		118	
75		97		119	

76		98		120	
77		99		121	

Additional Representative Compounds of the Invention:

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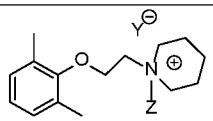
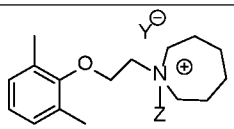
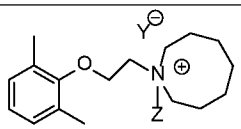
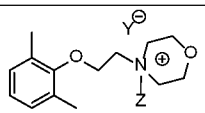
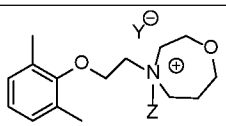
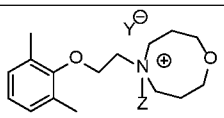
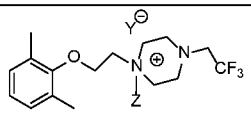
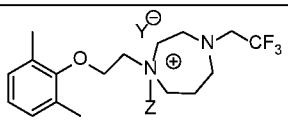
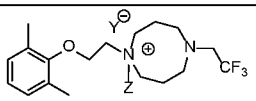
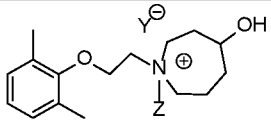
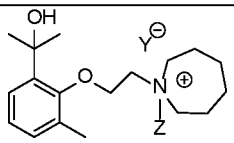
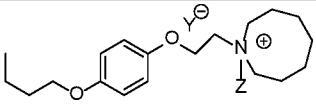
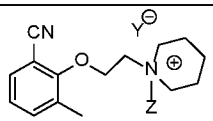
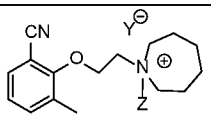
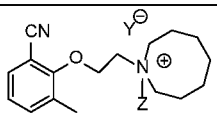
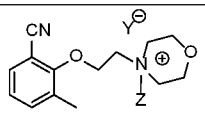
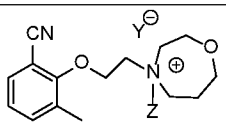
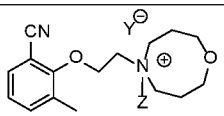
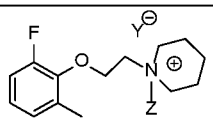
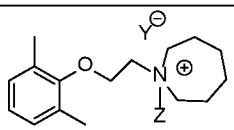
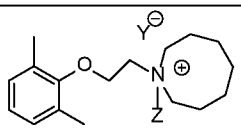
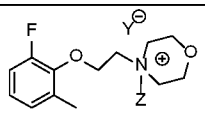
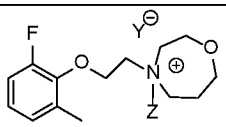
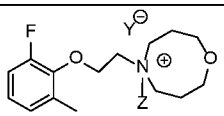
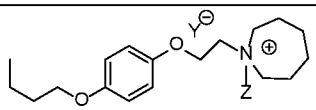
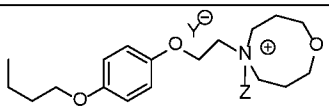
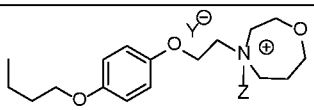
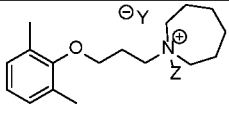
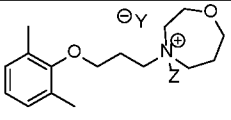
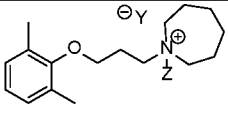
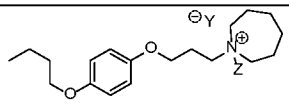
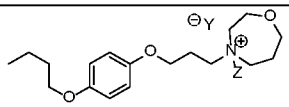
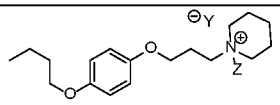
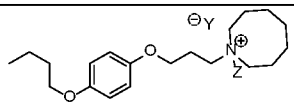
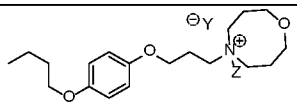
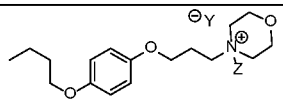
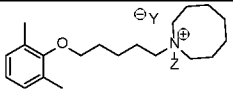
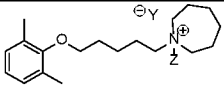
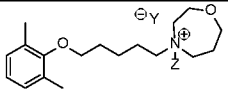
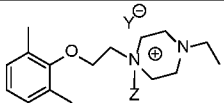
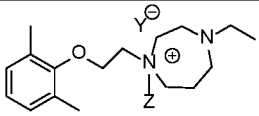
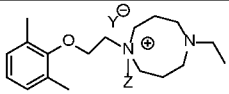
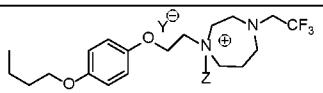
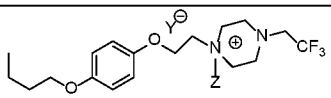
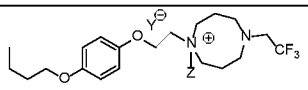
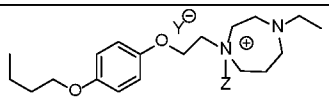
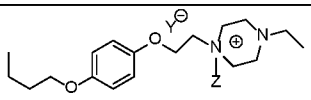
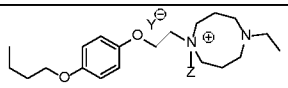
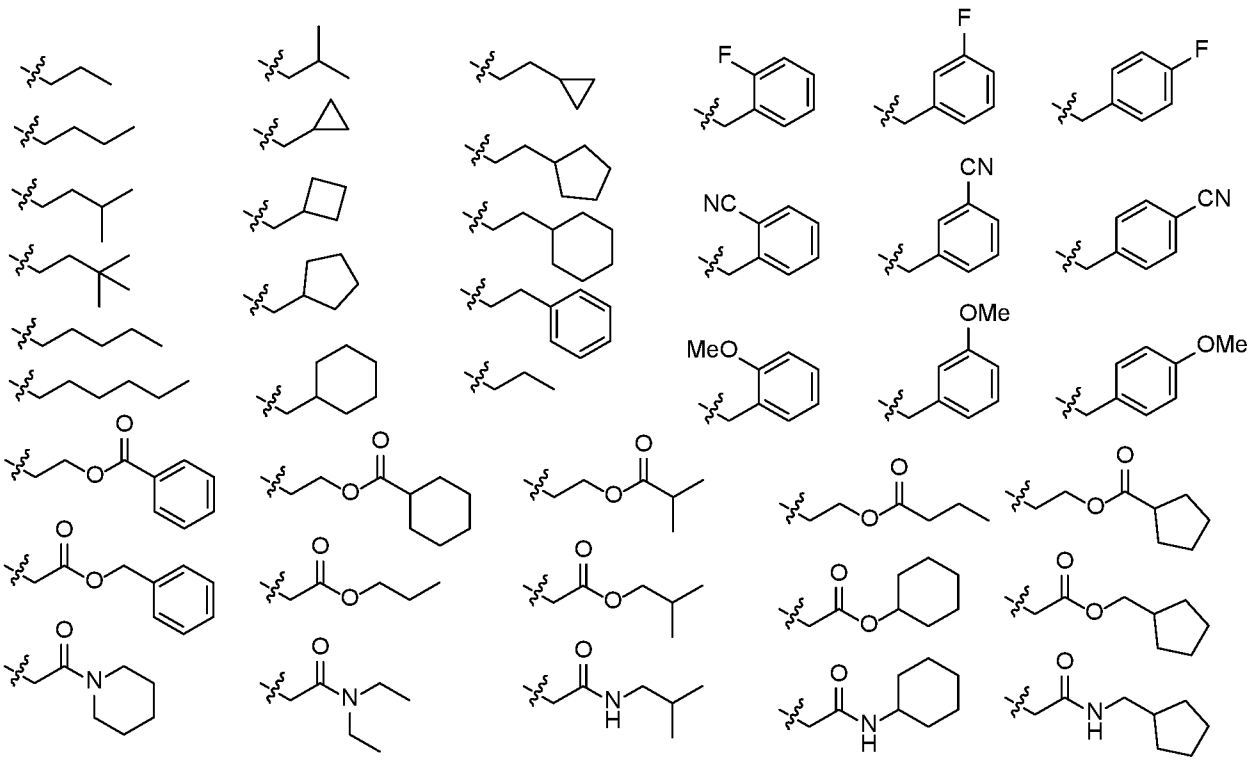
122		138		154	
123		139		155	
124		140		156	
125		141		157	
126		142		158	
127		143		159	
128		144		160	
129		145		161	
130		146		162	
131		147		163	

132		148		164	
133		149		165	
134		150		166	
135		151		167	
136		152		168	
137		153		169	

Where representative Z structures are:



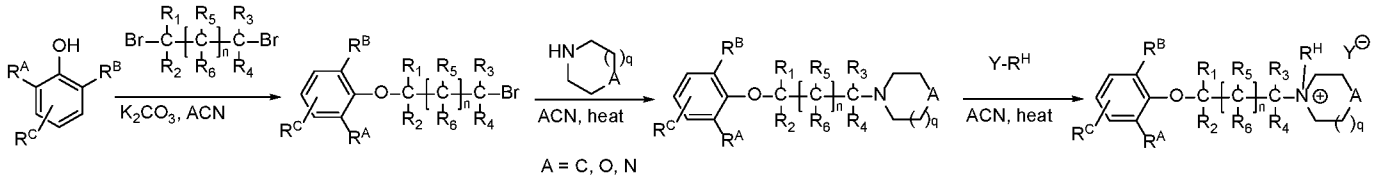
Compositions of the invention where R is methyl or ethyl can comprise racemic mixtures, pure enantiomers, or an excess of one enantiomer over the other. For example, a composition can comprise an enantiomeric excess of at least 5, 10, 20, 30, 40, 50, 60, 70, 80 or 90%. In one embodiment, the enantiomeric excess is at least 95%.

The compounds of the invention include all enantiomers which may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, as well as their racemic and optically pure forms, and is not limited to those described herein in any of their pharmaceutically acceptable forms, including enantiomers, salts, solvates, polymorphs, solvatomorphs, hydrates, anhydrous and other crystalline forms and combinations thereof.

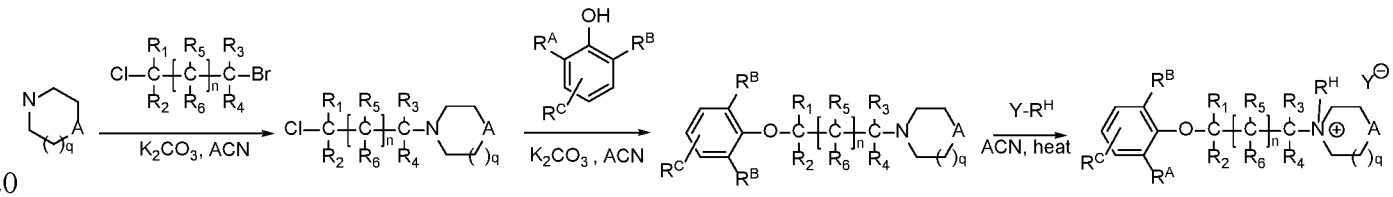
Preferably, a pharmaceutical composition comprises a compound of the invention as an R enantiomer in substantially pure form; or, a pharmaceutical composition comprises a compound of the invention as an S enantiomer in substantially pure form; or, a pharmaceutical composition comprises a compound of the invention as enantiomeric mixtures which contain an excess of the R enantiomer or an excess of the S enantiomer. It is particularly preferred that the pharmaceutical composition contains a compound of the invention which is a substantially pure optical isomer. For the avoidance of doubt, a compound of the invention can, if desired, be used in the form of solvates.

Compounds having Formula (**I**) can be prepared using methods analogous to that described in the Examples and the following synthetic schemes:

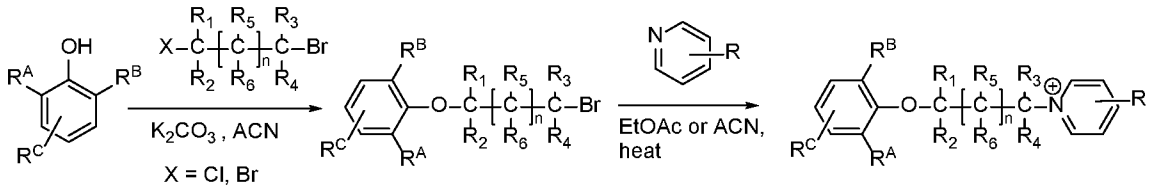
Scheme A:



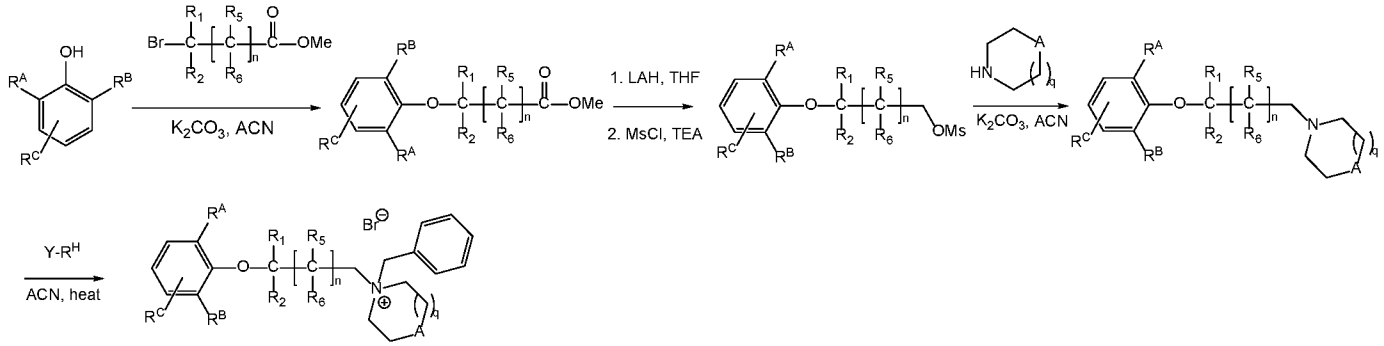
Scheme B:



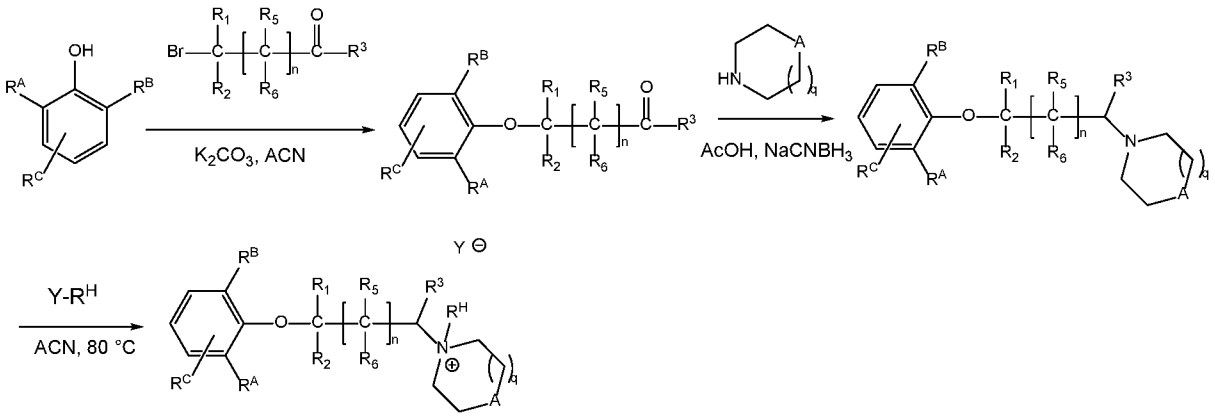
Scheme C:



Scheme D:



Scheme E:



Additional Biologically Active Agents and Exogenous Large Pore Channel Agonists

As described above, the compound or composition of the invention can be administered with a biologically active agent. For example, one or more additional biologically active agents, including those typically used to treat neurogenic inflammation, may be used in combination with a compound or composition of the invention described herein. The biologically active agents include, but are not limited to, TRPA1 receptor agonists, TRPV1-4 receptor agonists, TRPM8 agonists, ASIC agonists, P2X receptor agonists, acetaminophen, NSAIDs, glucocorticoids, narcotics, tricyclic antidepressants, amine transporter inhibitors, anticonvulsants, anti-proliferative and immune modulatory agents, an antibody or antibody fragment, an antibiotic, a polynucleotide, a polypeptide, a protein, an anti-cancer agent, a growth factor, and a vaccine.

