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Charged Ion Channel Blockers and Methods for Use

Abstract

The invention provides compounds of Formula (I), or pharmaceutically acceptable salts thereof: ##STR00001##

The compounds, compositions, methods and kits of the invention are useful for the treatment of pain, itch, and neurogenic inflammation.

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Background/Summary

RELATED APPLICATIONS [0001] This application is a continuation of U.S. application Ser. No. 18/078,511, filed on Dec. 9, 2022, which is a continuation of U.S. application Ser. No. 17/095,949, filed on Nov. 12, 2020, now U.S. Pat. No. 11,603,355, which is a continuation of U.S. application Ser. No. 16/815,426 filed on Mar. 11, 2020, now U.S. Pat. No. 10,968,179, which claims the benefit of U.S. Provisional Application Ser. No. 62/816,434 filed Mar. 11, 2019, and U.S. Provisional Application Ser. No. 62/931,590 filed Nov. 6, 2019. The entire contents of the above applications are incorporated by reference herein.

TECHNICAL FIELD

[0002] 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

[0003] The invention features compounds, compositions and methods for the selective inhibition of sensory neurons (nociceptors, cough receptors and pruriceptors) and the treatment of 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 pain-cough- and itch-sensing neurons but to a lesser extent or not at all in other types of neurons or in other types of tissue. [0004] Local anesthetics such as lidocaine and articaine 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 membranepermeable, 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.

[0005] 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. [0006] 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

[0007] 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.

injury.

[0008] 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.

[0009] Pain may occur in patients with cancer, which may be due to multiple causes; inflammation, compression, invasion, metastatic spread into bone or other tissues.

[0010] 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.

[0011] Migraine is a headache associated with the activation of sensory fibers innervating the meninges of the brain.

[0012] 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.

[0013] 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.

[0014] 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. [0015] 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., migraine, arthritis, rhinitis, gastritis, colitis, cystitis, and sunburn). One way to reduce neurogenic inflammation is to block excitability in nociceptors, thereby preventing the activation of nociceptor peripheral terminals and the release of pro-inflammatory chemicals.

[0016] 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

[0017] The present invention provides compounds represented by Formula (I) that can be used to treat or prevent pain, itch, and neurogenic inflammation:

##STR00002## [0018] wherein: [0019] Y.sup. – is a pharmaceutically acceptable anion; [0020] R.sup.A, R.sup.B, and R.sup.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.sup.I, CN, NR.sup.JR.sup.K, NR.sup.LC(O)R.sup.M, S(O)R.sup.N, S(O).sub.2R.sup.N, SO.sub.2R.sup.OR.sup.P, SO.sub.2NR.sup.QR.sup.R, SO.sub.3R.sup.S, CO.sub.2R.sup.T; C(O)R.sup.U, and C(O)NR.sup.VR.sup.W; (preferably H, F, Cl, or CN and more preferably H); [0021] each of R.sup.I, R.sup.J, R.sup.K, R.sup.L, R.sup.M, R.sup.N, R.sup.O, R.sup.P, R.sup.Q, R.sup.R, R.sup.S, R.sup.T, R.sup.U, R.sup.V, and R.sup.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.sup.J and R.sup.K or R.sup.V and R.sup.W or R.sup.Q and R.sup.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; [0022] R.sup.A, R.sup.B, and/or R.sup.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; [0023] X.sup.1 is selected from — CR.sup.XR.sup.Y—, —NR.sup.ZC(O)—, —OC(O)—, —SC(O)—, —C(O)NR.sup.1A—, — C(O)O—, —C(O)—, —(O)CS—, —NR.sup.1AS(O)—, —S(O)NR.sup.1A—, — NR.sup.1AC(O)NR.sup.1A—, —S(O)— and —S(O).sub.2—; X.sup.1 can also be — NR.sup.ZC(O)CR.sup.XR.sup.Y—; [0024] each of R.sup.X, R.sup.Y, R.sup.Z, and R.sup.1A is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted heteroalkyl; [0025] each of R.sup.D and R.sup.E is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

unsubstituted heteroalkyl, and substituted or unsubstituted cycloalkyl; or R.sup.D and R.sup.E together with the carbon to which they are attached form a substituted or unsubstituted 3-6-membered cycloalkyl (a C.sub.3-C.sub.6 cycloalkyl), substituted or unsubstituted heterocyclic, or substituted or unsubstituted heteroalkyl ring; [0026] or R.sup.D and R.sup.Z together with the carbon and the —N—C(O)— to which they are attached form an optionally substituted 5-8-membered lactam; [0027] R.sup.F and R.sup.G together with N.sup.+ form an optionally substituted heterocyclic ring having one or more nitrogen atoms; or, each of R.sup.F and R.sup.G is independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted or uns

[0029] In another embodiment, R.sup.H can be a substituted alkyl. The substituent is preferably an ester group, such as —OC(O)R.sup.1B wherein R.sup.1B is substituted or unsubstituted alkyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R.sup.1B is preferably a substituted or unsubstituted phenyl. R.sup.H is preferably — CH.sub.2OC(O)— phenyl.

Description

DETAILED DESCRIPTION OF THE INVENTION

[0030] 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. [0031] The invention further provides methods for treating pain, cough, itch, or a neurogenic inflammatory disorder in a patient, including administering to the patient a composition comprising a compound having Formula (I), wherein the compound inhibits one or more voltage-gated ion channels present in nociceptors and/or cough receptors and/or pruriceptors when exposed or applied to the internal face of the channels but does not substantially inhibit the channels when applied to the external face of the channels, and wherein the compound is capable of entering nociceptors, cough receptors or pruriceptors through a large pore channel when the channel is activated and inhibiting one or more voltage-gated ion channels present in the nociceptors cough receptors or pruriceptors.

[0032] In certain embodiments, the large pore channel is a transient receptor potential ion channel (TRP channel). In other embodiments, the TRP channel is activated by an exogenous or endogenous agonist. In yet other embodiments, the large pore channel is TRPA1, TRPV1-4, TRPM8, ASIC or P2X. In particular embodiments, the compound is capable of entering nociceptors, cough receptors or pruriceptors through the TRPA1 TRPV1-4, TRPM8, ASIC or P2X receptor/channel when the receptor/channel is activated. In yet other embodiments, the compound inhibits voltage-gated sodium channels. In yet another embodiment, the type of pain treated by the methods, compositions, and kits of the invention is selected from the group consisting of neuropathic pain, inflammatory pain, nociceptive pain, pain due to infections, and procedural pain, or wherein the neurogenic inflammatory disorder is selected from the group consisting of allergic

inflammation, asthma, chronic cough, conjunctivitis, rhinitis, psoriasis, inflammatory bowel disease, interstitial cystitis, and atopic dermatitis.

[0033] We have identified compounds having Formula (I)

##STR00003##

that are capable of passing through open large pore channels that are expressed on nociceptors and/or cough receptors and/or pruriceptors but not on motor neurons. Because the ion channel blocking compounds of the present invention are positively charged, they are not membrane-permeable and thus cannot enter cells that do not express large pore channels. Since large pore channels are often more active in tissue conditions associated with pain (such as inflammation) due to release of endogenous ligands or activation by thermal stimuli, the ion channel blocker of the invention can be used alone to selectively target activated nociceptors in order to effectively treat (e.g., eliminate or alleviate) pain, cough, itch, or neurogenic inflammation. The ion channel blockers of the invention can also be used in combination with one or more exogenous large pore channel agonists to selectively target nociceptors in order to effectively treat (e.g., eliminate or alleviate) pain, itch, or neurogenic inflammation.

[0034] Voltage-dependent ion channels in pain-sensing neurons are currently of great interest in developing drugs to treat pain. Blocking voltage-dependent sodium channels in pain-sensing neurons can block pain signals by interrupting initiation and transmission of the action potential. Moreover, blocking voltage-dependent sodium channels in nociceptors can reduce or eliminate neurogenic inflammation by preventing activation of nociceptor peripheral terminals and the release thereof pro-inflammatory chemicals.

[0035] Heretofore, a limitation in treating with molecules that block sodium channels or calcium channels is that the vast majority of such externally-applied molecules are hydrophobic and can pass through membranes. Because of this, they will enter all cells and thus have no selectivity for affecting only nociceptors.