TRPV1 agonists that can be employed in the methods, kits and compositions 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 (for example, a compound of the invention). 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. 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. Pat. 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-hydroperoxyeicosatetraenoic acid, inhibitor cysteine knot (ICK) peptides (vanillotoxins), piperine, MSK195 (N-[2-(3,4-d imethylbenzyl)-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.

Suitable TRPV2-4 agonists include, but are not limited to, are 2-APB, cannabinol, diphenylboronic anhydride, insulin-like growth factor 1, lysophosphatidylcholine, lysophosphatidylinositol, probenecid, Δ9-tetrahydrocannabinol, vanillin, eugenol, cinnamaldehyde, camphor, carvacrol, thymol, citral, farnesyl diphosphate,

tetrahydrocannabivarin, incensole acetate, diphenylboronic anhydride, 6-tert-butyl-m-cresol, dihydrocarveocarveol, borneol, (-)-menthol, GSK1016790A, 4α-PDH, 5,6-epoxyeicosatrienoic acid, 4α-PDD, bisandrographolide, citric acid, phorbol 12-myristate 13-acetate and RN1747.

Suitable TRPM8 agonists include, but are not limited to, are menthol, icilin, eucalyptus, linalool, geraniol, hydroxy-citronellal, WS-3, WS-23, Frescolat MGA, Frescolat ML, PMD 38, CPS125, Coolact P, M8-Ag, AITC, cryosim-3, AX-8 and Cooling Agent 10.

Suitable ASIC agonists include, but are not limited to, chlorophenylguanidine hydrochloride, GMQ hydrochloride, tetrahydropapaveroline (THP), reticulin, polyamine agmatine, lysophosphatidylcholine, arachidonic acid and neuropeptide SF.

Other biologically active agents which can be employed in the methods, compositions, and kits of the invention include any that activates TRPA1 receptors on nociceptors or pruriceptors and allows for entry of at least one inhibitor of voltage-gated ion channels. Suitable TRPA1 agonists include but are not limited to cinnamaldehyde, allyl-isothiocynanate (mustard oil), diallyl disulfide, icilin, cinnamon oil, wintergreen oil, clove oil, acrolein, hydroxy-alpha-sanshool, 2-aminoethoxydiphenyl borate, 4-hydroxynonenal, methyl p-hydroxybenzoate, and 3′-carbamoylbiphenyl-3-yl cyclohexylcarbamate (URB597).

P2X agonists that can be employed in the methods, compositions, 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 ATP, α,β-methylene ATP, 2-methylthio-ATP, 2′ and 3′-O-(4-benzoylbenzoyl)-ATP, and ATP5′-O-(3-thiotriphosphate).

Other biologically active agents that can be used in combination with the compounds of the invention include NSAIDs, glucocorticoids, narcotics, tricyclic antidepressants, amine transporter inhibitors, anticonvulsants, anti-proliferative and immune modulatory agents, an antibody or antibody fragment, an antibiotic, a polynucleotide, a polypeptide, a protein, an anti-cancer agent, a growth factor, and a vaccine.

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, fludrocortisone 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.

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.

Formulation of Compositions

The administration of the compounds of the invention may be by any suitable means that results in the reduction of perceived pain or itch sensation at the target region. The compounds of the invention may be contained in any appropriate amount in any suitable carrier substance, and are generally present in amounts totaling 1-99% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for oral, parenteral (e.g., intravenous, intramuscular), rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, vaginal, intrathecal, epidural, or ocular administration, or by injection, inhalation, or direct contact with the nasal or oral mucosa. Topical or dermal administration is preferred.

Thus, the composition may be in the form of, e.g., suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, sprays, aerosols, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, tablets, capsules, pills, powders, granulates. The compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: The Science and Practice of Pharmacy, 22nd edition, 2013, ed. L.V. Allen, Pharmaceutical Press, Philadelphia, and Encyclopedia of Pharmaceutical Technology, 4th Edition, ed. J. Swarbrick, 2013, CRC Press, New York).

Each compound may be formulated in a variety of ways that are known in the art. For example, a compound of the invention and a biologically active agent as defined herein may be formulated together or separately. Desirably, a compound of the invention and a biologically active agent are formulated together for their simultaneous or near simultaneous administration. In another embodiment, two or more biologically active agents may be formulated together with a compound of the invention, or separately. Other examples include, but are not limited to, two or more compounds of the invention formulated together, wherein the compounds are formulated together with or without one or more biologically active 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.

Topical Formulations

The compositions 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 topical formulation, including but not limited to a cream, gel, or ointment, 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 itch, pruritis, psoriasis, or atopic dermatitis.

The compositions can be formulated using any dermatologically acceptable carrier. Exemplary carriers include a solid carrier, such as alumina, clay, microcrystalline cellulose, silica, or talc; and/or a liquid carrier, such as an alcohol, a glycol, or a water-alcohol/glycol blend. The therapeutic agents may also be administered in liposomal formulations that allow therapeutic agents to enter the skin. Such liposomal formulations are described in U.S. Pat. Nos. 5,169,637; 5,000,958; 5,049,388; 4,975,282; 5,194,266; 5,023,087; 5,688,525; 5,874,104; 5,409,704; 5,552,155; 5,356,633; 5,032,582; 4,994,213; 8,822,537, and PCT Publication No. WO 96/40061. Examples of other appropriate vehicles are described in U.S. Pat. Nos. 4,877,805, 8,822,537, and EP Publication No. 0586106A1. Suitable vehicles of the invention may also include mineral oil, petrolatum, polydecene, stearic acid, isopropyl myristate, polyoxyl 40 stearate, stearyl alcohol, or vegetable oil.

The composition can further include a skin penetrating enhancer, such as those described in "Percutaneous Penetration enhancers", (eds. Smith E W and Maibach H I. CRC Press 1995). Exemplary skin penetrating enhancers include alkyl (N,N-disubstituted amino alkanoate) esters, such as dodecyl 2-(N,N dimethylamino) propionate (DDAIP), which is described in patents U.S. Pat. Nos. 6,083,996 and 6,118,020, which are both incorporated

herein by reference; a water-dispersible acid polymer, such as a polyacrylic acid polymer, a carbomer (e.g., Carbopol™ or Carbopol 940P™, available from B. F. Goodrich Company (Akron, Ohio)), copolymers of polyacrylic acid (e.g., Pemulen™ from B. F. Goodrich Company or Polycarbophil™ from A. H. Robbins, Richmond, Va.; a polysaccharide gum, such as agar gum, alginate, carrageenan gum, ghatti gum, karaya gum, kadaya gum, rhamsan gum, xanthan gum, and galactomannan gum (e.g., guar gum, carob gum, and locust bean gum), as well as other gums known in the art (see for instance, Industrial Gums: Polysaccharides & Their Derivatives, Whistler R. L., BeMiller J. N. (eds.), 3rd Ed. Academic Press (1992) and Davidson, R. L., Handbook of Water-Soluble Gums & Resins, McGraw-Hill, Inc., N.Y. (1980)); or combinations thereof.

Other suitable polymeric skin penetrating enhancers are cellulose derivatives, such as ethyl cellulose, methyl cellulose, hydroxypropyl cellulose. Additionally, known transdermal penetrating enhancers can also be added, if desired. Illustrative are dimethyl sulfoxide (DMSO) and dimethyl acetamide (DMA), 2-pyrrolidone, N,N-diethyl-m-toluamide (DEET), 1-dodecylazacycloheptane-2-one (Azone™, a registered trademark of Nelson Research), N,N-dimethylformamide, N-methyl-2-pyrrolidone, calcium thioglycolate and other enhancers such as dioxolanes, cyclic ketones, and their derivatives and so on.

Also illustrative are a group of biodegradable absorption enhancers which are alkyl N,N-2-(disubstituted amino) alkanoates as described in U.S. Pat. No. 4,980,378 and U.S. Pat. No. 5,082,866, which are both incorporated herein by reference, including: tetradecyl (N,N-dimethylamino) acetate, dodecyl (N,N-dimethylamino) acetate, decyl (N,N-dimethylamino) acetate, octyl (N,N-dimethylamino) acetate, and dodecyl (N,N-diethylamino) acetate.

Particularly preferred skin penetrating enhancers include isopropyl myristate; isopropyl palmitate; dimethyl sulfoxide; decyl methyl sulfoxide; dimethylalanine amide of a medium chain fatty acid; dodecyl 2-(N,N-dimethylamino) propionate or salts thereof, such as its organic (e.g., hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acid addition salts) and inorganic salts (e.g., acetic, benzoic, salicylic, glycolic, succinic, nicotinic, tartaric, maleic, malic, pamoic, methanesulfonic, cyclohexanesulfamic, picric, and lactic acid addition salts), as described in U.S. Pat. No. 6,118,020; and alkyl 2-(N,N-disubstituted amino)-alkanoates, as described in U.S. Pat. No. 4,980,378 and U.S. Pat. No. 5,082,866.

The skin penetrating enhancer in this composition by weight would be in the range of 0.5% to 10% (w/w). The most preferred range would be between 1.0% and 5% (w/w). In another embodiment, the skin penetrating enhancer comprises between 0.5%-1%, 1%-2%, 2%-3%, 3%-4%, or 4%-5%, (w/w) of the composition.

The compositions can be provided in any useful form. For example, the compositions of the invention may be formulated as solutions, emulsions (including microemulsions), suspensions, creams, ointments, foams, lotions, gels, powders, or other typical solid, semi-solid, or liquid compositions (e.g., topical sprays) used for application to the skin or other tissues where the compositions may be used. Such compositions may contain other ingredients typically used in such products, such as colorants, fragrances, thickeners (e.g., xanthan gum, a fatty acid, a fatty acid salt or ester, a fatty alcohol, a modified cellulose, a modified mineral material, Krisgel 100™, or a synthetic polymer), antimicrobials, solvents, surfactants, detergents, gelling agents, antioxidants, fillers, dyestuffs, viscosity-controlling agents, preservatives, humectants, emollients (e.g., natural or synthetic oils, hydrocarbon oils, waxes, or silicones), hydration agents, chelating agents, demulcents, solubilizing excipients, adjuvants, dispersants, skin penetrating enhancers, plasticizing agents, preservatives, stabilizers, demulsifiers, wetting agents, sunscreens, emulsifiers, moisturizers, astringents, deodorants, and optionally including anesthetics, anti-itch actives, botanical extracts, conditioning agents, darkening or lightening agents, glitter, humectants, mica, minerals, polyphenols, silicones or derivatives thereof, sunblocks, vitamins, and phytomedicinals.

The compositions can also include other like ingredients to provide additional benefits and improve the feel and/or appearance of the topical formulation. Specific classes of additives commonly use in these formulations include: isopropyl myristate, sorbic acid NF powder, polyethylene glycol, phosphatidylcholine (including mixtures of phosphatidylcholine, such as phospholipon G), Krisgel 100™ distilled water, sodium hydroxide, decyl methyl sulfoxide (as a skin penetrating enhancer), menthol crystals, lavender oil, butylated hydroxytoluene, ethyl diglycol reagent, and 95% percent (190 proof) ethanol.

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 patch, capsule or tablet that is administered to the patient.

Any pharmaceutically acceptable vehicle or formulation suitable for local application and/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. Controlled 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 controlled, 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 topical, transdermal, 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 anti-nociceptive 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. Pat. 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, 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. Pat. No. 4,757,128, incorporated herein by reference. Polyorthoester polymers may be prepared, e.g., as set forth in U.S. Pat. No. 4,070,347, incorporated herein by reference. Polyphosphoesters may be prepared and used as set forth in U.S. Pat. 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.

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, taste masking agents (such as hydroxypropyl methylcellulose, hydroxypropyl cellulose), and the like.

One or more compounds of the invention and one or more biologically active agents, as defined herein, may be mixed together in a tablet, capsule, or other vehicle, or may be partitioned. In one example, a compound of the invention is contained on the inside of the tablet, and the biologically active agent is on the outside of the tablet, such that a substantial portion of the biologically active agent is released prior to the release of the compound of the invention.

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.

Formulations for oral administration to the mouth may also be provided as a mouthwash, an oral spray, oral rinse solution, or oral ointment or oral gel.

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.

Parenteral Formulations

Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the compound is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additional contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilizers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the compound in the liquid is from about 1 ng/ml to about 10 μg/ml, for example from about 10 ng/ml to about 1 μg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Formulations for Ophthalmic Administration

The compounds of the invention can also be formulated with an ophthalmically acceptable carrier in sufficient concentration so as to deliver an effective amount of the active compound or compounds to the optic nerve site of the eye. Preferably, the ophthalmic, therapeutic solutions contain one or more of the active compounds in a concentration range of approximately 0.0001% to approximately 5 % (weight by volume) and more preferably approximately 0.0005% to approximately 0.1% (weight by volume).

An ophthalmically acceptable carrier does not cause significant irritation to the eye and does not abrogate the pharmacological activity and properties of the charged sodium channel blockers.

Ophthalmically acceptable carriers are generally sterile, essentially free of foreign particles, and generally have a pH in the range of 5-8. Preferably, the pH is as close to the pH of tear fluid (7.4) as possible. Ophthalmically acceptable carriers are, for example, sterile isotonic solutions such as isotonic sodium chloride or boric acid solutions. Such carriers are typically aqueous solutions contain sodium chloride or boric acid. Also useful are phosphate buffered saline (PBS) solutions.

Various preservatives may be used in the ophthalmic preparation. Preferred preservatives include, but are not limited to, benzalkonium potassium, chlorobutanol, thimerosal, phenylmercuric acetate, and phenylmercuric nitrate. Likewise, various preferred vehicles may be used in such ophthalmic preparation. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose and hydroxyethyl cellulose.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, etc., mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include but are not limited to, acetate buffers, citrate buffers, phosphate buffers, and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed. Ophthalmically acceptable antioxidants can also be include. Antioxidants include but are not limited to sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, and butylated hydroxytoluene.

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.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of, for example, gelatin or blisters of, for example, laminated aluminum foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di or ploy-saccharides (e.g., lactose or starch). Use of lactose is preferred. In one embodiment, each capsule or cartridge may contain between about 2 ug to about 100 mg of the compound of formula (**I**) optionally in combination with another therapeutically active ingredient. In a preferred embodiment, each capsule or cartridge may contain between about 10 ug to about 50 mg of the compound of formula (**I**) optionally in combination with another therapeutically active ingredient. In another embodiment, each capsule or cartridge may contain between about 20 ug to about 10 mg of the compound of formula (**I**) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be delivered without excipients.

Suitably, the packaging/medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain an aqueous medium, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient(s); a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Compositions formulated for nasal or inhalation administration may include one or more taste-masking agents such as flavoring agents, sweeteners, and other strategies, such as sucrose, dextrose, and lactose, carboxylic acids, menthol, amino acids or amino acid derivatives such as arginine, lysine, and monosodium glutamate, and/or synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits, etc. and combinations thereof. These may include cinnamon oils, oil of wintergreen, peppermint oils, clover oil, bay oil, anise oil, eucalyptus, vanilla, citrus oil such as lemon oil, orange oil, grape and grapefruit oil, fruit essences including apple, peach, pear, strawberry, raspberry, cherry, plum, pineapple, apricot, etc. Additional sweeteners include sucrose, dextrose, aspartame, acesulfame-K, sucralose and saccharin, organic acids (by non-limiting example citric acid and aspartic acid). Such flavors may be present at from about 0.05 to about 4 percent by weight, and may be present at lower or higher amounts as a factor of one or more of potency of the effect on flavor, solubility of the flavorant, effects of the flavorant on solubility or other physicochemical or pharmacokinetic properties of other formulation components, or other factors.

Indications

The compounds, compositions, methods, and kits of the invention can be used to treat itch, pain, or cough. Conditions include trigeminal trophic syndrome, erythromelalgia, back and neck pain, lower back pain, cancer pain, gynecological and labor pain, abdominal wall pain, chronic abdominal wall pain, fibromyalgia, allergic rhinitis, arthritis, rheumatoid arthritis, osteoarthritis, rheumatological pains, orthopedic pains, acute and post herpetic neuralgia and other neuropathic pains (including peripheral neuropathy), sickle cell crises, muscle pain, vulvodynia, rectal pain, Levator ani syndrome, proctalgia fugax, peri-anal pain, hemorrhoid pain, stomach pain, ulcers, inflammatory bowel disease, irritable bowel disease, irritable bowel syndrome, oral mucositis, esophagitis, interstitial cystitis, urethritis and other urological pains, dental pain, burn pain, headaches, ophthalmic irritation, conjunctivitis (e.g., allergic conjunctivitis), eye redness, dry eye, dry eye syndrome (chronic ocular pain), complex regional pain syndrome, acute postoperative pain, postoperative pain, post-surgical

ocular pain, and procedural pain (i.e., pain associated with injections, draining an abscess, surgery, dental procedures, ophthalmic procedures, ophthalmic irritation, conjunctivitis (e.g., allergic conjunctivitis), eye redness, dry eye, arthroscopies and use of other medical instrumentation, cosmetic surgical procedures, dermatological procedures, setting fractures, biopsies, and the like).

Since a subclass of nociceptors mediate itch sensation, the compounds, compositions, methods, and kits of the invention are particularly suitable to treat itch in patients with conditions like pruritus (including, but not limited to, brachioradial, chronic idiopathic, genital/anal, notalgia paresthetica, and scalp), allergic dermatitis, atopic dermatitis, contact dermatitis, poison ivy, infections, parasites, insect bites, pregnancy, metabolic disorders, liver or renal failure, drug reactions, allergic reactions, eczema, hand eczema, genital and anal itch, hemorrhoid itch, and cancer.

Since a subclass of nociceptors can initiate aberrant cough reflexes, the compounds, compositions, methods, and kits of the invention can also be used to treat cough in patients with conditions like asthma, COPD, asthma-COPD overlap syndrome (ACOS), interstitial pulmonary fibrosis (IPF), idiopathic pulmonary fibrosis, post viral cough, post-infection cough, chronic idiopathic cough and lung cancer.

The compounds, compositions, methods, and kits of the invention can also be used to treat neurogenic inflammation and neurogenic inflammatory disorders. Inflammation is a complex set of responses to harmful stimuli that results in localized redness, swelling, and pain. Inflammation can be innate or adaptive, the latter driven by antigens and is mediated by immune cells (immune-mediated 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 peptide containing vesicles, and the pro-inflammatory neuropeptides include substance P, neurokinin A and B (collectively known as tachykinins), calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptide (VIP).

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, gastritis, 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").

Genomic analysis of lung resident ILC2 cells has revealed expression of receptors for several neuropeptides released by sensory neurons, including SP, CGRP and VIP, providing an opportunity for nociceptors to directly communicate with these cells. In particular, VIP is found to be expressed in NaV1.8+ nodose ganglion neurons, including lung afferents in OVA-exposed mice. Cultured nodose ganglion neurons stimulated with capsaicin or IL5 also released VIP while BALF from OVA-exposed mice contained elevated VIP compared to vehicle-challenged mice (Talbot et al., *Neuron*. 2015 July 15; 87(2): 341–354). These data indicate that VIP is released in the inflamed lung and can be blocked by silencing neurons with charged sodium channel blockers of the present invention. In addition, when CD4+ T cells cultured under T_H2 skewing conditions were exposed to recombinant mouse VIP, the transcript levels of IL-13 and IL-5 increased, suggesting that VIP contributes to the competence of T_H2 cells to transcribe these type II regulatory cytokines.

Nociceptors including those which are $Nav1.8^+/TRPV1^+$ have been demonstrated to be integral in the immune response in models of psoriasis and contact dermatitis (Riol-Blanco et al., Nature 2014 June 5; 510(7503): 157-161). In the study on imiquimod-induced psoriasis, pharmacological or genetic ablation of nociceptors caused dermal dendritic cells (DDCs) to no longer no longer produce IL-23. This lack of IL-23 significantly reduced the

production of inflammatory cytokines dermal Th17 cells and also significantly reduced the influx of inflammatory cells into the skin. By confocal microscopy 75% of DDCs were in either direct contact or in close proximity to sensory nerves. Pharmacological ablation of $Nav1.8^{+}/TRPV1^{+}$ nociceptors also significantly reduced skin inflammation in the IL-12 driven DNFB model of contact dermatitis (Riol-Blanco et al., Nature 2014 June 5; 510(7503): 157-161).

Immune mediator release from immune cells can also activate nociceptors. Mast cells are found close to primary nociceptive neurons and contribute to nociceptor sensitization in a number of contexts. Injection of the secretagogue compound 48/80 promotes degranulation of mast cells in the dura and leads to excitation of meningeal nociceptors. Mast cell degranulation also contributes to the rapid onset of nerve growth factor-induced thermal hyperalgesia. Macrophages contribute to nociceptor sensitization by releasing several soluble mediators. Expression of the chemokine macrophage inflammatory protein-1α (MIP-1α) and its receptors CCR1 and CCR5 is increased in macrophages and Schwann cells after partial ligation of the sciatic nerve and contributes to the development of neuropathic pain. Lymphocytes contribute to the sensitization of peripheral nociceptors. T cells infiltrate the sciatic nerve and dorsal root ganglion (DRG) after nerve injury. Hyperalgesia and allodynia induced by nerve injury are markedly attenuated or abrogated in rodents lacking T cells and the immunosuppressant rapamycin attenuates neuropathic pain in rats, partly owing to an effect on T cells. Among the subsets of T cells, type 1 and 2 helper T cells (T_H1 and T_H2 cells) have been shown to have different roles in neuropathic pain. T_H1 cells facilitate neuropathic pain behavior by releasing proinflammatory cytokines (IL-2 and interferon-γ (IFNγ)), whereas T_H2 cells inhibit it by releasing anti-inflammatory cytokines (IL-4, IL-10 and IL-13). The complement system also has a role in inflammatory hyperalgesia and neuropathic pain. C5a, an anaphylatoxin, is an important effector of the complement cascade and upon binding to C5aR1 receptors on neutrophils it becomes a potent neutrophil attractant (Ren & Dubner, *Nat. Med.* 16:1267-1276 (2010)).

Bacterial infections have been shown to directly activate nociceptors, and that the immune response mediated through TLR2, MyD88, T cells, B cells, and neutrophils and monocytes is not necessary for *Staphylococcus aureus*-induced pain in mice (Chiu et al., *Nature* 501:52-57 (2013)). Mechanical and thermal hyperalgesia in mice is correlated with live bacterial load rather than tissue swelling or immune activation. Bacteria induce calcium flux and action potentials in nociceptor neurons, in part via bacterial N-formylated peptides and the pore-forming toxin α-haemolysin, through distinct mechanisms. Specific ablation of

Nav1.8-lineage neurons, which include nociceptors, abrogated pain during bacterial infection, but concurrently increased local immune infiltration and lymphadenopathy of the draining lymph node. Thus, bacterial pathogens produce pain by directly activating sensory neurons that modulate inflammation, an unsuspected role for the nervous system in host-pathogen interactions. Data from Talbot et al., (*Neuron*. 2015 July 15; 87(2): 341–354.) have also suggested that nociceptors are activated during exposure to allergens in sensitized animals.

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, but are not limited to, allergic inflammation, inflammatory bowel disease, interstitial cystitis, atopic dermatitis, asthma, conjunctivitis, arthritis, colitis, contact dermatitis, diabetes, eczema, cystitis, gastritis, migraine headache, psoriasis, rhinitis, rosacea, 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.

Assessment of Itch, Pain, Cough, and Neurogenic Inflammation

In order to measure the efficacy of any of the compounds, compositions, methods, and kits of the invention in the treatment of pain associated with musculoskeletal, immunoinflammatory and neuropathic disorders, a measurement index may be used. Indices that are useful include a visual analog scale (VAS), a Likert scale, categorical pain scales, descriptors, the Lequesne index, the WOMAC index, and the AUSCAN index, each of which is well known in the art. Such indices may be used to measure pain, itch, function, stiffness, or other variables.

A visual analog scale (VAS) provides a measure of a one-dimensional quantity. A VAS generally utilizes a representation of distance, such as a picture of a line with hash marks drawn at regular distance intervals, e.g., ten 1-cm intervals. For example, a patient can be asked to rank a sensation of pain or itch by choosing the spot on the line that best corresponds to the sensation of pain or itch, where one end of the line corresponds to “no pain” (score of 0 cm) or “no itch” and the other end of the line corresponds to “unbearable pain” or “unbearable itch” (score of 10 cm). This procedure provides a simple and rapid

approach to obtaining quantitative information about how the patient is experiencing pain or itch. VAS scales and their use are described, e.g., in U.S. Pat. Nos. 6,709,406 and 6,432,937.

A Likert scale similarly provides a measure of a one-dimensional quantity. Generally, a Likert scale has discrete integer values ranging from a low value (e.g., 0, meaning no pain) to a high value (e.g., 7, meaning extreme pain). A patient experiencing pain is asked to choose a number between the low value and the high value to represent the degree of pain experienced. Likert scales and their use are described, e.g., in U.S. Pat. Nos. 6,623,040 and 6,766,319.

The Lequesne index and the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index assess pain, function, and stiffness in the knee and hip of OA patients using self-administered questionnaires. Both knee and hip are encompassed by the WOMAC, whereas there is one Lequesne questionnaire for the knee and a separate one for the hip. These questionnaires are useful because they contain more information content in comparison with VAS or Likert. Both the WOMAC index and the Lequesne index questionnaires have been extensively validated in OA, including in surgical settings (e.g., knee and hip arthroplasty). Their metric characteristics do not differ significantly.

The AUSCAN (Australian-Canadian hand arthritis) index employs a valid, reliable, and responsive patient self-reported questionnaire. In one instance, this questionnaire contains 15 questions within three dimensions (Pain, 5 questions; Stiffness, 1 question; and Physical function, 9 questions). An AUSCAN index may utilize, e.g., a Likert or a VAS scale.

Indices that are useful in the methods, compositions, and kits of the invention for the measurement of pain include the Pain Descriptor Scale (PDS), the Visual Analog Scale (VAS), the Verbal Descriptor Scales (VDS), the Numeric Pain Intensity Scale (NPIS), the Neuropathic Pain Scale (NPS), the Neuropathic Pain Symptom Inventory (NPSI), the Present Pain Inventory (PPI), the Geriatric Pain Measure (GPM), the McGill Pain Questionnaire (MPQ), mean pain intensity (Descriptor Differential Scale), numeric pain scale (NPS) global evaluation score (GES) the Short-Form McGill Pain Questionnaire, the Minnesota Multiphasic Personality Inventory, the Pain Profile and Multidimensional Pain Inventory, the Child Heath Questionnaire, and the Child Assessment Questionnaire.

Itch can be measured by subjective measures (VAS, Lickert, descriptors). Another approach is to measure scratch which is an objective correlate of itch using a vibration transducer or movement-sensitive meters.

Cough can be measured by standard questionnaires like the Leicester Cough Questionnaire as well as validated objective instruments to measure cough frequency (e.g., VitaloJAK).

EXAMPLES

The following examples are intended to illustrate the invention and are not intended to limit it.