[0036] The inhibitors of the present invention are membrane-impermeable and are only effective when present inside the nociceptor cell, and thus must pass through the cell membrane via a channel or receptor, such as large pore channels (e.g., TRPAV1-4, TRPA1, TRPM8, ASIC and P2X(2/3)), in order to produce an effect. Under normal circumstances, most large pore channels in nociceptors are not active but require a noxious thermal, mechanical, or chemical stimulus to activate them. For example, TRP channels in nociceptors can be activated by an exogenous TRP ligand (i.e. TRP agonist) such as capsaicin, which opens the TRPV1 channel. Thus, one approach to selectively targeting nociceptors is to co-administer the membrane-impermeable ion channel inhibitor with an exogenous TRP ligand that permits passage of the inhibitor through the TRP channel into the cell. In addition to capsaicin, the exogenous TRP ligand can also be another capsaicinoid, mustard oil, or lidocaine. In another example, TRP channels may be active in response to exogenous irritant activators such as inhaled acrolein from smoke or chemical warfare agents such as tear gas.

[0037] Under certain circumstances, large pore channels can be activated in the absence of exogenous large pore channel agonists/ligands by endogenous inflammatory activators that are generated by tissue damage, infection, autoimmunity, atopy, ischemia, hypoxia, cellular stress, immune cell activation, immune mediator production, and oxidative stress. Under such conditions, endogenous molecules (e.g., protons, lipids, and reactive oxygen species) can activate large pore channels expressed on nociceptors, allowing membrane-impermeable, voltage-gated ion channel blockers to gain access to the inside of the nociceptor through the endogenously-activated large pore channels. Endogenous inflammatory activators of large pore channels include, for example, prostaglandins, nitric oxide (NO), peroxide (H.sub.2O.sub.2), cysteine-reactive inflammatory mediators like 4-hydroxynonenal, endogenous alkenyl aldehydes, endocannabinoids, and immune mediators (e.g., interleukin 1 (IL-1), nerve growth factor (NGF), and bradykinin, whose receptors are coupled to large pore channels).

Definitions

[0038] As used herein, the words "a" and "an" are meant to include one or more unless otherwise specified.

[0039] 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.

[0040] Biologically active agents that can be used in the methods and kits described herein include, without limitation, TRP1A 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.

[0041] 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. [0042] 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.

[0043] 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.

[0044] 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.

[0045] The term "somatic pain" is used to refer to pain arising from bone, joint, muscle, skin, or connective tissue. This type of pain is typically well localized.

[0046] 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

[0047] The term "inflammatory pain" includes pain associates with active inflammation that may be caused by trauma, surgery, infection and autoimmune diseases.

[0048] 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.

[0049] 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.

inflammation as in cystitis or reflux esophagitis.

[0050] The term "itch" is used herein in the broadest sense and refers to all types of 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.

[0051] 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).

[0052] 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, Dgluconic 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, (-)-Lmalic 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, (-)-Lpyroglutamic 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.

[0053] 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.

[0054] In the generic descriptions of compounds of this invention, the number of atoms of a particular type in a substituent group is generally given as a range, e.g., an alkyl group containing from 1 to 4 carbon atoms or C.sub.1-4 alkyl of C.sub.1-C.sub.4 alkyl. Reference to such a range is intended to include specific references to groups having each of the integer number of atoms within the specified range. For example, an alkyl group from 1 to 4 carbon atoms includes each of C.sub.1, C.sub.2, C.sub.3, and C.sub.4 alkyls. Other numbers of atoms and other types of atoms may be indicated in a similar manner.

[0055] "D" is deuterium.

[0056] 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 or 3 to 7 carbon atoms, inclusive. Exemplary cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups. [0057] By "C.sub.1-4 alkyl" or "C.sub.1-C.sub.4 alkyl" is meant a branched or unbranched

hydrocarbon group having from 1 to 4 carbon atoms. Similarly, a "C.sub.1-6 alkyl" or "C.sub.1-C.sub.6" is a branched or unbranched hydrocarbon group having from 1 to 6 carbon atoms. An alkyl, including, for example, a C.sub.1-4 alkyl or C.sub.1-6 alkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, alkylamino, disubstituted amino, quaternary amino, alkylcarboxy, and carboxyl groups. Exemplary substituents also 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. C.sub.1-4 alkyls include, without limitation, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and cyclobutyl. C.sub.1-6 alkyls include, without limitation, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0058] An 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, and S. By "C.sub.1-7 heteroalkyl" is meant a branched or unbranched alkyl, alkenyl, or alkynyl group having from 1 to 7 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.sub.1-7 heteroalkyls include, without limitation, methoxymethyl and ethoxyethyl. [0059] An alkenyl is a branched or unbranched hydrocarbon group containing one or more double bonds. For example, by "C.sub.2-6 alkenyl" or "C.sub.2-C.sub.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

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.sub.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. [0060] An alkynyl is a branched or unbranched hydrocarbon group containing one or more triple bonds. For example, by "C.sub.2-6 alkynyl" or "C.sub.2-C.sub.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.sub.2-6 alkynyls include, without limitation, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 3-butynyl. [0061] By "heterocyclyl," "heterocyclic," or "heterocycloalkyl" is meant a stable monocyclic or 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 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 9membered ring system. By "C.sub.2-6 heterocyclyl" is meant a stable 5- to 7-membered monocyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (including heteroaryl or aromatic), and which consists of 2 to 6 carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from N, O, and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, heteroaryl, cycloalkyl or heterocycloalkyl. The heterocyclyl or heteroaryl group may be substituted or unsubstituted. Exemplary substituents include substituted or unsubstituted alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, alkylamino, disubstituted amino, quaternary amino, alkylcarboxy, oxo, and carboxyl groups. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be covalently attached via any heteroatom or carbon atom which results in a stable structure, e.g., an imidazolinyl ring may be linked at either of the ringcarbon atom positions or at the nitrogen atom. A nitrogen 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, 1Hindazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aHcarbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, bcarbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroguinolinyl, 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, 1,2,5oxadiazolyl, 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, 1,2,3thiadiazolyl, 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, 7-lactam and 6-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, thiazolyl, pyrrolyl, piperazinyl, piperidinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and tetrazolyl. Preferred substituents include phenyl, methyl, propyl, butyl, chloro, bromo, fluoro, iodo and oxo.

[0062] By "aryl" is meant an aromatic group having a ring system comprised of carbon atoms with conjugated π electrons (e.g., phenyl). A "C.sub.6-C.sub.12 aryl" or "C.sub.6-C.sub.10 aryl" is an aryl group that 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. A bicyclic or tricyclic ring system can be fused (e.g., naphthyl) or not (e.g., biphenyl). The aryl group may be substituted or unsubstituted. Exemplary substituents include substituted or unsubstituted alkyl, hydroxyl, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, fluoroalkyl, carboxyl, alkylcarboxy, amino, alkylamino, monosubstituted amino, disubstituted amino, and quaternary amino groups. A preferred aryl group is phenyl.

[0063] 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). [0064] By "C.sub.7-14 aralkyl" is meant an alkyl substituted by an aryl group (e.g., benzyl, phenethyl, or 3,4-dichlorophenethyl) having from 7 to 14 carbon atoms.

[0065] By "C.sub.3-10 heterocycloalkyl" is meant an alkyl substituted heterocyclic group having from 3 to 10 carbon atoms in addition to one or more heteroatoms (e.g., 3-furanylmethyl, 2-furanylmethyl, 3-tetrahydrofuranylmethyl, or 2-tetrahydrofuranylmethyl).

[0066] By "halide" or "halogen" is meant bromine, chlorine, iodine, or fluorine.

[0067] By "fluoroalkyl" is meant an alkyl group that is substituted with a fluorine atom.