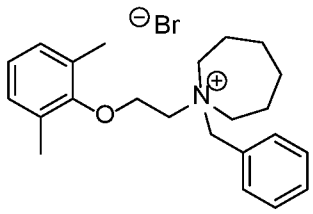
Example 1 – Synthesis of Compounds 1A' to 51A'

General Abbreviation Definitions

ACN	acetonitrile
AcOH	acetic acid
aq.	aqueous
BBr_3	boron tribromide
CDCl3	D_3-chloroform
δ	chemical shift (ppm)
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
ESI	electrospray ionization
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hour
HPLC	high performance liquid chromatography
K_2CO_3	potassium carbonate
LAH	lithium aluminum hydride
MeOH	methanol
mHz	*megahertz*
MS	mass spectrometry
m/z	mass to charge ratio
$NaCNBH_3$	sodium cyanoborohydride
Na_2SO_4	sodium sulphate
NMR	nuclear magnetic resonance
pet ether	petroleum ether

RT	room temperature
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet light

Synthesis of 1-benzyl-1-(2-(2, 6-dimethylphenoxy) ethyl) azepan-1-ium bromide



Compound 1A

- *Synthesis of 2-(2-bromoethoxy)-1, 3-dimethylbenzene*:

To a stirred solution of 2, 6-dimethylphenol (0.50 g, 4.1 mmol) in acetonitrile (8.0 mL) was added potassium carbonate (1.7 g, 12.3 mmol) and 1, 2-dibromoethane (3.85 g, 20.5 mmol). The resulting reaction mixture was stirred at 90°C for 16 h as progress of the reaction was monitored by TLC (Mobile phase: 5% EtOAc in pet ether, Visualization: UV). The reaction mixture was cooled to RT and concentrated under reduced pressure, diluted with water (100 mL) and extracted with dichloromethane (3 X 50 mL). The combined organic extracts were washed with brine solution (50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude which was purified by silica gel chromatography (eluted with pet ether) to afford pure 2-(2-bromoethoxy)-1, 3-dimethylbenzene (0.20 g) as a colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.00 – 7.25 (m, 2 H), 6.91 – 6.95 (m, 1 H), 4.01 – 4.10 (m, 2 H), 3.65 – 3.68 (m, 2 H), 2.30 (s, 6 H).

- *Synthesis of intermediate 1-(2-(2, 6-dimethylphenoxy) ethyl) azepane*:

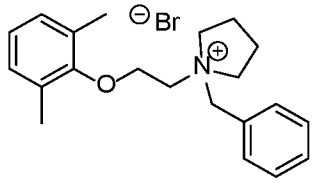
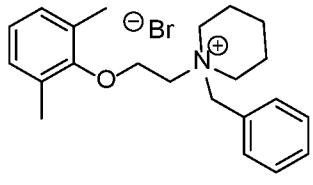
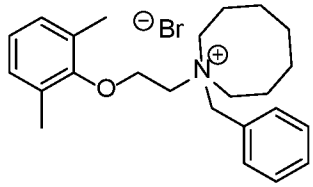
To a solution of 2-(2-bromoethoxy)-1, 3-dimethylbenzene (200 mg, 0.87 mmol) in acetonitrile (3.0 mL) was added DIPEA (0.45g, 3.5 mmol) and azepane (0.12g, 1.2 mmol). The resulting reaction mixture was stirred at 90°C for 16 h as progress of the reaction was monitored by TLC. (Mobile phase: 10% EtOAc in pet ether, Visualization: UV). The reaction mixture was cooled to RT and concentrated under reduced pressure, diluted with water (20 mL) and extracted with dichloromethane (3 X 20 mL). The combined organic

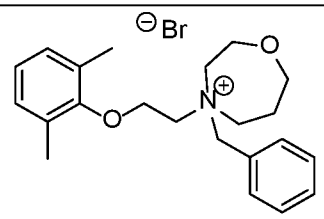
extracts were washed with brine solution (20 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 1-(2-(2, 6-dimethylphenoxy) ethyl) azepane (210 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.98 - 7.00 (m, 2 H), 6.88 – 6.92 (m, 1 H), 3.85 - 3.88 (m, 2 H), 2.93 – 2.96 (m, 2 H), 2.75 – 2.77 (m, 4 H), 2.28 (s, 6 H), 1.59-1.68 (m, 8 H).

- *Synthesis of 1-benzyl-1-(2-(2, 6-dimethylphenoxy) ethyl) azepan-1-ium bromide:*

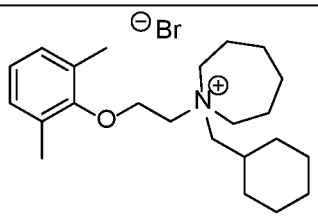
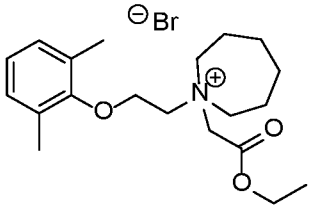
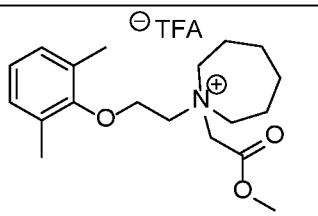
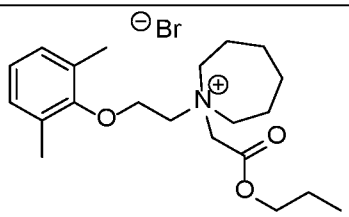
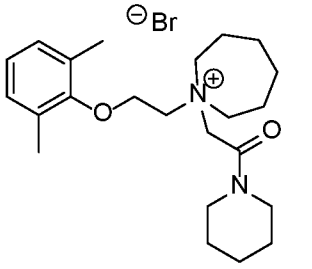
To a solution of 1-(2-(2, 6-dimethylphenoxy) ethyl) azepane (0.1 g, 0.4 mmol) in acetonitrile (1.5 mL) was added benzyl bromide (0.072 ml, 0.6 mmol) and the resulting reaction mixture was stirred at 90°C for 16 h in sealed tube as progress of the reaction was monitored by TLC (Mobile phase: 50% EtOAc in pet ether, Visualization: UV). The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford crude product which was triturated with ethyl acetate (3 X 5 ml) to afford 1-benzyl-1-(2-(2, 6-dimethylphenoxy) ethyl) azepan-1-ium bromide (80.5 mg) as an off white solid. MS (ESI): m/z 338.41 $[M]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.63 – 7.65 (m, 2 H), 7.49-7.57 (m, 3 H), 7.04 – 7.08 (m, 2 H), 6.96 – 6.98 (m, 1 H), 4.72 (s, 2 H), 4.29 (t, 2 H), 3.52-3.69 (m, 6 H), 2.29 (s, 6 H), 1.88 – 1.92 (m, 4 H), 1.59 – 1.62 (m, 4 H).

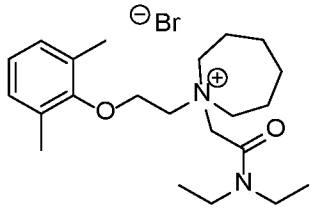
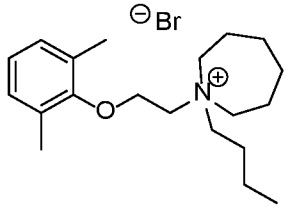
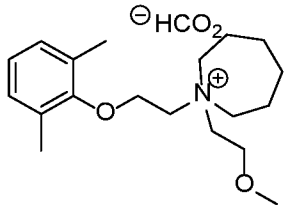
Examples 2-5 were prepared from intermediate 2-(2-bromoethoxy)-1, 3-dimethylbenzene, the appropriate azacycloalkane and benzyl bromide following procedures described for the synthesis of compound 1A.

Compound #	Structure	MS (ESI): m/z
2A		310.2 $[M]^+$
3A		324.2 $[M]^+$
4A		352.3 $[M]^+$

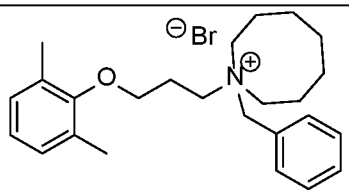
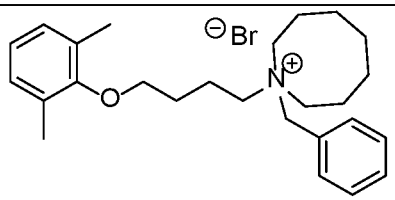
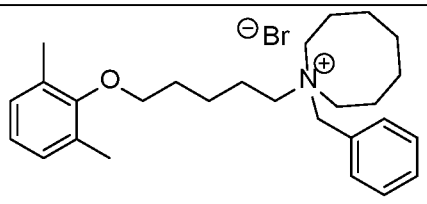
5A		329.4 $[M]^+$

Examples 6-13 were prepared from intermediate 1-(2-(2, 6-dimethylphenoxy) ethyl) azepane and the appropriate alkyl bromide following procedures described for the synthesis of compound 1A. All compounds were isolated by titration or purified by reverse phase HPLC.

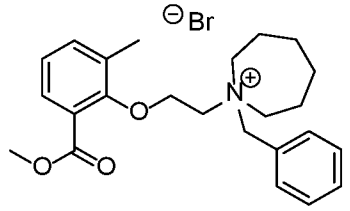
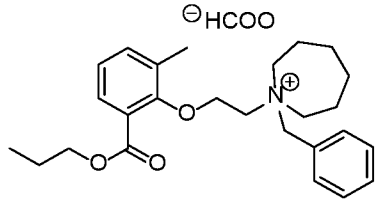
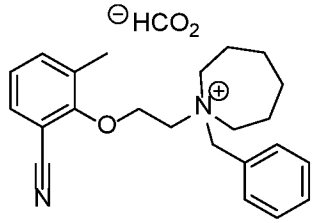
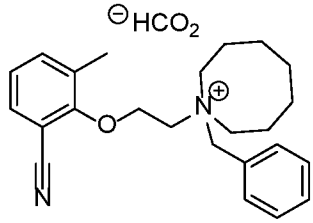
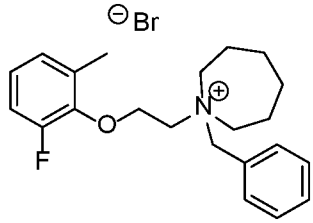
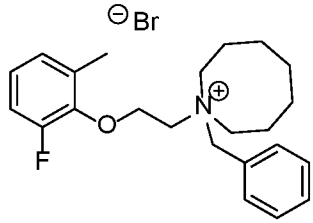
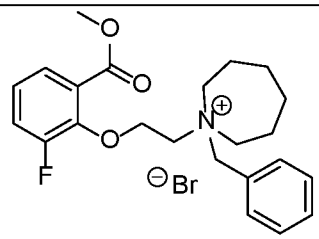
Compound #	**Structure**	**MS (ESI): m/z**
6A		344.3 $[M]^+$
7A		334.2 $[M]^+$
9A		320.3 $[M]^+$
9A		348.3$[M]^+$
10A		373.3 $[M]^+$

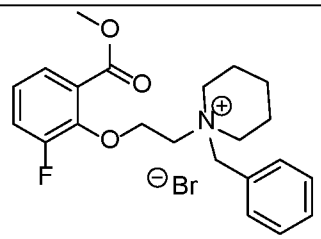
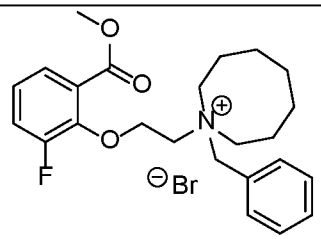
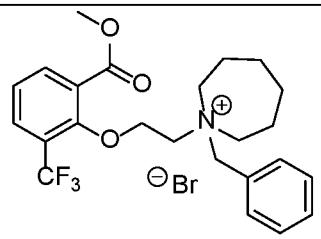
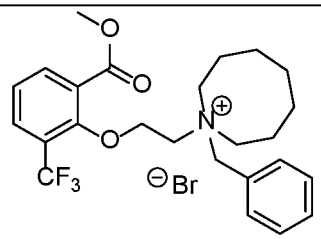
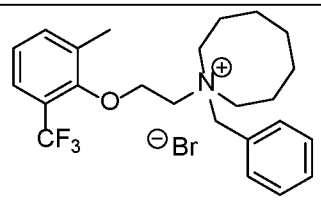
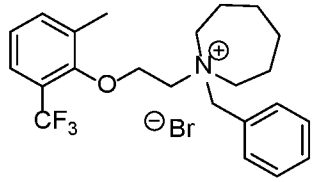
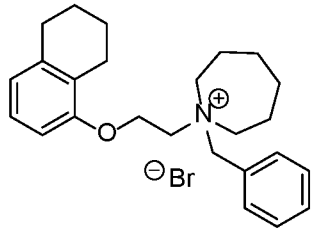
11A		361.3 $[M]^+$
12A		344.3 $[M]^+$
13A		306.2 $[M]^+$

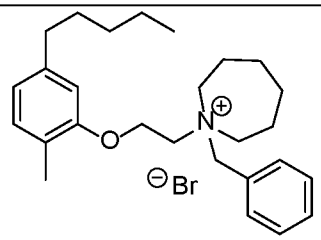
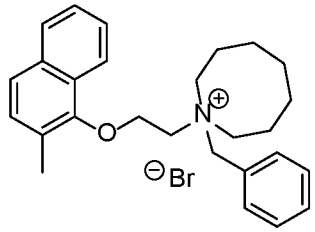
Examples 14-16 were prepared according to procedures described for the synthesis of compound 1A from 2,6-dimethyl phenol, the appropriate dibromoalkane, azocane and benzyl bromide.

Compound #	**Structure**	**MS (ESI): m/z**
14A		366.3 $[M]^+$
15A		380.3 $[M]^+$
16A		394.3 $[M]^+$

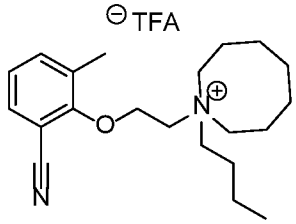
Examples 17-32 were prepared following procedures described for the synthesis of compound 1A from the appropriately substituted phenol, 1,2-dibromoethane, azacyclolkane and benzyl bromide. All compounds were isolated by titration or purified by reverse phase HPLC.

Compound #	Structure	MS (ESI): m/z
17A		382.1 $[M]^+$
18A		410.2 $[M]^+$
19A		349.3$[M]^+$
20A		363.3 $[M]^+$
21A		342.2 $[M]^+$
22A		356.2 $[M]^+$
23A		386.2 $[M]^+$

24A		372.1 $[M]^+$
25A		400.2 $[M]^+$
26A		436.4 $[M]^+$
27A		450.4 $[M]^+$
28A		406.2 $[M]^+$
29A		392.3 $[M]^+$
30A		364.4 $[M]^+$

31A		394.3 $[M]^+$
32A		388.2 $[M]^+$

Synthesis of 1-butyl-1-(2-(2-cyano-6-methylphenoxy)ethyl)azocan-1-ium:



Compound 33A

- *Synthesis of intermediate 2-(2-bromoethoxy)-3-methylbenzonitrile:*

To a stirred solution of 2-hydroxy-3-methylbenzonitrile (0.8 g, 6.0 mmol) and K_2CO_3 (1.66 g, 12.0 mmol) in acetonitrile (10 mL) was added dibromoethane (2.7 mL, 30.0 mmol) and the resulting reaction was heated to 80 °C for 16 hours as progress of the reaction was monitored by TLC (Mobile phase 10% EtOAc in pet ether, Visualization: UV). The crude reaction mixture was concentrated under reduced pressure to afford a residue which was diluted with water (10 mL) and extracted with EtOAc (2 X 50 mL). The combined organic extracts were dried over anhydrous Na2SO4 and concentrated under reduced pressure to afford the crude product which was purified by silica gel chromatography (eluted with 10%-15% of EtOAc in pet ether). The combined pure fractions were concentrated under reduced pressure to afford 2-(2-bromoethoxy)-3-methylbenzonitrile (1 g) as a pale yellow gum. Mass (ESI): M/z = 240.10 [M+H] + 1H NMR (400 MHz, CDCl3) δ ppm: 7.44-7.40 (m, 2 H), 7.09 (t, 1 H), 4.43 (t, 2 H), 3.71 (t, 2 H), 2.36 (s, 3 H).