[0068] By "alkylcarboxy" is meant a chemical moiety with the formula —(R)—COOH, wherein R is selected from C.sub.1-7 alkyl, C.sub.2-7 alkenyl, C.sub.2-7 alkynyl, C.sub.2-6 heterocyclyl, C.sub.6-12 aryl, C.sub.7-14 aralkyl, C.sub.3-10 heterocycloalkyl, or C.sub.1-7 heteroalkyl. [0069] By "alkoxy" is meant a chemical substituent of the formula OR, wherein R is a substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl or R can be selected from C.sub.1-7 alkyl, C.sub.2-7 alkenyl, C.sub.2-7 alkynyl, C.sub.2-6 heterocyclyl, C.sub.6-12 aryl, C.sub.7-14 aralkyl, C.sub.3-10 heterocycloalkyl, or C.sub.1-7 heteroalkyl.

[0070] By "aryloxy" is meant a chemical substituent of the formula OR, wherein R is a C.sub.6-12 aryl group. By "alkylthio" is meant a chemical substituent of the formula SR, wherein R is selected from C.sub.1-7 alkyl, C.sub.2-7 alkenyl, C.sub.2-7 alkynyl, C.sub.2-6 heterocyclyl, C.sub.6-12 aryl, C.sub.7-14 aralkyl, C.sub.3-10 heterocycloalkyl, or C.sub.1-7 heteroalkyl.

[0071] By "arylthio" is meant a chemical substituent of the formula SR, wherein R is a C.sub.6-12 aryl group.

[0072] 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.

[0073] 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. asthma, arthritis, colitis, contact dermatitis, diabetes, eczema, cystitis, chronic refractory cough, post-viral cough, gastritis, migraine headache, psoriasis, rhinitis, rosacea, or sunburn).

[0074] "Solvates" means solvent addition forms that contain either stoichiometric or nonstoichiometric amounts of solvent.

[0075] 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. [0076] 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. [0077] Compounds that can be used in the compositions, kits, and methods of the invention include compounds having Formula (I), or a pharmaceutically acceptable salt thereof: ##STR00004## [0078] wherein: [0079] Y.sup. – is a pharmaceutically acceptable anion; [0080] R.sup.A, R.sup.B, and R.sup.C are each independently selected from H, D, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, OR.sup.I, NR.sup.JR.sup.K, NR.sup.LC(O)R.sup.M, S(O)R.sup.N, S(O).sub.2R.sup.N, SO.sub.2R.sup.OR.sup.P, SO.sub.2NR.sup.QR.sup.R, SO.sub.3R.sup.S, CO.sub.2R.sup.T, C(O)R.sup.U, and C(O)NR.sup.VR.sup.W; [0081] each of R.sup.I, R.sup.J, R.sup.K, R.sup.L, R.sup.M, R.sup.N, R.sup.O, R.sup.P, R.sup.Q, R.sup.R, R.sup.S, R.sup.T, R.sup.U, R.sup.V, and R.sup.W is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; [0082] X.sup.1 is selected from — CR.sup.XR.sup.Y—, —NR.sup.ZC(O)—, —NR.sup.ZC(O)CR.sup.XR.sup.Y—, —OC(O)—, — SC(O)—, —C(O)NR.sup.1A—, —C(O)O—, —C(O)—, —(O)CS—, —NR.sup.1AS(O)—, — S(O)NR.sup.1A—, —NR.sup.1AC(O)NR.sup.1A—, —S(O)— and —S(O).sub.2—; [0083] each of R.sup.X, R.sup.Y, R.sup.Z, and R.sup.1A is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; [0084] each of R.sup.D and R.sup.E is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted cycloalkyl; or R.sup.D and R.sup.E together with the carbon to which they are attached form a substituted or unsubstituted C.sub.3-C.sub.6 cycloalkyl or a substituted or unsubstituted heterocyclic (for example, a 5- to 7-membered heterocyclic ring); [0085] R.sup.F and R.sup.G together with the N.sup.+ to which they are attached form an optionally substituted heterocyclic ring having zero, one or more nitrogen atoms in addition to the N.sup.+; or, each of R.sup.F and R.sup.G is independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted C.sub.3-6 cycloalkyl; and [0086] R.sup.H is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl. [0087] In a preferred embodiment, R.sup.H is independently selected from a substituted or unsubstituted C.sub.5-10 aryl or a substituted or unsubstituted C.sub.5-10 heteroaryl. [0088] In a further preferred embodiment, R.sup.H is independently selected from a substituted or unsubstituted C.sub.6-10 aryl or a substituted or unsubstituted 5- to 10-membered heteroaryl. [0089] In some embodiments, R.sup.H is a substituted C.sub.5-10 aryl or a substituted C.sub.5-10 heteroaryl optionally substituted with C.sub.1-6 alkane, C.sub.1-6 heteroalkane, carbocycle, substituted carbocycle, heterocarbocycle, substituted heterocarbocycle, phenyl, substituted phenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, carboxamide, hydroxyl, ether, amide, ester, sulfonamide, sulfone, amino, amino alkyl, urea, nitrile, or halogen. In a preferred embodiment, the C.sub.1-6 alkane is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, npentyl, isopentyl, neopentyl, and n-hexyl. In a preferred embodiment, the C.sub.1-6 heteroalkane is selected from —O-methyl, —O-ethyl, —O-propyl, —O-isopropyl, —O-butyl, —O-isobutyl, —O — cyclohexyl, —O-cyclopentyl, and -ethyl-O-methyl. In a preferred embodiment, the carbocycle is selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In a preferred embodiment, the heterocarbocycle is selected from aziridine, azetidine, furan, pyrrolidine, pyran, piperidine,

piperazine, azepine, and diazapine.

[0090] In yet another preferred embodiment, R.sup.H is a substituted or unsubstituted C.sub.6-10 aryl or a substituted or unsubstituted 5- to 10-membered heteroaryl. In certain aspects, R.sup.H is an unsubstituted C.sub.6-10 aryl or an unsubstituted 5- to 10-membered heteroaryl. In additional aspects, R.sup.H is a C.sub.6-10 aryl or a 5- to 10-membered heteroaryl, each optionally substituted with a substituted or unsubstituted C.sub.1-C.sub.6 alkyl, halo, nitrile, hydroxyl, and alkoxy. In yet additional aspects, R.sup.H is a C.sub.6-10 aryl or a 5- to 10-membered heteroaryl, each optionally substituted with a substituted or unsubstituted C.sub.1-C.sub.6 alkyl, halo, nitrile, and OR.sup.2B, wherein R.sup.2B is hydrogen or substituted or unsubstituted C.sub.1-C.sub.6 alkyl. In a further preferred embodiment, R.sup.H is an unsubstituted phenyl. In additional embodiments, R.sup.H is phenyl substituted with a substituent selected from the group consisting of substituted or unsubstituted C.sub.1-C.sub.6 alkyl, halo, nitrile, hydroxyl, and alkoxy. In additional aspects, R.sup.H is phenyl is substituted with a substituent selected from the group consisting of substituted or unsubstituted C.sub.1-C.sub.6 alkyl, halo, nitrile, and OR.sup.2B, wherein R.sup.2B is hydrogen or substituted, and unsubstituted C.sub.1-C.sub.6 alkyl. In yet additional embodiments, R.sup.H is phenyl substituted with an unsubstituted C.sub.1-C.sub.6 alkyl, halo, nitrile, hydroxyl, or alkoxy. In further aspects, R.sup.H is phenyl substituted with a substituent selected from the group consisting of unsubstituted C.sub.1-C.sub.6 alkyl, halo, nitrile, and OR.sup.2B, wherein R.sup.2B is hydrogen or substituted or unsubstituted C.sub.1-C.sub.6 alkyl.

[0091] In yet further aspects, R.sup.H is selected from the Z groups shown in Tables 1 to 3. [0092] In a preferred embodiment, X.sup.1 is —NHC(O)— or —C(O)NH—. In another preferred embodiment, X.sup.1 is —NHC(O)—.

[0093] In preferred embodiments, R.sup.A, R.sup.B, and R.sup.C are each independently selected from H, D, halogen, substituted or unsubstituted C.sub.1-4 alkyl, and NR.sup.JR.sup.K; and each of R.sup.J and R.sup.K is independently selected from H and substituted or unsubstituted C.sub.1-4 alkyl.

[0094] In a preferred embodiment, each of R.sup.A and R.sup.B is CH.sub.3, and R.sup.C is H, CH.sub.3, halogen, nitrile, methoxy, or ethoxy.

[0095] In yet additional preferred aspects, R.sup.A, R.sup.B, and R.sup.C are independently selected from H, D, halogen, OR.sup.I, substituted or unsubstituted C.sub.1-C.sub.4 alkyl, and NR.sup.JR.sup.K; wherein each of R.sup.I, R.sup.J and R.sup.K is independently selected from H and substituted or unsubstituted C.sub.1-C.sub.4 alkyl. In a preferred embodiment, each of R.sup.A and R.sup.B is CH.sub.3, and R.sup.C is selected from the group consisting of H, CH.sub.3, halogen, nitrile (cyano), methoxy, and ethoxy. In further preferred embodiments, each of R.sup.A and R.sup.B is CH.sub.3, and R.sup.C is selected from the group consisting of H, CH.sub.3, fluoro, chloro, nitrile, methoxy, and ethoxy. In additional preferred embodiments, each of R.sup.A and R.sup.B are CH.sub.3 and R.sup.C is hydrogen.

[0096] In certain other embodiments, R.sup.D is C.sub.1-4 alkyl optionally substituted with a substituent selected from the group consisting of halogen, oxygen, C.sub.3-8 cycloalkyl, aryl, or heteroaryl, and/or R.sup.E is H or C.sub.1-4 alkyl optionally substituted with a substituent selected from the group consisting of halogen, oxygen, C.sub.3-8 cycloalkyl, aryl, or heteroaryl. [0097] In preferred embodiments each of R.sup.D and R.sup.E is independently selected from H, D, CH.sub.3, CH.sub.2CH.sub.3, (CH.sub.2).sub.2CH.sub.3, and (CH.sub.2).sub.3CH.sub.3. In a more preferred embodiment, R.sup.E is hydrogen and R.sup.D is CH.sub.3, CH.sub.2CH.sub.3, (CH.sub.2).sub.3CH.sub.3. In certain, other preferred embodiments R.sup.D and R.sup.E together form a substituted or unsubstituted C.sub.3-C.sub.6 cycloalkyl. [0098] In certain preferred embodiments, R.sup.D and R.sup.E are both hydrogen. In yet additional preferred embodiments, R.sup.D is hydrogen and R.sup.E is an alkyl, for example, a C.sub.1-C.sub.6 alkyl or a C.sub.1-C.sub.4 alkyl including, but not limited to, methyl, ethyl, propyl and

butyl. In certain additional preferred embodiments, R.sup.D and R.sup.E are taken together with the carbon to which they are attached to form a C.sub.3-C.sub.6 cycloalkyl including, but not limited to, cyclopropyl or cyclobutyl.

[0099] In preferred embodiments, R.sup.F and R.sup.G together with the N.sup.+ to which they are attached form a five, six, seven, or eight membered heterocyclic ring, each optionally substituted, resulting in a compound of Formula Ia:

##STR00005##

[0100] Wherein each variable is as defined above, including preferred or alternative embodiments, n is 1, 2, 3, 4 or 5; and R.sup.1B is H or a substituent, such as 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.sup.1I, CN, NR.sup.1JR.sup.1K, NR.sup.1LC(O)R.sup.1M, S(O)R.sup.1N, S(O).sub.2R.sup.1N, SO.sub.2R.sup.1OR.sup.1P, SO.sub.2NR.sup.1QR.sup.1R, SO.sub.3R.sup.1S, CO.sub.2R.sup.1T, C(O)R.sup.1U, and C(O)NR.sup.1VR.sup.1W; and wherein each of R.sup.1I, R.sup.1J, R.sup.1K, R.sup.1L, R.sup.1M, R.sup.1N, R.sup.1I, R.sup.1P, R.sup.1Q, R.sup.1R, R.sup.1S, R.sup.1T, R.sup.1U, R.sup.1V, and R.sup.1W 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.sup.1J and R.sup.1K or R.sup.1V and R.sup.1W or R.sup.1Q and R.sup.1R 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. [0101] In preferred embodiments, R.sup.F and R.sup.G together with the N.sup.+ to which they are attached form a five, six, seven, or eight-membered nitrogen-containing heterocyclic ring, including, but not limited to:

##STR00006##

each optionally substituted. Preferred substituents include phenyl, CO.sub.2R.sup.1T and C(O)NR.sup.1VR.sup.1W.

[0102] In a further aspect, R.sup.F and R.sup.G are independently a C.sub.1-C.sub.4 alkyl. In another embodiment, R.sup.F and R.sup.G are independently selected from CH.sub.3 and CH.sub.2CH.sub.3. In certain other aspects, R.sup.F and R.sup.G are the same and are substituted or unsubstituted C.sub.1-C.sub.4 alkyl. In yet addition aspects, R.sup.F and R.sup.G are the same and are methyl, ethyl, propyl, or butyl. In yet another embodiment, R.sup.F and R.sup.G are the same and are CH.sub.3 or CH.sub.2CH.sub.3.

[0103] In some embodiments Y.sup.— is a halide anion, a carboxylate, or a sulfonate. Y.sup.— can, for example, be a halide ion, a substituted or unsubstituted alkylsulfonate, a substituted or unsubstituted arylsulfonate, a substituted or unsubstituted or unsubstituted or unsubstituted or unsubstituted heterocyclyl carboxylate.

[0104] 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 ptoluenesulfonate, 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.sup.— is a halide anion.

- [0105] In a preferred embodiment, the anion is selected from the halide ions bromide, chloride, or iodide.
- [0106] Each preferred group stated above can be taken in combination with one, any or all other preferred groups.
- [0107] In a preferred embodiment, the present invention relates to compounds of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R.sup.H is an optionally substituted aryl or optionally substituted heteroaryl selected from one of the following: ##STR00007## ##STR00008##
- [0108] In certain preferred aspects, R.sup.H is substituted or unsubstituted phenyl.
- [0109] In certain additional aspects, the compound has the Formula (II):
- ##STR00009## [0110] wherein: [0111] Y.sup.— is a pharmaceutically acceptable anion; [0112] q is 0, 1, 2, or 3; [0113] R.sup.D is hydrogen, methyl, or ethyl; and [0114] R.sup.1B is as defined above.
- [0115] In some embodiments, the compound has the Formula (II), wherein Y.sup.— is a halide anion, a carboxylate, or a sulfonate. Y.sup.— can, for example, be a halide ion, a substituted or unsubstituted alkylsulfonate, a substituted or unsubstituted arylsulfonate, a substituted or unsubstituted aryl carboxylate, or a substituted or unsubstituted heterocyclyl carboxylate.
- [0116] In certain embodiments, the compound has the Formula (II), wherein Y.sup.— 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.
- [0117] In one embodiment, the compound has the Formula (II) and Y.sup.— is halide anion. In a preferred embodiment, Y.sup.— is selected from the halide ions bromide, chloride, or iodide. [0118] As will be understood, when q is 0, 1, 2, or 3, the N.sup.+-containing ring of Formula (II) is: ##STR00010##
- respectively. In certain preferred embodiments, q is 0. In other preferred aspects, q is 1. In other preferred aspects, q is 2. In yet further preferred aspects, q is 3.
- [0119] In yet additional preferred aspects, the compound has the Formula (II) and R.sup.D is hydrogen.
- [0120] In further aspects, the compound has the Formula (II) and R.sup.D is methyl.
- [0121] In yet other aspects, the compound has the Formula (II) and R.sup.D is ethyl.
- [0122] In yet further aspects, the compound has the Formula (II), q is 0 and R.sup.D is hydrogen.
- [0123] In additional preferred aspects, the compound has the Formula (II), q is 1 and R.sup.D is hydrogen.
- [0124] In further preferred aspects, the compound has the Formula (II) and q is 2, and R.sup.D is hydrogen.
- [0125] In additional aspects, the compound has the Formula (II), q is 3, and R.sup.D is hydrogen.
- [0126] In yet additional preferred embodiments, the compound has the Formula (II), and q is 0 and R.sup.D is methyl.
- [0127] In additional preferred aspects, the compound has the Formula (II), q is 1 and R.sup.D is methyl.
- [0128] In further preferred aspects, the compound has the Formula (II), q is 2 and R.sup.D is