- *Synthesis of intermediate 2-(2-(azocan-1-yl)ethoxy)-3-methylbenzonitrile:*

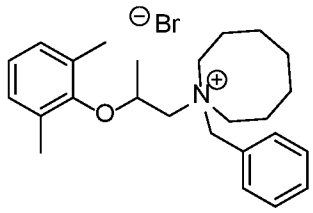
To a stirred solution of 2-(2-bromoethoxy)-3-methyl benzonitrile (800 mg, 3.3 mmol) and N-DIPEA (1.8 mL, 10.078 mmol, 3 eq) in acetonitrile (10 mL) was treated with azocane (0.57

g, 5.0 mmol) and the resulting reaction mixture was heated to 80 °C for 16 hours as progress of the reaction was monitored by TLC (Mobile phase 50% ethyl acetate in pet ether, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude residue which was diluted with water (40 mL) and extracted with EtOAc (2 X 50 mL). The combined organic extracts were dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford the crude product which was purified by silica gel chromatography (eluted with 50%-60% of EtOAc in pet ether). The combined pure fractions were concentrated under reduced pressure to afford pure 2-(2-(azocan-1-yl)ethoxy)-3-methylbenzonitrile as a pale yellow oil (0.5 g). Mass (ESI): M/z = 273.29 [M+H] + 1H NMR (400 MHz, CDCl3) δ ppm: 7.42-7.37 (m, 2 H), 7.03 (t, 1 H), 4.18 (t, 2 H), 2.96 (t, 2 H), 2.68 (s, 4 H), 2.31 (s, 3 H), 1.59-1.54 (m, 10 H).

- *Synthesis of 1-butyl-1-(2-(2-cyano-6-methylphenoxy)ethyl)azocan-1-ium TFA salt:*

To a stirred solution of 2-(2-(azocan-1-yl)ethoxy)-3-methylbenzonitrile (0.4 g, 1.5 mmol) in acetonitrile (10 mL) was added 1-bromobutane (0.475 mL, 4.4 mmol) and the resulting reaction mixture was stirred at 80 °C for 16 hours as progress of the reaction was monitored by TLC (Mobile phase: 10% MeOH in DCM; Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude product which was purified by reverse phase HPLC (Column: X-Select CSH C18 (150X19) mm, 5µ; Mobile phase A/B: 0.1% TFA (aq.)/ 1:1 acetonitrile: MeOH; Flow: 18 mL/min). The collected pure fractions were lyophilized to afford 1-butyl-1-(2-(2-cyano-6-methylphenoxy) ethyl) azocan-1-ium trifluoroacetate salt (220 mg). Mass (ESI): M/z = 329.28 [M] +. 1H NMR (400 MHz, DMSO-d6) δ ppm: 7.70-7.67 (m, 1 H), 7.64-7.62 (m, 1 H), 7.28 (t, 1 H), 4.40 (t, 2 H), 3.83 (t, 2 H), 3.62-3.42 (m, 6 H), 2.33 (s, 3 H), 1.91 (br s, 4 H), 1.71-1.62 (m, 8 H), 1.35-1.30 (m, 2 H), 0.92 (t, 3 H).

1-benzyl-1-(2-(2,6-dimethylphenoxy)propyl)azocan-1-ium bromide:



Compound 34A

- *Synthesis of Intermedaite methyl 2-(2, 6-dimethylphenoxy) propanoate:*

To a stirred solution of 2, 6-dimethylphenol (7 g, 57.3 mmol) in acetonitrile (120 mL) was added K_2CO_3 (23.7 g, 171.8 mmol) and methyl 2-bromopropanoate (9.6 mL, 85.9 mmol) and the resulting reaction mixture was stirred for 16 h at 80°C as progress of the reaction mixture was monitored by TLC (Mobile phase: 20% EtOAc in pet ether, Visualization: UV). The crude reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 250 mL). The combined organic extracts were washed with water (200 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford methyl 2-(2,6-dimethylphenoxy)propanoate (9 g) as yellow liquid. Mass (ESI): 209.17 m/z [M+H] +. 1H NMR (400 MHz, CDCl3) δ ppm 6.99 (d, 2 H), 6.93-6.89 (m, 1 H), 4.51 (q, 1 H), 3.77 (s, 3 H), 2.27 (s, 6 H), 1.52 (d, 3 H).

- *Synthesis of intermediate 2-(2, 6-dimethylphenoxy) propan-1-ol:*

To a cooled (0°C) solution of methyl 2-(2, 6-dimethylphenoxy) propanoate (5 g, 24.0 mmol) in THF (100 mL) was added a 1M solution of LAH in THF (48.016 mL, 48.0 mml) and the resulting reaction mixture was stirred for 16 h at room temperature as progress of the reaction was monitored by TLC (Mobile phase: 20% EtOAc in pet ether, Visualization: UV). The reaction mixture was cooled to 0°C, quenched with saturated NaCl solution (200 mL) and extracted with EtOAc (2 x 300 mL). The combined organic extracts were washed with water (300 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude product which was purified by silica gel flash chromatography (eluted with 5%-10% EtOAc in pet ether). The combined pure fractions were concentrated under reduced pressure to afford 2-(2, 6-dimethylphenoxy)propan-1-ol (2.8 g, 64.7%) as yellow colour liquid. 1H NMR (400 MHz, CDCl3) δ ppm 7.01 (d, 2 H), 6.94-6.90 (m, 1 H), 4.26-4.22 (m, 1 H), 3.82-3.74 (m, 2 H), 2.29 (s, 6 H), 2.17-2.14 (m, 1 H), 1.17 (d, 3 H).

- *Synthesis of intermedaite 2-(2, 6-dimethylphenoxy) propyl methanesulfonate:*

To a cooled (0°C) solution of 2-(2,6-dimethylphenoxy)propan-1-ol (1 g, 5.55 mmol) in DCM (10 mL) was added TEA (2.3 mL, 16.6 mmol) and methanesulfonyl chloride (0.6 mL, 8.3 mmol) and the resulting reaction mixture was stirred for 16 h at room temperature as progress of the reaction mixture was monitored by TLC (Mobile phase: 20% EtOAC in pet ether, Visualization: UV). The reaction mixture was diluted with water (50 mL), extracted with DCM (2 x 100 mL), and the combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 2-(2,6-dimethylphenoxy)propyl methanesulfonate (1.3 g) as a yellow

liquid. 1H NMR (400 MHz, CDCl3) δ ppm 7.01 (d, 2 H), 6.94-6.91 (m, 1 H), 4.36-4.32 (m, 3 H), 3.02 (s, 3 H), 2.27 (s, 6 H), 1.28 (d, 3 H).

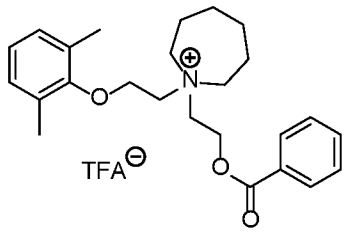
- *Synthesis of intermediate 1-(2-(2, 6-dimethylphenoxy) propyl) azocane:*

To a stirred solution of 2-(2, 6-dimethylphenoxy) propyl methanesulfonate (1.3 g, 5.0 mmol, 1.0) in ACN (15 mL) was added K_2CO_3 (2 g, 15.0 mmol) and azocane (0.9 mL, 7.5 mmol) at room temperature and the resulting reaction mixture was stirred for 16 h at 80°C as progress of the reaction mixture was monitored by TLC (Mobile phase: 20% EtOAc in pet ether, Visualization: UV). The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude product which was purified by silica gel flash chromatography (eluted with 5%-10% of EtOAc in pet ether). The combuined pure fractions were concentrated under reduced pressure to afford 1-(2-(2, 6-dimethylphenoxy) propyl) azocane (560 mg) as colourless liquid. Mass (ESI): 276.37 m/z [M+H] +. 1H NMR (400 MHz, CDCl3) δ ppm 6.98 (d, 2 H), 6.89-6.86 (m, 1 H), 4.08-4.05 (m, 1 H), 2.87-2.83 (m, 1 H), 2.58-2.53 (m, 5 H), 2.27 (s, 6 H), 1.60-1.50 (m, 10 H), 1.27 (d, 3 H).

- *Synthesis of 1-benzyl-1-(2-(2, 6-dimethylphenoxy) propyl) azocan-1-ium bromide:*

To a stirred solution of 1-(2-(2,6-dimethylphenoxy)propyl)azocane (500 mg, 1.8 mmol) in acetonitrile (10 mL) was added benzyl bromide (0.43 mL, 3.6 mmol) and the resulting reaction mixture was stirred for 16 h at 80°Cas progress of the reaction mixture was monitored by TLC (Mobile phase: 10% MeOH in DCM, Visualization: UV). The reaction was concentrated under reduced pressure to afford crude product was triturated with EtOAc (50 mL) to afford 1-benzyl-1-(2-(2, 6-dimethylphenoxy) propyl) azocan-1-ium bromide (546 mg) as an off white solid. Mass (ESI): 366.3 m/z [M] +. 1H NMR (400 MHz, DMSO-d6) δ ppm 7.67-7.65 (m, 2 H), 7.56-7.51 (m, 3 H), 7.05 (d, 2 H), 6.97-6.93 (m, 1 H), 4.97-4.93 (m, 1 H), 4.81-4.70 (m, 2 H), 3.78-3.72 (m, 1 H), 3.65-3.50 (m, 4 H), 3.43-3.39 (m, 1 H), 2.26 (s, 6 H), 2.03-1.90 (m, 4 H), 1.75-1.50 (m, 6 H), 0.98 (d, 3 H).

Synthesis of 1-(2-(benzoyloxy)ethyl)-1-(2-(2,6-dimethylphenoxy)ethyl)azepan-1-ium:



Compound 35A

- *Synthesis of intermediate 1-(2-(2,6-dimethylphenoxy)ethyl)-1-(2-hydroxyethyl)azepan-1-ium:*

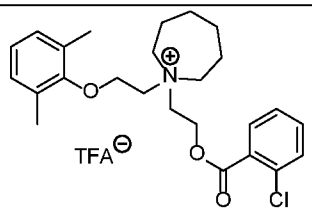
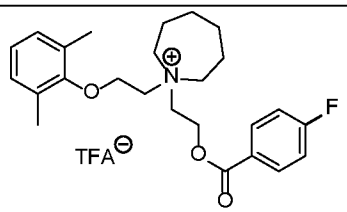
To 1-(2-(2, 6-dimethylphenoxy) ethyl) azepane (0.718 g, 2.90 mmol) was added neat 2-bromoethan-1-ol (0.544 g, 4.35 mmol) and the resulting reaction mixture was heated at 90°C for 16 hours in a sealed tube as progress of the reaction mixture was monitored by TLC (Mobile phase: 10% Methanol in DCM, Visualization: UV). The reaction mixture was diluted with DCM (70 mL) and concentrated under reduced pressure to afford crude product which was purified by silica gel flash chromatography (eluted with 7% MeOH in DCM). The combined fractions were concentrated under reduced pressure to afford 1-(2-(2,6-dimethylphenoxy)ethyl)-1-(2-hydroxyethyl)azepan-1-ium bromide (0.450 g) as an off white solid. MS (ESI): m/z 292.25 [M] +. 1H NMR (400 MHz, DMSO-d6) δ ppm 7.06-7.04 (m, 2 H), 6.97-6.94 (m, 1 H), 5.36 (t, 1 H), 4.16-4.11 (m, 2 H), 3.92-3.87 (m, 4 H), 3.69-3.65 (m, 4 H), 3.62-3.56 (m, 2 H), 2.27 (s, 6 H), 1.90 (br s, 4 H), 1.62 (br s, 4 H).

- *Synthesis of 1-(2-(2,6-dimethylphenoxy)ethyl)-1-(2-((4-fluorobenzoyl)oxy)ethyl)azepan-1-ium:*

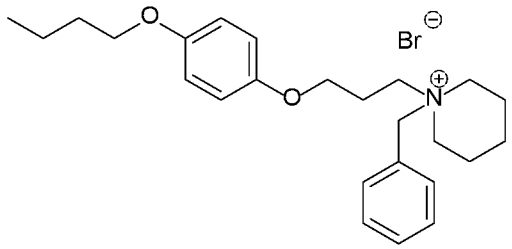
To a stirred solution of 1-(2-(2,6-dimethylphenoxy)ethyl)-1-(2-hydroxyethyl)azepan-1-ium (200 mg, 0.54 mmol) and DMAP (5.25 mg, 0.04 mmol) in pyridine (2 mL) was added benzoyl chloride (377 mg, 2.69 mmol) at 0°C. The resulting reaction mixture was stirred at room temperature for 16 h as progress of the reaction mixture was monitored by TLC (Mobile phase: 10% MeOH in DCM, Visualization: UV). The precipitated solid was filtered, washed with ethyl acetate (50 mL), and dried under high vacuum to afford crude product which was purified by HPLC (Column: LUNA C18 (250*21.2) mm, 5u; Mobile phase A/B: 0.1%TFA (Aq)/Acetonitrile). The combined pure fractions were lyophilized to afford 1-(2-(2,6-dimethylphenoxy)ethyl)-1-(2-((4-fluorobenzoyl)oxy)ethyl)azepan-1-ium As a TFA salt (91 mg) MS (ESI): M/z = 396.37 [M]+. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.00-7.98 (m, 2

H), 7.71-7.68 (m, 1 H), 7.54 (t, 2 H), 7.04 (d, 2 H), 6.97-6.94 (m, 1 H), 4.79 (br s, 2 H), 4.20 (t, 2 H), 4.01-4.00 (m, 4 H), 3.74-3.72 (m, 4 H), 2.25 (s, 6 H), 1.95 (br s, 4 H), 1.65 (br s, 4 H).

Examples 36 and 37 were prepared from intermediate 1-(2-(2,6-dimethylphenoxy)ethyl)-1-(2-hydroxyethyl)azepan-1-ium and the appropriate benzoyl chloride following procedures described for the synthesis of compound 32A.