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methyl.
[0129] In additional aspects, the compound has the Formula (II), q is 3 and R.sup.D is methyl.
[0130] In further preferred embodiments, the compound has the Formula (II), q is 0 and R.sup.D is
ethyl.
[0131] In additional preferred aspects, the compound has the Formula (II), q is 1 and R.sup.D is
ethyl.
[0132] In further preferred aspects, the compound has the Formula (II), q is 2 and R.sup.D is ethyl.
[0133] In additional aspects, the compound has the Formula (II), q is 3 and R.sup.D is ethyl.
[0134] In yet an additional aspect, the compound is selected from Table A below, or a
pharmaceutically acceptable salt thereof, wherein Y.sup. – is a pharmaceutically acceptable anion.
TABLE-US-00001 TABLE A Compound # Structure 1 [00011] embedded image 2 [00012]
embedded image 3 [00013] embedded image 4 [00014] embedded image 5 [00015]
embedded image 6 [00016] embedded image 7 [00017] embedded image 8 [00018]
embedded image 9 [00019] embedded image 10 [00020] embedded image 11 [00021]
embedded image 12 [00022] embedded image 13 [00023] embedded image 14 [00024]
embedded image 15 [00025] embedded image 16 [00026] embedded image 17 [00027]
embedded image 18 [00028] embedded image 19 [00029] embedded image 20 [00030]
embedded image 21 [00031] embedded image 22 [00032] embedded image 23 [00033]
Embedded image 24 [00034] embedded image 25 [00035] embedded image 26 [00036]
embedded image 27 [00037] embedded image 28 [00038] embedded image 29 [00039]
embedded image 30 [00040] embedded image 31 [00041] embedded image
[0135] In additional preferred aspects, the compound is selected from the compounds in the
following Tables, or a pharmaceutically acceptable salt thereof, wherein Y- is as indicated or a
pharmaceutically acceptable anion:
TABLE-US-00002 TABLE B Compound # Y.sup. – Structure 1A Br.sup. – [00042]
embedded image 1B Cl.sup. – [00043] embedded image 2A Br.sup. – [00044]
embedded image 2B Cl.sup. – [00045] embedded image 3A Br.sup. – [00046]
embedded image 3B Cl.sup. – [00047] embedded image 4A Br.sup. – [00048]
embedded image 4B Cl.sup. – [00049] embedded image 5A Br.sup. – [00050]
embedded image 5B Cl.sup. – [00051] embedded image 6A Br.sup. – [00052]
embedded image 6B Cl.sup. – [00053] embedded image 7A Br.sup. – [00054]
embedded image 7B Cl.sup. – [00055] embedded image 8A Br.sup. – [00056]
embedded image 8B Cl.sup. – [00057] embedded image 9A Br.sup. – [00058]
embedded image 9B Cl.sup. – [00059] embedded image 10A Br.sup. – [00060]
embedded image 10B Cl.sup. – [00061] embedded image 11A Br.sup. – [00062]
embedded image 11B Cl.sup. – [00063] embedded image 12A Br.sup. – [00064]
embedded image 12B Cl.sup. – [00065] embedded image 13A Br.sup. – [00066]
embedded image 13B Cl.sup. – [00067] embedded image 14A Br.sup. – [00068]
embedded image 14B Cl.sup. – [00069] embedded image 15A Br.sup. – [00070]
embedded image 15B Cl.sup. – [00071] embedded image 16A Br.sup. – [00072]
embedded image 16B Cl.sup. – [00073] embedded image 17A Br.sup. – [00074]
embedded image 17B Cl.sup. – [00075] embedded image 18A Br.sup. – [00076]
embedded image 18B Cl.sup. – [00077] embedded image 19A Br.sup. – [00078]
embedded image 19B Cl.sup. – [00079] embedded image 20A Br.sup. – [00080]
embedded image 20B Cl.sup. – [00081] embedded image 21A Br.sup. – [00082]
embedded image 21B Cl.sup. – [00083] embedded image 22A Br.sup. – [00084]
embedded image 22B Cl.sup. – [00085] embedded image 23A Br.sup. – [00086]
embedded image 23B Cl.sup. – [00087] embedded image 24A Br.sup. – [00088]
embedded image 24B Cl.sup. – [00089] embedded image 25A Br.sup. – [00090]
Eembedded image 25B Cl.sup. – [00091] embedded image 26A Br.sup. – [00092]
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embedded image 26B Cl.sup. – [00093] embedded image 27A Br.sup. – [00094]
Rembedded image 27B Cl.sup.− [00095] embedded image 28 TFA.sup.− [00096]
Rembedded image 29 CO.sub.3.sup.− [00097] embedded image 30A Br.sup.− [00098]
embedded image 30B Cl.sup. – [00099] embedded image 31A Br.sup. – [00100]
embedded image [00104] embedded image [00105] embedded image [00106]
embedded image [00107] embedded image [00108] embedded image [00109]
embedded image [00110] embedded image [00111] embedded image [00112]
embedded image [00113] embedded image [00114] embedded image [00115]
embedded image [00116] embedded image [00117] embedded image [00118]
embedded image [00119] embedded image [00120] embedded image [00121]
embedded image [00122] embedded image [00123] embedded image [00124]
embedded image [00125] embedded image [00126] embedded image [00127]
embedded image [00128] embedded image [00129] embedded image [00130]
embedded image [00131] embedded image [00132] embedded image [00133]
embedded image [00134] embedded image [00135] embedded image [00136]
embedded image [00137] embedded image [00138] embedded image [00139]
embedded image [00140] embedded image [00141] embedded image [00142]
embedded image [00143] embedded image [00144] embedded image [00145]
embedded image [00146] embedded image [00147] embedded image [00148]
embedded image [00149] embedded image [00150] embedded image [00151]
embedded image [00152] embedded image [00153] embedded image [00154]
embedded image [00155] embedded image [00156] embedded image [00157]
embedded image [00158] embedded image [00159] embedded image [00160]
embedded image [00161] embedded image [00162] embedded image [00163]
embedded image [00164] embedded image [00165] embedded image [00166]
embedded image [00167] embedded image [00168] embedded image [00169]
embedded image [00170] embedded image [00171] embedded image [00172]
embedded image [00173] embedded image [00174] embedded image [00175]
embedded image [00176] embedded image [00177] embedded image [00178]
embedded image [00179] embedded image [00180] embedded image [00181]
embedded image [00182] embedded image [00183] embedded image [00184]
embedded image [00185] embedded image [00186] embedded image [00187]
embedded image [00188] embedded image [00189] embedded image [00190]
embedded image [00191] embedded image [00192] embedded image [00193]
embedded image [00194] embedded image [00195] embedded image [00196]
embedded image [00197] embedded image [00198] embedded image [00199]
embedded image [00200] embedded image [00201] embedded image [00202]
embedded image [00203] embedded image [00204] embedded image [00205]
embedded image [00206] embedded image [00207] embedded image
[0136] Representative compounds according to the invention and their enantiomers and
pharmaceutically acceptable salts thereof are those selected from Table C below, wherein Y.sup. – is
a pharmaceutically acceptable anion, as defined above, and Z is either an aryl or a heteroaryl
structure selected from one of the structures in Table 1, or a substituted aryl or substituted
heteroaryl structure selected from one of the structures in Tables 2-3.
TABLE-US-00003 TABLE C Representative Compounds of the Invention No. Structure 1 [00208]
embedded image 2 [00209] embedded image 3 [00210] embedded image 4 [00211]
embedded image 5 [00212] embedded image 6 [00213] embedded image 7 [00214]
embedded image 8 [00215] embedded image 9 [00216] embedded image 10 [00217]
embedded image 11 [00218] embedded image 12 [00219] embedded image 13 [00220]
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embedded image 14 [00221] embedded image 15 [00222] embedded image 16 [00223]
embedded image 17 [00224] embedded image 18 [00225] embedded image 19 [00226]
embedded image 20 [00227] embedded image 21 [00228] embedded image 22 [00229]
embedded image 23 [00230] embedded image 24 [00231] embedded image 25 [00232]
embedded image 26 [00233] embedded image 27 [00234] embedded image 28 [00235]
embedded image 29 [00236] embedded image 30 [00237] embedded image 31 [00238]
embedded image 32 [00239] embedded image 33 [00240] embedded image 34 [00241]
embedded image 35 [00242] embedded image 36 [00243] embedded image 37 [00244]
embedded image 38 [00245] embedded image 39 [00246] embedded image 40 [00247]
embedded image 41 [00248] embedded image 42 [00249] embedded image 43 [00250]
embedded image 44 [00251] embedded image 45 [00252] embedded image 46 [00253]
embedded image 47 [00254] embedded image 48 [00255] embedded image 49 [00256]
embedded image 50 [00257] embedded image 51 [00258] embedded image 52 [00259]
embedded image 53 [00260] embedded image 54 [00261] embedded image 55 [00262]
embedded image 56 [00263] embedded image 57 [00264] embedded image 58 [00265]
embedded image 59 [00266] embedded image 60 [00267] embedded image 61 [00268]
embedded image 62 [00269] embedded image 63 [00270] embedded image 64 [00271]
embedded image 65 [00272] embedded image 66 [00273] embedded image 67 [00274]
embedded image 68 [00275] embedded image 69 [00276] embedded image 70 [00277]
embedded image 71 [00278] embedded image 72 [00279] embedded image 73 [00280]
embedded image 74 [00281] embedded image 75 [00282] embedded image 76 [00283]
embedded image 77 [00284] embedded image 78 [00285] embedded image 79 [00286]
embedded image 80 [00287] embedded image 81 [00288] embedded image 82 [00289]
embedded image 83 [00290] embedded image 84 [00291] embedded image 85 [00292]
embedded image 86 [00293] embedded image 87 [00294] embedded image 88 [00295]
embedded image 89 [00296] embedded image 90 [00297] embedded image 91 [00298]
Embedded image 92 [00299] embedded image 93 [00300] embedded image 94 [00301]
embedded image 95 [00302] embedded image 96 [00303] embedded image 97 [00304]
Embedded image 98 [00305] embedded image 99 [00306] embedded image 100 [00307]
Embedded image 101 [00308] embedded image 102 [00309] embedded image 103 [00310]
Embedded image 104 [00311] embedded image 105 [00312] embedded image 106 [00313]
mbedded image 107 [00314] embedded image 108 [00315] embedded image 109 [00316]
Embedded image 110 [00317] embedded image 111 [00318] embedded image 112 [00319]
Embedded image 113 [00320] embedded image 114 [00321] embedded image 115 [00322]
Embedded image 116 [00323] embedded image 117 [00324] embedded image 118 [00325]
Embedded image 119 [00326] embedded image 120 [00327] embedded image 121 [00328]
Embedded image 122 [00329] embedded image 123 [00330] embedded image 124 [00331]
embedded image 125 [00332] embedded image 126 [00333] embedded image 127 [00334]
embedded image 128 [00335] embedded image 129 [00336] embedded image 130 [00337]
mbedded image 131 [00338] embedded image 132 [00339] embedded image 133 [00340]
embedded image 134 [00341] embedded image 135 [00342] embedded image 136 [00343]
embedded image 137 [00344] embedded image 138 [00345] embedded image 139 [00346]
Embedded image 140 [00347] embedded image 141 [00348] embedded image 142 [00349]
Eembedded image 143 [00350] embedded image 144 [00351] embedded image 145 [00352]
Eembedded image 146 [00353] embedded image 147 [00354] embedded image 148 [00355]
mbedded image 149 [00356] embedded image 150 [00357] embedded image 151 [00358]
mbedded image 152 [00359] embedded image 153 [00360] embedded image 154 [00361]
embedded image 155 [00362]
embedded image 156 [00363]
embedded image 157 [00364]
Eembedded image 158 [00365] embedded image 159 [00366] embedded image 160 [00367]
Embedded image 161 [00368] embedded image 162 [00369] embedded image 163 [00370]
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embedded image 164 [00371] embedded image 165 [00372] embedded image 166 [00373]
embedded image 167 [00374] embedded image 168 [00375] embedded image 169 [00376]
embedded image 170 [00377] embedded image 171 [00378] embedded image 172 [00379]
Eembedded image 173 [00380] embedded image 174 [00381] embedded image 175 [00382]
embedded image 176 [00383] embedded image 177 [00384] embedded image 178 [00385]
embedded image 179 [00386] embedded image 180 [00387] embedded image 181 [00388]
Eembedded image 182 [00389] embedded image 183 [00390] embedded image 184 [00391]
embedded image 185 [00392] embedded image 186 [00393] embedded image 187 [00394]
Embedded image 188 [00395] embedded image 189 [00396] embedded image 190 [00397]
embedded image 191 [00398] embedded image 192 [00399] embedded image 193 [00400]
Embedded image 194 [00401] embedded image 195 [00402] embedded image 196 [00403]
embedded image 197 [00404] embedded image 198 [00405] embedded image 199 [00406]
Embedded image 200 [00407] embedded image 201 [00408] embedded image 202 [00409]
embedded image 203 [00410] embedded image 204 [00411] embedded image 205 [00412]
embedded image 206 [00413] embedded image 207 [00414] embedded image 208 [00415]
embedded image 209 [00416] embedded image 210 [00417] embedded image 211 [00418]
Eembedded image 212 [00419] embedded image 213 [00420] embedded image 214 [00421]
Eembedded image 215 [00422] embedded image 216 [00423] embedded image 217 [00424]
Embedded image 218a [00425] embedded image 218b [00426] embedded image 219 [00427]
Embedded image 220 [00428] embedded image 221 [00429] embedded image 222 [00430]
Embedded image 223 [00431] embedded image 224 [00432] embedded image 225 [00433]
embedded image 226 [00434] embedded image 227 [00435] embedded image 228 [00436]
Embedded image 229 [00437] embedded image 230 [00438] embedded image 231 [00439]
Embedded image 232 [00440] embedded image 233 [00441] embedded image 234 [00442]
Eembedded image 235 [00443] embedded image 236 [00444] embedded image 237 [00445]
Embedded image 238 [00446] embedded image 239 [00447] embedded image 240 [00448]
Eembedded image 241 [00449] embedded image 242 [00450] embedded image 243 [00451]
embedded image 244 [00452] embedded image 245 [00453] embedded image 246 [00454]
Eembedded image 247 [00455] embedded image 248 [00456] embedded image 249 [00457]
Embedded image 250 [00458] embedded image 251 [00459] embedded image 252 [00460]
Eembedded image 253 [00461] embedded image 254 [00462] embedded image 255 [00463]
embedded image 256 [00464] embedded image 257 [00465] embedded image 258 [00466]
embedded image 259 [00467] embedded image 260 [00468] embedded image 261 [00469]
Eembedded image 262 [00470] embedded image 263 [00471] embedded image 264 [00472]
Embedded image 265 [00473] embedded image 266 [00474] embedded image 267 [00475]
Embedded image 268 [00476] embedded image 269 [00477] embedded image 270 [00478]
Eembedded image 271 [00479] embedded image 272 [00480] embedded image 273 [00481]
embedded image 274 [00482] embedded image 275 [00483] embedded image 276 [00484]
embedded image 277 [00485] embedded image
TABLE-US-00004 TABLE 1 Representative Z Structures No. Structure 1 [00486]
embedded image 2 [00487] embedded image 3 [00488] embedded image 4 [00489]
embedded image 5 [00490] embedded image 6 [00491] embedded image 7 [00492]
embedded image 8 [00493] embedded image 9 [00494] embedded image 10 [00495]
embedded image 11 [00496] embedded image 12 [00497] embedded image 13 [00498]
embedded image 14 [00499] embedded image 15 [00500] embedded image 16 [00501]
embedded image 17 [00502] embedded image 18 [00503] embedded image 19 [00504]
mbedded image 20 [00505] embedded image 21 [00506] embedded image 22 [00507]
embedded image 23 [00508] embedded image 24 [00509] embedded image 25 [00510]
embedded image 26 [00511] embedded image 27 [00512] embedded image 28 [00513]
embedded image 29 [00514] embedded image 30 [00515] embedded image 31 [00516]
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embedded image TABLE-US-00005 TABLE 2 Representative Z Structures No. Structure 1 [00517] 2 [00518] embedded image 3 [00519] embedded image embedded image 4 [00520] 5 [00521] embedded image 6 [00522] embedded image embedded image 7 [00523] embedded image 8 [00524] embedded image 9 [00525] embedded image 10 [00526] embedded image 11 [00527] embedded image 12 [00528] embedded image 13 [00529] embedded image 14 [00530] embedded image 15 [00531] embedded image 16 [00532] embedded image 17 [00533] embedded image 18 [00534] embedded image 19 [00535] embedded image 20 [00536] embedded image 21 [00537] embedded image 22 [00538] embedded image 23 [00539] embedded image 24 [00540] embedded image 25 [00541] embedded image 26 [00542] embedded image 27 [00543] embedded image 28 [00544] embedded image 29 [00545] embedded image 30 [00546] embedded image 31 [00547] embedded image 32 [00548] embedded image 33 [00549] embedded image 34 [00550] embedded image 35 [00551] **embedded** image 36 [00552] embedded image 37 [00553] embedded image 38 [00554] **embedded** image 39 [00555] embedded image 40 [00556] embedded image 41 [00557] embedded image 42 [00558] embedded image 43 [00559] embedded image 44 [00560] embedded image 45 [00561] embedded image 46 [00562] embedded image 47 [00563] embedded image 48 [00564] embedded image 49 [00565] embedded image 50 [00566] embedded image 51 [00567] embedded image 52 [00568] embedded image 53 [00569] embedded image 54 [00570] embedded image 55 [00571] embedded image 56 [00572] embedded image 57 [00573] embedded image 58 [00574] embedded image 59 [00575] embedded image 60 [00576] embedded image 61 [00577] embedded image 63 [00579] embedded image 62 [00578] embedded image 64 [00580] embedded image 65 [00581] embedded image 66 [00582] embedded image 67 [00583] embedded image 68 [00584] embedded image 69 [00585] embedded image 70 [00586] embedded image 72 [00588] embedded image 71 [00587] embedded image 73 [00589] embedded image 74 [00590] embedded image 75 [00591] embedded image 76 [00592] embedded image 78 [00594] embedded image 77 [00593] embedded image 79 [00595] embedded image 80 [00596] embedded image 81 [00597] embedded image 82 [00598] 84 [00600] embedded image embedded image 83 [00599] **E**embedded image 85 [00601] 87 [00603] embedded image embedded image 86 [00602] embedded image 88 [00604] embedded image 89 [00605] embedded image 90 [00606] embedded image 91 [00607] embedded image 92 [00608] embedded image 93 [00609] embedded image 94 [00610] embedded image 95 [00611] embedded image 96 [00612] embedded image 97 [00613] embedded image 98 [00614]
embedded image 99 [00615]
embedded image 100 [00616] Eembedded image 101 [00617] embedded image 102 [00618] embedded image 103 [00619] Eembedded image 104 [00620] embedded image 105 [00621] embedded image 106 [00622] mbedded image 107 [00623] embedded image 108 [00624] embedded image 109 [00625] Eembedded image 110 [00626] embedded image 111 [00627] embedded image 112 [00628] mbedded image 113 [00629] embedded image 114 [00630] embedded image 115 [00631] embedded image 116 [00632]
embedded image 117 [00633]
embedded image 118 [00634] embedded image 119 [00635] embedded image 120 [00636] embedded image 121 [00637] embedded image 122 [00638]
embedded image 123 [00639]
embedded image 124 [00640] embedded image 125 [00641] embedded image 126 [00642] embedded image 127 [00643] embedded image 128 [00644] embedded image 129 [00645] embedded image 130 [00646] embedded image 131 [00647] embedded image 132 [00648] embedded image 133 [00649] Dembedded image 134 [00650] embedded image 135 [00651] embedded image TABLE-US-00006 TABLE 3 Representative Z Structures No. Structure 1 [00652] embedded image 2 [00653] embedded image 3 [00654] embedded image 4 [00655] embedded image 5 [00656] embedded image 6 [00657] embedded image 7 [00658]