Compound #	Structure	MS (ESI): m/z
36A		430.2 $[M]^+$
37A		414.2 $[M]^+$

Synthesis of 1-benzyl-1-(3-(4-butoxyphenoxy) propyl) piperidin-1-ium bromide:



Compound 38A

- *Synthesis of intermediate 1-butoxy-4-(3-chloropropoxy) benzene:*

To a stirred solution of 4-butoxy phenol (10 g, 60.2 mmol) in ACN (100.0 mL) was added K_2CO_3 (24.9 g, 180.5 mmol). After stirring 10 minutes, 1-bromo-3-chloropropane (14.2 g, 90.2 mmol) was added at room temperature and the resulting reaction mixture was heated at 80 °C for 16 h as progress of the reaction was monitored by TLC (Mobile phase: 10% ethyl acetate in pet ether, visualization by UV). The reaction mixture was diluted with water (150 mL) and extracted with EtOAc (2 X 150 mL). The combined organic extracts were washed with brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude was purified by silica gel chromatography (eluted

with 10%-30% of EtOAc in pet ether). Pure fractions were combined and concentrated under reduced pressure to afford 1-butoxy-4-(3-chloropropoxy) benzene (7 g) as a red liquid. Mass (ESI): m/z 243.2 [M+H] +. ^{1}H NMR (400 MHz, CDCl3) δ ppm 6.82 (s, 4 H), 4.05 (t, 2 H), 3.90 (t, 2 H), 3.73 (t, 2 H), 2.23-2.17 (m, 2 H), 1.77-1.70 (m, 2 H), 1.55-1.49 (m, 2 H), 0.95-0.92 (m, 3 H).

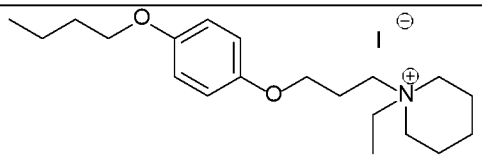
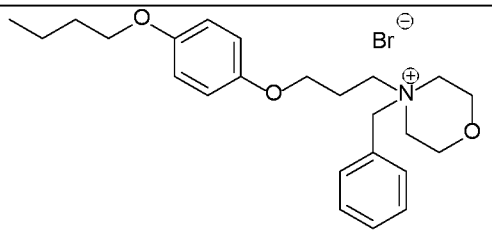
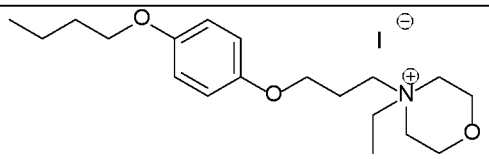
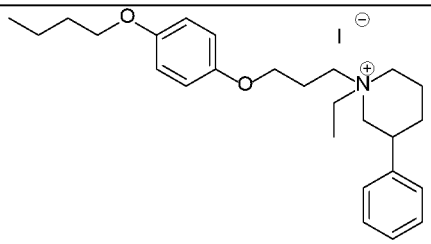
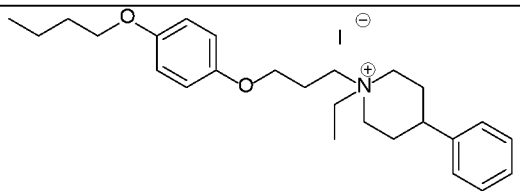
- *Synthesis of intermediate 1-(3-(4-butoxyphenoxy) propyl) piperidine*:

To a stirred solution of 1-butoxy-4-(3-chloropropoxy) benzene (0.5 g, 2.1 mmol) and K_2CO_3 (0.85 g, 6.2 mmol) in acetonitrile (20 mL) was added piperidine (0.26 g, 3.1 mmol) and the resulting reaction mixture was heated at 80 °C for 16 h as progress of the reaction was monitored by TLC (Mobile phase: 50% EtOAc in pet ether, visualization by UV). The reaction mixture was cooled to room temperature, quenched with ice cold water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with water (2 x 20 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluted with 20%-30% of EtOAc in pet ether). Pure fractions were combined and concentrated under reduced pressure to afford 1-(3-(4-butoxyphenoxy) propyl) piperidine (0.25 g) as an off white solid. MS (ESI): m/z 292.05 [M+H] +.

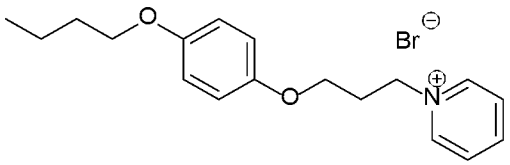
- *Synthesis of 1-benzyl-1-(3-(4-butoxyphenoxy) propyl) piperidin-1-ium bromide*:

To a solution of 1-(3-(4-butoxyphenoxy) propyl) piperidine (0.2 g, 0.69 mmol) in acetonitrile (10 mL) was treated with benzyl bromide (0.25 g, 1.4 mmol) and the resulting reaction mixture was heated at 80 °C for 16 h in a sealed tube as progress of the reaction was monitored by TLC (Mobile phase: 10% MeOH in DCM, visualization by UV). The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Crude product was purified silica gel chromatography (eluted with 3 %-5 % of MeOH in DCM). Pure fractions were combined and concentrated under reduced pressure to afford 1-benzyl-1-(3-(4-butoxyphenoxy) propyl) piperidin-1-ium bromide salt (0.70 g) as an off-white solid. Mass (ESI): m/z 382.3 [M] +. 1H NMR (400 MHz, DMSO-d6) δ ppm 7.57-7.51 (m, 5 H), 6.87 (d, 4 H), 4.61 (s, 2 H), 4.03 (t, 2 H), 3.89 (t, 2 H), 3.37-3.28 (m, 6 H), 2.28 (d, 2 H), 1.86 (d, 4 H), 1.68-1.64 (m, 3 H), 1.44-1.39 (m, 3 H), 0.92 (t, 3 H).

Examples 39-43 were prepared from intermediate 1-butoxy-4-(3-chloropropoxy) benzene according to procedures described for Compound 35A using the appropriately substituted piperidine or morpholine and alkylating agent benzyl bromide or ethyl iodide.

Compound #	Structure	MS (ESI): m/z
39A		320.3 $[M]^+$
40A		384.3 $[M]^+$
41A		322.3 $[M]^+$
42A		396.3 $[M]^+$
43A		396.3 $[M]^+$

Synthesis of 1-(3-(4-butoxyphenoxy)propyl)pyridin-1-ium bromide:

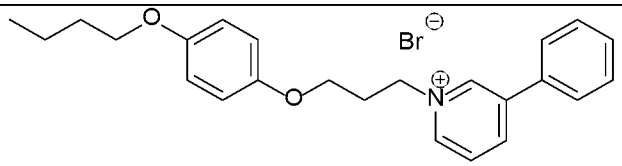
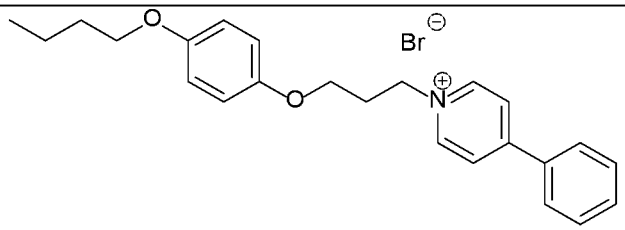


Compound 44A

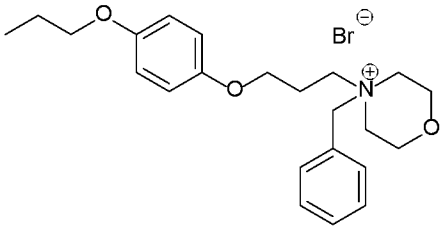
To a stirred solution of 1-butoxy-4-(3-chloropropoxy) benzene (0.5 g, 2.1 mmol) in acetonitrile (3 mL) was added pyridine (0.325 g, 4.1 mmol) and the resulting reaction mixture was stirred for 24 h at 90°C as progress of the reaction was monitored TLC (Mobile phase: 10% methanol in DCM, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude compound which was triturated with ethyl acetate (15

mL) to afford 1-(3-(4-butoxyphenoxy) propyl) pyridin-1-ium chloride (0.145 g). Mass (ESI): m/z 286.2 [M] +. 1H NMR (400 MHz, DMSO-d6) δ ppm 9.14 (d, 2 H), 8.63-8.59 (m, 1 H), 6.83-6.79 (m, 2 H), 6.71-6.69 (m, 2 H), 4.79 (t, 2 H), 4.00 (t, 2 H), 3.87 (t, 2 H), 2.43-2.36 (m, 2 H), 1.68-1.61 (m, 2 H), 1.45-1.38 (m, 2 H), 0.93 (t, 3 H).

Examples 45 and 46 were prepared from intermediate 1-butoxy-4-(3-chloropropoxy) benzene and the appropriately substituted pyridine according to procedures described for Compound 41A.

Compound #	Structure	MS (ESI): m/z
45A		362.2 $[M]^+$
46A		362.2 $[M]^+$

Synthesis of Synthesis of 4-benzyl-4-(3-(4-propoxyphenoxy)propyl)morpholin-4-ium bromide:



Compound 47A

- *Synthesis of Intermediate 4-(3-(4-propoxyphenoxy) propyl) morpholine:*

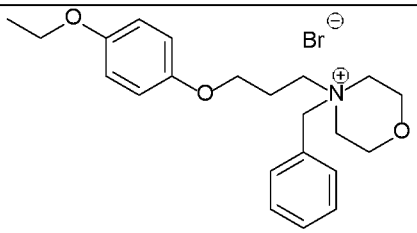
To a stirred solution of 4-propoxyphenol (1 g, 6.6 mmol) and potassium carbonate (1.8 g, 13.1 mmol) in acetonitrile (20 mL) was added 4-(3-chloropropyl) morpholine (1.2 g, 7.2 mmol) and the resulting reaction mixture was heated at 80 °C for 16 hours as progress of the reaction was monitored by TLC (Mobile phase: 50% EtOAc in pet ether, Visualization: UV). The reaction mixture was cooled to room temperature, diluted with ice cold water (10 mL)

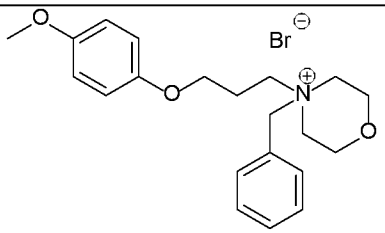
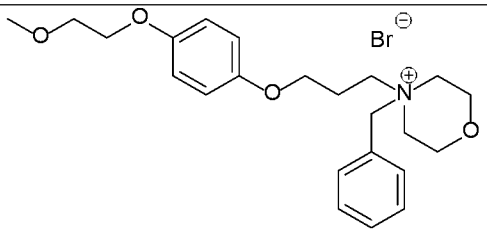
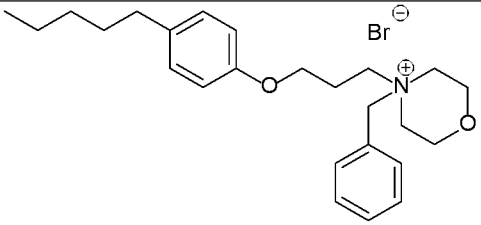
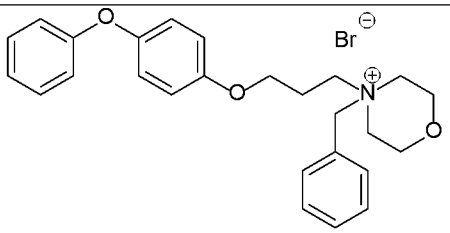
and then extracted with EtOAc (40 mL). The organic extract was washed with water (10 mL) and brine solution (10 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluted with 40%-50% EtOAc in pet ether). The combined pure fractions were concentrated under reduced pressure to afford pure 4-(3-(4-propoxyphenoxy) propyl) morpholine (1.2 g). MS (ESI): m/z 280.25 [M+H] +. 1H NMR (400 MHz, CDCl3) δ ppm 6.82 (s, 4 H), 3.96 (t, 2 H), 3.86 (t, 2 H), 3.72 (t, 4 H), 2.53-2.45 (m, 6 H), 1.94 (t, 2 H), 1.80-1.75 (m, 2 H), 1.02 (t, 3 H).

- *Synthesis of 4-benzyl-4-(3-(4-propoxyphenoxy)propyl)morpholin-4-ium bromide:*

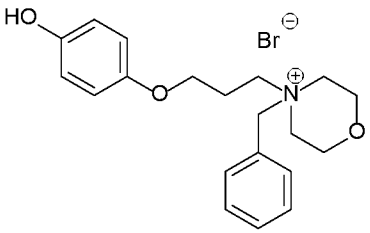
To a stirred solution of 4-(3-(4-propoxyphenoxy) propyl) morpholine (0.4 g, 1.4 mmol) in acetonitrile (10 mL) was added benzyl bromide (0.98 g, 5.73 mmol) and the resulting reaction mixture was heated at 80 °C for 16 h in a sealed tube as progress of the reaction was monitored by TLC (Mobile phase: 10% Methanol in DCM, visualization: UV). The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluted with 3 %-5 % MeOH in DCM). The combined pure fractions were concentrated under reduced pressure to afford 4-benzyl-4-(3-(4-propoxyphenoxy) propyl) morpholin-4-ium bromide (0.28 g) as an off-white solid. Mass (ESI): m/z 370.2 [M] +. 1H NMR (400 MHz, DMSO-d6) δ ppm 7.60-7.51 (m, 5 H), 6.86 (t, 4 H), 4.74 (s, 2 H), 4.05-3.99 (m, 6 H), 3.85 (t, 2 H), 3.53-3.40 (m, 6 H), 2.33-2.29 (m, 2 H), 0.96 (t, 3 H).

Examples 48-52 were prepared according to the procedures described for compound 44A from 4-(3-chloropropyl) morpholine, the appropriately substituted phenol and benzyl bromide.

Compound #	Structure	MS (ESI): m/z
48A		356.2 $[M]^+$

49A		342.2 $[M]^+$
50A		386.2 $[M]^+$
51A		382.3 $[M]^+$
52A		404.2 $[M]^+$

Synthesis of 4-benzyl-4-(3-(4-hydroxyphenoxy)propyl)morpholin-4-ium bromide:

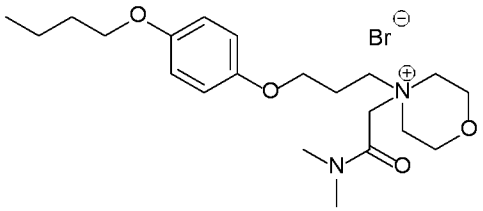


Compound 53A

To a cooled (-78 °C) solution of 4-benzyl-4-(3-(4-methoxyphenoxy)propyl)morpholin-4-ium bromide (150 mg) in DCM (3 mL) was added a 1 M solution of BBr3 in DCM (1.065 mL, drop-wise addition). Once the addition was complete, the reaction mixture was stirred at room temperature for 1 h as progress was monitored by TLC (Mobile phase: 20% MeOH in DCM, visualization with Ninhydrine). The reaction mixture was concentrated under reduced pressure to afford crude compound which was purified by silica gel chromatography (eluted

with 20% MeOH in DCM). The combined pure fractions were concentrated under reduced pressure to afford 4-(3-(4-methoxyphenoxy) propyl) morpholine (30 mg) as an off-white solid. Mass (ESI): m/z 328.2 [M] +. UPLC: 98.88%. 1H NMR (400 MHz, DMSO-d6) δ ppm 8.97 (s, 1 H), 7.60-7.51 (m, 5 H), 6.78-6.75 (m, 2 H), 6.72-6.69 (m, 2 H), 4.74 (s, 2 H), 4.01-3.98 (m, 6 H), 3.53-3.47 (m, 4 H), 3.41 (d, 2 H), 2.32-3.20 (m, 2 H).

Synthesis of4-(3-(4-butoxyphenoxy) propyl)-4-(2-(dimethylamino)-2-oxoethyl) morpholin-4-ium bromide:



Compound 54A

- *Synthesis of Intermediate 4-(3-(4-butoxyphenoxy) propyl) morpholine*:

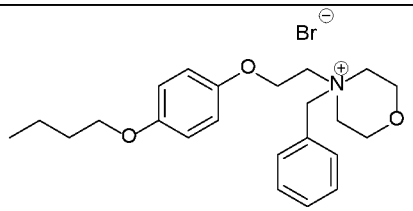
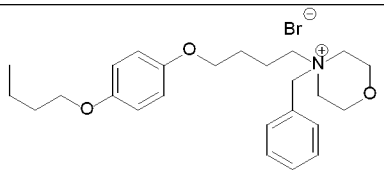
To a stirred solution of 1-butoxy-4-(3-chloropropoxy)benzene (0.5 g, 2.1 mmol) and K_2CO_3 (0.57 g , 4.2 mmol) in acetonitrile (15 mL) was added morpholine (0.215 g , 2.5 mmol) and the resulting reaction mixture was heated at 80 °C for 16 h as progress of the reaction was monitored by TLC (Mobile phase 50% EtOAc in pet ether, Visualization: UV). The reaction was diluted with DCM (80 mL) and washed with water (2 x 25 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude product which was purified by flash chromatography (eluted with 20%-30% EtOAc in Pet ether). The combined pure fractions were concentrated under reduced pressure to afford 4-(3-(4-butoxyphenoxy) propyl) morpholine (560 mg) as a pale yellow oil. MS (ESI): m/z 294.18 [M + H] +.

- *Synthesis of 4-(3-(4-butoxyphenoxy) propyl)-4-(2-(dimethylamino)-2-oxoethyl) morpholin-4-ium bromide*

To a stirred suspension of 4-(3-(4-butoxyphenoxy) propyl) morpholine (0.2 g, 0.68 mmol) in ACN (10 mL) was added 2-bromo-N, N-dimethylacetamide (0.452 g, 2.73 mmol). The resulting reaction mixture was heated to 80°C for 16 h as progress of the reaction was monitored by TLC (Mobile phase: 10% MeOH in DCM, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude product which was purified by reverse phase prep HPLC (column: X select phenyl hexyl C18 (19*250) 5um, Mobile

Phase A/B: 0.1% FA (aq)/ACN) to afford product 4-(3-(4-butoxyphenoxy) propyl)-4-(2-(dimethylamino)-2-oxoethyl) morpholin-4-ium bromide (160 mg). MS (ESI): m/z 379.2 [M]+. 1H NMR (400 MHz, DMSO-d6) δ ppm 6.87-6.82 (m, 4 H), 4.60 (s, 2 H), 3.99-3.90 (m, 8 H), 3.88-3.81 (m, 4 H), 3.69-3.64 (m, 2 H), 2.99 (s, 3 H), 2.86 (s, 3 H), 2.07-2.03 (m, 2 H), 1.67-1.63 (m, 2 H), 1.44-1.38 (m, 2 H), 0.92 (m, 3 H).

Examples 55 and 56 were prepared from 4-butoxy phenol, morpholine, benzyl bromide and the appropriate the appropriate dihaloalkane following procedures described for the synthesis of compound 38.

Compound #	Structure	MS (ESI): m/z
55A		370.2 $[M]^+$
56A		398.3 $[M]^+$

Example 2 - Inhibition of Nav1.7 Current

The compounds were synthesized according to the described methods and tested for the ability to inhibit voltage-gated sodium channels.

Cell Culture

NaV1.7 was expressed upon induction with tetracycline. Cells were cultured in DMEM containing 10% dialyzed Fetal Bovine Serum (VWR, Radnor, PA), 1% Glutamax (VWR, Radnor, PA), 1% Penicillin-Streptomycin (VWR, Radnor, PA), 100 mg/L Hygromycin (Thermo Fisher Scientific, Waltham, MA and 5 mg/L Blasticidin (Alfa Aesar, Haverhill, MA). Cells were grown and maintained at 37 °C in a humidified environment containing 10% CO_2 in air. Cells were detached from the culture flask for passage and harvested using 0.05% Trypsin-EDTA (Thermo Fisher Scientific, Waltham, MA). To induce NaV1.7, cells were induced with tetracycline (0.1 - 1 μg/mL, IBI Scientific, Peosta, IA) the day before recording and plated onto 24-well plates. Cells were washed with DPBS (VWR, Radnor, PA), trypsinized and then triturated five times in 10 mL of growth media to break

apart cell aggregates. For one 24-well plate, 2 mL of cell suspension was mixed with 23 mL of fresh growth media and 0.1 - 1 μg/mL tetracycline added. 1 ml of mixed media with cells was then added to each well of a 24-well plate, with a 12 mm coverslip already placed in the bottom of the well. Cells were then incubated in 37°C and 10% CO_2 overnight.

Patch Clamp Solutions & Drugs

The intracellular solution contained the following (in mM) CsCl 135, NaCl 10, EGTA 10, HEPES 10, $MgCl_2$ 2, adjusted to pH 7.2 with CsOH. The external solution was a normal Ringer solution containing (in mM) NaCl 155, HEPES 10, glucose 10, KCl 3.5, $CaCl_2$ 1.5, $MgCl_2$ 1 adjusted to pH 7.4 with NaOH. CsCl is from Alfa Aesar, Haverhill, MA. All other chemicals are from Sigma-Aldrich, St. Louis, MO. In order to test the degree of internal block by test compounds the compounds were dissolved in internal solution at the indicated test concentration. In control experiments the internal solution did not contain any compound. In order to test the degree of external block by test compounds the compounds were dissolved in external solution at the indicated test concentration.

Whole Cell Patch Clamp Protocol

18-24 hours after cells were induced with tetracycline, coverslips were placed into a chamber filled with Normal Ringer solution at room temperature and the chamber placed on a microscope. Pipettes were pulled from borosilicate glass on a P97 puller (Sutter Instrument, Novato, CA) and polished with a MF-830 Microforge (Narishige International USA, Inc, Amityville, NY) to have a resistance of 1.5-2.5 MΩ when filled with CsCl internal solution at room temperature. Healthy cells (those that are round and translucent with no visible blemishes) were chosen for seal formation. A seal was formed between the pipette and the cell, and a brief pulse of suction was used to "break in" and establish the whole-cell configuration. The membrane potential was held at -100 mV before the voltage protocol began. Only cells with series resistance between 1.5-5 MΩ were retained for analysis. The voltage protocol was as follows: Cells were held at -100 mV for 12 ms followed by a hyperpolarizing step to -105 mV for 12 ms to monitor the leak. Cells were then stepped back to -100 mV for 40 ms. Cells were then depolarized to -20 mV for 10 ms and then returned to -100 mV for 26.

Internal Block by Test Compounds

Once the recording was started, the voltage protocol was run at 30 second intervals for 5 minutes to get a stable baseline. This was followed by four 30-second periods of 5 Hz stimulation of the same voltage protocol separated by 1 minute of rest which was then followed by 0.33 Hz stimulation after the last train. Currents were recorded using PatchMaster software with Heka EPC10 (HEKA Electronics, Lambrecht, Germany). Only cells with inward current amplitudes at -20 mV between 400 pA and 4 nA were accepted. In addition, cells having leak currents greater than 10% of their current amplitudes were discarded.

Data Analysis: Internal Block

The data was plotted using the Patchmaster software (HEKA Electronics, Lambrecht, Germany) and analyzed by plotting the minimum current during the voltage step to -20 mV (peak inward current) as a function of time. In order to determine the degree of rundown over the course of an experiment, the average peak inward current amplitude (2-3 points) before 5 Hz stimulation was designated as the baseline ($I_{baseline}$). The average peak inward current during the last 2 second of the last 5 Hz train was measured (I_{test}). The control fraction current remaining was calculated by dividing I_{test} by $I_{baseline}$. On each recording day three cells were tested with control internal solution and the average fraction of current remaining calculated (Ctrl fraction current).

To determine the %block produced by test compounds applied internally the following was done. The average peak inward current amplitude (2-3 points) before 5 Hz stimulation was designated as 0% block ($I_{0\%block}$). To correct for the current change under control conditions, $I_{0\%block}$ was multiplied by the average Ctrl fraction current remaining to get the corrected 0% block current. The average peak inward current during the last 2 seconds of the last 5 Hz train was designated as the unblocked current ($I_{unblocked}$). The %block was calculated using the following equation: $(1 - I_{unblocked}/(I_{0\%block} * \text{Ctrl fraction current remaining}) \times 100)$.

Compounds 1A' to 6A' (Example 1) were tested for intracellular inhibition of NaV 1.7. Activity Range is % inhibition: "+++" >70%, "++" (70-30%) or "+" (< 30%). The results are presented below.

Example	Test Conc	Internal Block	Example	Test Conc	Internal Block
Compound-1	3 μM	+++	Compound-26	1 μM	++
Compound-2	3 μM	++	Compound-27	1 μM	+
Compound-3	3 μM	++	Compound-28	1 μM	+
Compound-4	1 μM	+++	Compound-29	1 μM	+
Compound-6	3 μM	+++	Compound-30	3 μM	++
Compound-7	10 μM	+++	Compound-31	3 μM	+
Compound-8	1 μM	+	Compound-32	3 μM	+++
Compound-9	3 μM	++	Compound-34	3 μM	+++
Compound-10	1 μM	++	Compound-35	3 μM	+++
Compound-11	10 μM	+++	Compound-36	3 μM	++
Compound-12	3 μM	+++	Compound-37	3 μM	++
Compound-13	1 μM	+	Compound-38	10 μM	+++
Compound-14	3 μM	++	Compound-39	3 μM	+
Compound-15	3 μM	+++	Compound-40	3 μM	++
Compound-16	3 μM	+++	Compound-42	10 μM	++
Compound-17	10 μM	+++	Compound-43	10 μM	+++
Compound-18	3 μM	+++	Compound-44	10 μM	++
Compound-19	1 μM	++	Compound-45	10 μM	++
Compound-20	1 μM	+++	Compound-46	10 μM	++
Compound-21	1 μM	++	Compound-47	10 μM	++
Compound-22	1 μM	+++	Compound-48	10 μM	++
Compound-23	1 μM	++	Compound-49	10 μM	+
Compound-24	1 μM	++	Compound-51	10 μM	++
Compound-25	1 μM	++	Compound-52	10 μM	++
Compound-26	1 μM	++	Compound-53	10 μM	+
Compound-27	1 μM	+	Compound-54	10 μM	++
Compound-28	1 μM	+	Compound-55	3 μM	+++
Compound-29	1 μM	+	Compound-56	10 μM	++

External Block by Test Compounds

Once the recording was started, the voltage protocol was run at 30 second intervals for 5 minutes to get a stable baseline. This is followed by 5 Hz stimulation of the same voltage protocol run until the end of experiment. The test compound is added during the 5 Hz stimulation train making sure to wait until the cell shows stable current rundown rate before addition of the compound. The test compound is added for 5 minutes before washing out with normal Ringer's solution. Currents were recorded using PatchMaster software with Heka EPC10 (HEKA Electronics, Lambrecht, Germany). Only cells with inward current amplitudes at -20 mV between 400 pA and 4 nA were accepted. In addition, cells having leak currents greater than 10% of their current amplitudes were discarded.

Data Analysis: External Block

The data was plotted using the Patchmaster software (HEKA Electronics, Lambrecht, Germany) and analyzed by plotting the minimum current during the voltage step to -20 mV (peak inward current) as a function of time. To determine the % block produced by test compounds applied externally the following was done. After the stable current rundown rate was established during the 5 Hz stimulation train, the $Rate_{rundown}$ was calculated by dividing the change in peak current amplitude by time. The average peak inward current amplitude (2-3 seconds) before addition of compound was used to determine 0% block ($I_{0\%block}$). To correct for the rundown, $I_{0\%block}$ is subtracted by the ($Rate_{rundown}$* 5 min) to get the corrected 0% block current. The average peak inward current during the last 2-3 seconds of the 5 minutes of compound application time before washing is the unblocked current ($I_{unblocked}$). The %block was then calculated using the following equation: Fraction current block=1-$I_{unblocked}$/($I_{0\%block}$ - $Rate_{rundown}$* 5 min).

Representative compounds of Example 1 were tested for extracellular inhibition of NaV 1.7. Activity Range is % inhibition: "+++" >70%, "++" (70-40%) or "+" (< 40%). The results are presented below.

Compound	Test Concentration	$Na_V1.7$ Extracellular Inhibition
Compound-1	1 μM	++
Compound-4	1 μM	++
Compound-12	3 μM	+
Compound-38	10 μM	+

Compound-40	10 μM	+
Compound-43	10 μM	++

Example 3 – Antipruritic Activity

The anti-pruritic activity of representative compounds of the invention was determined in C57BL/6 mice according to similar published procedures (Ramachandran et al, *JPET* 2020). Briefly, mice were anesthetized using 2.5% isoflurane and a solution of test compound (10 mg/mL, 100 μL) was topically applied to a shaven area at the nape using a solvent pipette (T =0). Test article was messaged into the skin until complete absorption occurred. Chloroquine (100 μg in 50 μL 0.9% saline) was injected intradermal at the indicated time to induce itch. Scratching activity was monitored over 40 minutes using an infrared camera.

Representative compounds of Example 1 significantly reduce chloroquine-induced itch up to 8 hours a following topical administration. See FIG. 1A, 1B and 1C.