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embedded image 8 [00659] embedded image 9 [00660] embedded image 10 [00661]
embedded image 11 [00662] embedded image 12 [00663] embedded image 13 [00664]
embedded image 14 [00665] embedded image 15 [00666] embedded image 16 [00667]
embedded image 17 [00668] embedded image 18 [00669] embedded image 19 [00670]
embedded image 20 [00671] embedded image 21 [00672] embedded image 22 [00673]
Eembedded image 23 [00674] embedded image 24 [00675] embedded image 25 [00676]
embedded image 26 [00677] embedded image 27 [00678] embedded image 28 [00679]
embedded image 29 [00680] embedded image 30 [00681] embedded image 31 [00682]
embedded image 32 [00683] embedded image 33 [00684] embedded image 34 [00685]
embedded image 35 [00686] embedded image 36 [00687] embedded image 37 [00688]
Embedded image 38 [00689] embedded image 39 [00690] embedded image 40 [00691]
embedded image 41 [00692] embedded image 42 [00693] embedded image 43 [00694]
embedded image 44 [00695] embedded image 45 [00696] embedded image
[0137] Preferred compounds according to the invention and their enantiomers and
pharmaceutically acceptable salts thereof are represented by Formula (III),
##STR00697##
wherein the preferred substituent combinations R.sup.C, R.sup.D, N.sup.+/R.sup.F/R.sup.G, and Z
are as defined in Table 4, and Y.sup. – is a pharmaceutically acceptable anion as defined above. The
compounds can be made according to the methods generally described below.
TABLE-US-00007 TABLE 4 Preferred Combinations of R.sup.C, R.sup.D,
N.sup.+/R.sup.F/R.sup.G, and Z Substituents according to Formula (III). Combination Number
R.sup.C R.sup.D N.sup.+/R.sup.F/R.sup.G Z 1 H H [00698] embedded image [00699]
embedded image 2 Cl H [00700] embedded image [00701] embedded image 3 CH.sub.3 H
[00702] embedded image [00703] embedded image 4 H CH.sub.3 [00704] embedded image
[00705] embedded image 5 Cl CH.sub.3 [00706] embedded image [00707] embedded image 6
CH.sub.3 CH.sub.3 [00708] embedded image [00709] embedded image 7 H CH.sub.2CH.sub.3
[00710] embedded image [00711] embedded image 8 Cl CH.sub.2CH.sub.3 [00712]
embedded image [00713] embedded image 9 CH.sub.3 CH.sub.2CH.sub.3 [00714]
embedded image [00715] embedded image 10 H (CH.sub.2).sub.2 CH.sub.3 [00716]
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[0138] Each preferred embodiment described herein can be taken in combination with one, any or
all other preferred embodiments, as though presented herein in every permutation.
[0139] Compositions of the invention 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%.
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[0140] 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. Likewise, all tautomeric forms are intended to be included. [0141] 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 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.