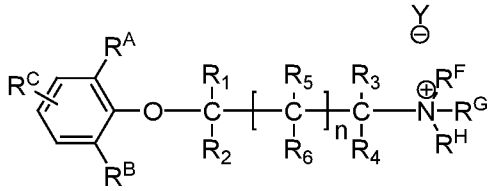
The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims. It will also be understood that none of the embodiments described herein are mutually exclusive and may be combined in various ways without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound represented by Formula (**I**):



(**I**),

wherein:

Y^- is a pharmaceutically acceptable anion;

R^A, R^B, and R^C are each independently selected from H, D, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, OR^I, CN, CF_3, NR^JR^K, $NR^LC(O)R^M$, $S(O)R^N$, $S(O)_2R^N$, $SO_2R^OR^P$, $SO_2NR^QR^R$, SO_3R^S, CO_2R^T; $C(O)R^U$, and $C(O)NR^VR^W$;

each of R^I, R^J, R^K, R^L, R^M, R^N, R^O, R^P, R^Q, R^R, R^S, R^T, R^U, R^V, and R^W is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl; R^J and R^K or R^V and R^W or R^Q and R^R can also be taken together with the nitrogen to which they are attached to form a substituted or unsubstituted 5, 6, 7, or 8 membered ring; or

R^A, R^B, and/or R^C can be taken together with the phenyl ring to which they are attached can form a fused bicyclic or tricyclic ring system, such as naphthyl, dihydroindenyl, tetrahydronaphthyl, quinolinyl, indolyl;

R_1, R_2, R_3, R_4, R_5, and R_6 are independently selected from hydrogen, C_1-C_4 alkyl, cycloalkyl, C_1-C_4 heteroalkyl, aryl or heteroaryl, preferably hydrogen, methyl or ethyl;

or R_1, R_2, R_3, R_4, R_5, and/or R_6 together with the carbon(s) to which they are attached form a substituted or unsubstituted cycloalkyl (such as a C_3-C_6 cycloalkyl) or a substituted or unsubstituted heterocyclic (such as a 3- to 15-membered heterocyclic ring);

n is 0, 1, 2, 3, 4 and 5;

R^F and R^G together with the N^+ form an optionally substituted heterocyclic ring having, zero, one or more heteroatoms in addition to the N^+, preferably 5, 6, 7, 8, or 9 ring members;

R^H is selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl (such as -CH_2-cycloalkyl, -C_2H_4-cycloalkyl, substituted or unsubstituted –CH_2-C_5-C_{10} aryl, substituted or unsubstituted –C_2H_4-C_5-C_{10} aryl, substituted or unsubstituted –CH_2-C_5-C_{10} heteroaryl, substituted or unsubstituted –C_2H_4-C_5-C_{10} heteroaryl, -CH_2 $OC(O)R^T$, -CH_2 CO_2R^T, -$CH_2C(O)NR^VR^W$, -$C_2H_4OCOR^T$, -$C_2H_4OR^I$) or

R^F, R^G and R^H together with the N^+ form heteroaryl ring or bridged heterocyclic ring.

2. The compound of claim 1 wherein R^A is selected from H, methyl, halo (such as F, Cl or Br), CF_3, CN, CO_2R^T, or OR^I, more preferably methyl, F, CF_3 or CN, most preferably methyl.

3. The compound of claim 1 or 2, wherein R^B is selected from H and methyl, preferably methyl.

4. The compound of any preceding claim, wherein R^C is selected from H, methyl, halo (such as F, Cl or Br), CF_3, CN, CO_2R^T, or OR^I, more preferably H or OR^I, most preferably H.

5. The compound of any preceding claim, wherein each R_1, R_2, R_3, R_4, R_5, and/or R_6 are hydrogen.

6. The compound of any one of claims 1-4, wherein R_1 is methyl or ethyl and R_2, R_3, R_4, R_5, and R_6 are hydrogen.

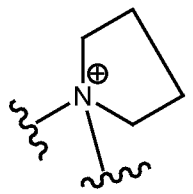
7. The compound of any one of claims 1-4, wherein R_3 is methyl or ethyl and R_1, R_2, R_4, R_5, and R_6 are hydrogen.

8. The compound of any preceding claim, wherein n is 0.

9. The compound of any preceding claim, wherein n is 1.

10. The compound of any preceding claim, wherein n is 3.

11. The compound of any preceding claim, wherein R^F and R^G together with the N^+ form a ring selected from a substituted or unsubstituted ring selected from: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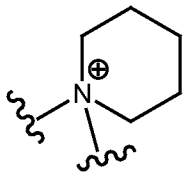
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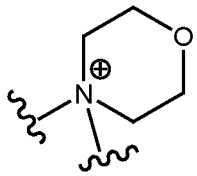
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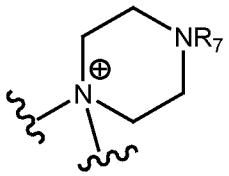
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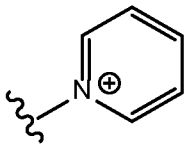
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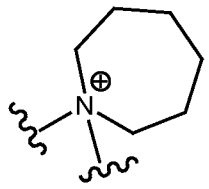
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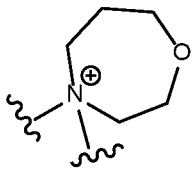
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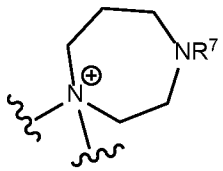
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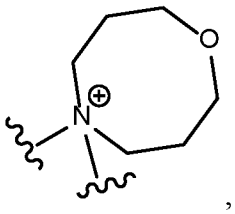
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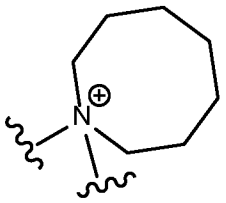
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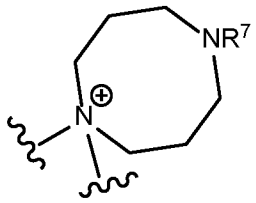
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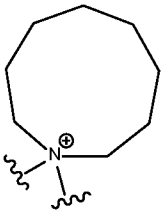
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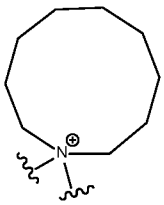
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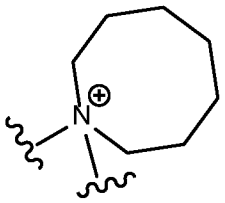
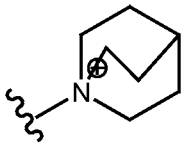
and, most preferably,


Wherein R_7 is hydrogen or a substituted or unsubstituted alkyl.

12. The compound of claim 11, wherein the ring is unsubstituted.

13. The compound according to any preceding claim, wherein R^H is benzyl or substituted benzyl, preferably benzyl.

14. The compound according to any one of claims 1 to 10, wherein R^F, R^G and R^H together with the N^+ form a pyridinyl or

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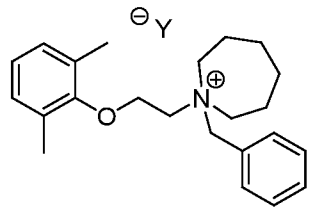
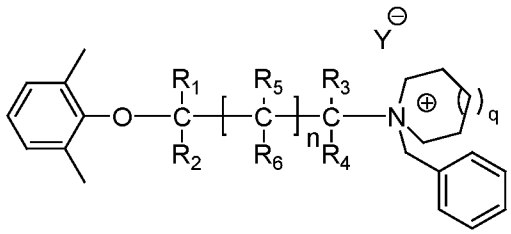
15. The compound according to any preceding claim with the proviso that the compound is not:



16. A compound represented by Formula (**I**):



(**II**),

wherein:

Y^- is a pharmaceutically acceptable anion;

R_1, R_2, R_3, R_4, R_5, and R_6 are independently selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, aryl or heteroaryl, preferably hydrogen, methyl or ethyl;

n is 0, 1, 2, 3, 4 and 5; and

q is 0, 1, 2, 3, 4 or 5.

17. The compound of claim 16, wherein q is 3.

18. The compound of claim 16 or 17, wherein R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen.

19. The compound of claim 16, wherein q is 2.

20. The compound of claim 19, wherein R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen.

21. The compound of claim 16, wherein q is 1.

22. The compound of claim 21, wherein R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen.

23. The compound of claim 16, wherein q is 0.

24. The compound of claim 23, wherein R_1, R_2, R_3, R_4, R_5, and R_6 are hydrogen.

25. The compound of claim 16, wherein R_1 is methyl R_2, R_3, R_4, R_5, and R_6 are hydrogen.

26. The compound of claim 16, wherein R_3 is methyl R_1, R_2, R_4, R_5, and R_6 are hydrogen.

27. The compound of any one of claims 16-26, wherein n is 0.

28. The compound of any one of claims 16-26, wherein n is 1.

29. The compound of any one of claims 16-26, wherein n is 2.

30. The compound of any one of claims 16-26, wherein n is 3.

31. The compound of any one of claims 16-26, wherein n is 4.

32. The compound of any one of claims 16-26, wherein n is 5.

33. The compound of any one of the preceding claims, wherein Y- is bromide or chloride.

34. A pharmaceutical composition comprising the compound of any one of the preceding claims and a pharmaceutically acceptable excipient.

35. The composition of claim 34, wherein said composition is formulated for topical or dermal administration.

36. A method for treating itch, pain, cough, or a neurogenic inflammatory disorder in a patient, comprising administering to said patient an effective amount of the compound of any one of claims 1-33.

37. The method of claim 36, wherein said itch is selected from the group consisting of itch due to pruritus, brachioradial pruritus, chronic idiopathic pruritus, genital/anal pruritus, notalgia paresthetica, scalp pruritus, allergic dermatitis, contact dermatitis, atopic dermatitis, hand eczema, poison ivy, infections, parasites, insect bites, pregnancy, metabolic disorders, liver or renal failure, drug reactions, allergic reactions, eczema, genital and anal itch, hemorrhoid itch, and cancer.

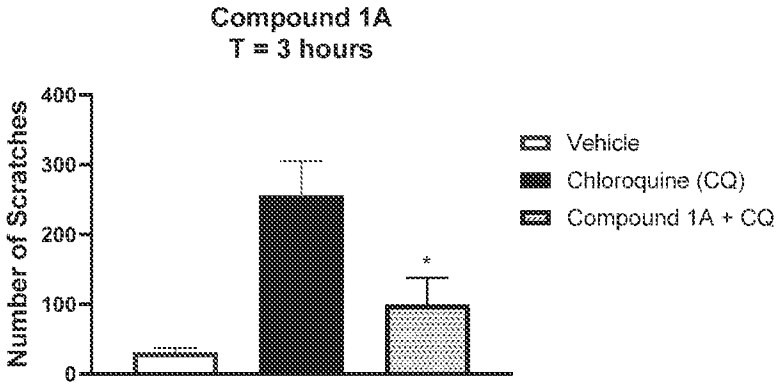


FIG. 1A

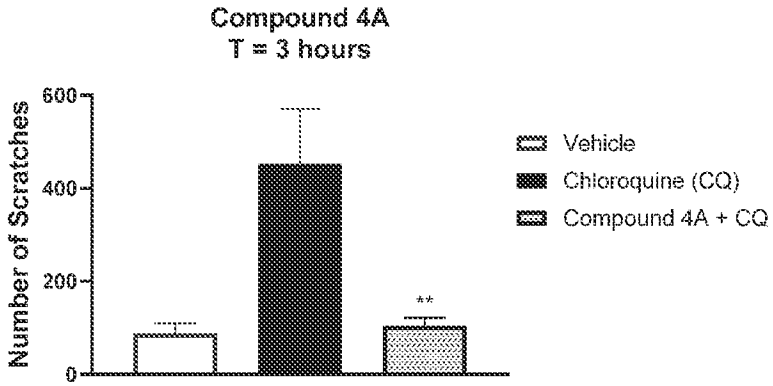


FIG. 1B

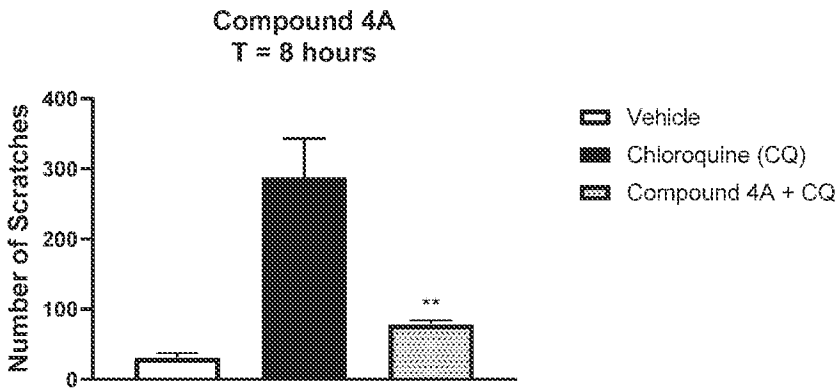


FIG. 1C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/21697

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07C 237/04; C07D 207/08; C07D 207/16 (2021.01)

CPC - A61K 31/14; A61K 31/40; A61K 31/4425; A61K 31/452

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Joshi et al. 'Studies on Solubilization. (Part I). Note on the synthesis of some quaternary N-(w-aryloxyalkyl) piperidinium, pyridinium, benzyl-dimethyl-ammonium, and trimethyl-ammonium bromides', Helvetica Chimica Acta, 1971, Vol.54, pages112-117; p113	1-3
A	PubChem Compound Summary for CID 117588874, '1-(1-Benzylazepan-1-ium-1-yl)-3-(2,4,6-trimethylphenoxy)propan-2-ol;chloride', U.S. National Library of Medicine, 18 February 2016 (18.02.2016), page1-8; p2 (https://pubchem.ncbi.nlm.nih.gov/compound/117588874)	1-3
A	WO 2019/199863 A1 (The Board Of Trustees Of The University Of Illinois) 17 October 2019 (17.10.2019); entire document	1-3
A	WO 2005/000815 A2 (Novartis Ag) 06 January 2005 (06.01.2005); entire document	1-3
P/A	WO 2020/064175 A1 (Antabio Sas) 02 April 2020 (02.04.2020); entire document	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
22 June 2021	JUL 23 2021
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. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/21697

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.: 4-15, and 27-37
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 Supplemental Box

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.:
1-3

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 21/21697

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 searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-3, and 16-26 directed to a compound represented by Formula (I). The compound represented by Formula (I) will be searched to the extent that it encompasses the compound represented by Formula (I), wherein: Y- is a pharmaceutically acceptable anion; RA, RB, and RC are each independently H; R1, R2, R3, and R4 are independently hydrogen; n is 0; RF and RG together with the N+ form an optionally substituted heterocyclic ring having zero heteroatom in addition to the N+, preferably 5 ring members; RH is substituted or unsubstituted alkyl. It is believed that claims 1-3(in part) read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound represented by Formula (I), wherein: Y- is a pharmaceutically acceptable anion; RA, RB, and RC are each independently D; R1, R2, R3, and R4 are independently C1-C4 alkyl; n is 0; RF and RG together with the N+ form an optionally substituted heterocyclic ring having one heteroatom in addition to the N+, preferably 6 ring members; RH is substituted or unsubstituted alkenyl (i.e., claim 1(in part)).

The group of inventions listed above 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:

Special Technical Features:

Group I+ includes the technical feature of a unique compound represented by Formula (I), containing the same, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound represented by Formula (I)containing the same.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by PubChem CID 117588874 (hereinafter 'CID'). CID discloses a compound represented by Formula (I), wherein: Y- is a pharmaceutically acceptable anion; RA, RB, and RC are each independently unsubstituted alkyl; R1, R2, R3, R4, and R5 are independently hydrogen; R6 is OR1, wherein R1 is H; n is 1; RF and RG together with the N+ form a heterocyclic ring having zero heteroatom in addition to the N+, preferably 7 ring members; RH is unsubstituted -CH2-C6 aryl (p2, "1.1 2D Structure").

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note Re: Item 4: claims 4-15, and 27-37 are determined unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).