Synthesis

[0142] Compounds having Formula (I) can be prepared using methods analogous to the following general synthetic schemes:

##STR01442##

and

##STR01443##

For example,

##STR01444##

[0143] Compounds having Formula (II) can be prepared using methods analogous to that described in the Examples and the following synthetic schemes:

[0144] As described above, the compound or composition of the invention can be administered

Additional Biologically Active Agents and Exogenous Large Pore Channel Agonists

##STR01445##

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, TRP1A 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. [0145] 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-vanillylalkanedienyls, 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, Noleyl-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.

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[0146] Additional suitable TRPV1 agonists include but are not limited to eugenol, arvanil (N-
arachidonovlvanillamine), 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.
[0147] Suitable TRPV2-4 agonists include, but are not limited to, are 2-APB, cannabinol,
diphenylboronic anhydride, insulin-like growth factor 1, lysophosphatidylcholine,
lysophosphatidylinositol, probenecid, \Delta 9-tetrahydrocannabinol, vanillin, eugenol, cinnamaldehyde,
camphor, carvacrol, thymol, citral, farnesyl diphosphate, tetrahydrocannabivarin, incensole acetate,
diphenylboronic anhydride, 6-tert-butyl-m-cresol, dihydrocarveocarveol, borneol, (–)-menthol,
GSK1016790A, 4\alpha-PDH, 5,6-epoxyeicosatrienoic acid, 4\alpha-PDD, bisandrographolide, citric acid,
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[0148] 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 and Cooling Agent 10.

phorbol 12-myristate 13-acetate and RN1747.

- [0149] Suitable ASIC agonists include, but are not limited to, chlorophenylguanidine hydrochloride, GMQ hydrochloride, tetrahydropapaveroline (THP), reticulin, polyamine agmatine, lysophosphatidylcholine, arachidonic acid and neuropeptide SF.
- [0150] Other biologically active agents which can be employed in the methods, compositions, and kits of the invention include any that activates TRP1A receptors on nociceptors or pruriceptors and allows for entry of at least one inhibitor of voltage-gated ion channels. Suitable TRP1A agonists include but are not limited to cinnamaldehyde, allyl-isothiocynanate (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).
- [0151] 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, \Box , \Box -methylene ATP, 2-methylthio-ATP, 2' and 3'-O-(4-benzoylbenzoyl)-ATP, and ATP5'-O-(3-thiotriphosphate).
- [0152] 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.
- [0153] 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, 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. [0154] 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. [0155] 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. [0156] 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.

[0157] 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

[0158] The administration of the compounds of the invention may be by any suitable means that results in the reduction of perceived pain 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.

[0159] Thus, the composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols. 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, 4.sup.th Edition, ed. J. Swarbrick, 2013, CRC Press, New York).

[0160] 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.

[0161] 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.

[0162] The kit may be manufactured as a single use unit dose for one patient, multiple uses for a particular patient (at a constant dose or in which the individual compounds may vary in potency as therapy progresses); or the kit may contain multiple doses suitable for administration to multiple patients ("bulk packaging"). The kit components may be assembled in cartons, blister packs, bottles, tubes, and the like.

Controlled Release Formulations

[0163] Each compound of the invention, alone or in combination with one or more of the biologically active agents as described herein, can be formulated for controlled release (e.g., sustained or measured) administration, as described in U.S. Patent Application Publication Nos. 2003/0152637 and 2005/0025765, each incorporated herein by reference. For example, a compound of the invention, alone or in combination with one or more of the biologically active agents as described herein, can be incorporated into a capsule or tablet that is administered to the patient.

[0164] 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 subcutaneous or intramuscular administration.

[0165] 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.

[0166] 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.

[0167] 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.

[0168] 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.

[0169] 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.

[0170] 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.
[0171] 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. [0172] 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

[0173] 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.

[0174] 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.

[0175] 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.

[0176] Formulations for oral administration to the mouth may also be provided as a mouthwash, an oral spray, oral rinse solution, oral ointment, or oral gel.

[0177] 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.

[0178] 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.

[0179] 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.

[0180] 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

[0181] 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,

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Topical Formulations

[0182] 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). [0183] 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 arthritic fingers.

[0184] 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.

[0185] 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 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.

[0186] 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 (AzoneTM, 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.

[0187] Also illustrative are a group of biodegradable absorption enhancers which are alkyl N,N-2-(disubstituted amino) alkanoates as described in U.S. Pat. Nos. 4,980,378 and 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.

[0188] 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. Nos. 4,980,378 and 5,082,866.

[0189] 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.

[0190] 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 100TM, 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. [0191] 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 100TM 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.

Formulations for Ophthalmic Administration

[0192] 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).

[0193] 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. [0194] 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.

[0195] 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. [0196] 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.

[0197] 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

[0198] 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.

[0199] 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.

[0200] 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.

[0201] Suitably, the packaging/medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), single use inhaler (capsule or blister inhaler), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

[0202] 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.

[0203] 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

[0204] The compounds, compositions, methods, and kits of the invention can be used to treat pain, cough or itch associated with any of a number of conditions, including 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). [0205] Since a subclass of nociceptors mediate itch sensation, the compounds, compositions, methods, and kits of the invention can also be used 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.

[0206] 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.

[0207] 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).

[0208] 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.

[0209] 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"). [0210] 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 TH2 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.sub.H2 cells to transcribe these type II regulatory cytokines. [0211] 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.sub.H1 and T.sub.H2 cells) have been shown to have different roles in neuropathic pain. T.sub.H1 cells facilitate neuropathic pain behavior by releasing proinflammatory cytokines (IL-2 and interferon-y (IFNy)), whereas T.sub.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)).

[0212] 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.

[0213] 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 Pain, Cough, Itch, and Neurogenic Inflammation

[0214] 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.

[0215] 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.

[0216] 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.

[0217] 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.

[0218] 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.

[0219] 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.

[0220] 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.

[0221] 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

[0222] The following examples are intended to illustrate the invention and are not intended to limit it.

General Abbreviation Definitions

TABLE-US-00008 ACN acetonitrile AcOH acetic acid aq. aqueous Bn benzyl Boc tert-butyloxycarbonyl brine saturated sodium chloride solution in water $^{\circ}$ C. degrees Celius δ chemical shift (ppm) d deuterium DCM dichloromethane DIPEA diisopropylethylamine DMAP 4-dimethylaminopyridine DMSO dimethyl sulfoxide ESI electrospray ionization Et.sub.2O diethyl ether EtOAc ethyl acetate g gram h hour HATU 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide MeOH methanol mHz megahertz min minute ml milliliter mmol millimole MS mass spectrometry m/z mass to charge ratio NMR nuclear magnetic resonance Pet ether petroleum ether RT room temperature TEA triethylamine TLC thin layer chromatography UV ultraviolet light

1. Synthesis of N-benzyl-2-((2, 6-dimethylphenyl) amino)-N, N-diethyl-2-oxoethan-1-aminium bromide

##STR01446##

[0223] To a stirred solution of 2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide (0.15 g, 0.640 mmol, 1 eq; Comb-Blocks, Inc., San Diego, CA Catalogue no: QA-3221) in ACN (3 mL) was added benzyl bromide (0.164 g, 0.960 mmol, 1.5 eq) and the reaction mixture was stirred for 12 h at 75° C. as progress of the reaction was monitored by TLC (mobile phase 10% Methanol in DCM; visualization by UV). The reaction mixture was evaporated under reduced pressure to afford crude product, which was triturated with EtOAc (2×5 mL) to afford product N-benzyl-2-((2,6-dimethylphenyl)amino)-N,N-diethyl-2-oxoethan-1-aminium bromide (0.08 g) as a white solid. MS (ESI): m/z 325.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 10.03 (br s, 1H), 7.66-7.39 (m, 5H), 7.13 (s, 3H), 4.82 (s, 2H), 4.17 (s, 2H), 3.52 (q, J=6.7 Hz, 4H), 2.20 (s, 6H), 1.42 (br t, J=6.9 Hz, 6H).

2. Synthesis of N-benzyl-2-((2, 6-dimethylphenyl) amino)-N, N-dimethyl-2-oxoethan-1-amminium bromide

##STR01447##

Synthesis of intermediate 2-bromo-N-(2,6-dimethylphenyl)acetamide

[0224] To a suspension of 2, 6-dimethylaniline (30.5 mL, 247.56 mmol, 1.0 eq) in water (300 mL) was added bromoacetyl bromide (23.8 mL, 272.31 mmol, 1.1 eq) at 10° C. The reaction mixture was maintained at pH 9-10 with 15% Na.sub.2CO.sub.3 (aq.) solution for 1 hour as the progress of the reaction was monitored by TLC (mobile phase: 30% EtOAc in hexane, visualization by UV). The reaction mixture was extracted with EtOAc (2×600 mL) and the combined organic extracts were washed with brine (200 mL), dried over Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure. The resulting crude product was triturated with Et.sub.2O (2×200 mL) to afford 2-bromo-N-(2, 6-dimethylphenyl) acetamide (21 g) as a white solid. MS (ESI): m/z 244.02 [M+2].sup.+. .sup.1H NMR (400 MHz, CDCl.sub.3) δ 7.75 (br s, 1H), 7.20-7.02 (m, 3H), 4.07 (s, 2H), 2.24 (s, 6H).

Synthesis of intermediate 2-(dimethylamino)-N-(2, 6-dimethylphenyl) acetamide [0225] To a stirred solution of 2-bromo-N-(2,6-dimethylphenyl) acetamide (5 g, 20.7 mmol, 1.0 eq) in EtOAc (75 mL) was added a 2.0 M solution of dimethyl amine in THF (51.8 mL, 103.5 mmol, 5 eq) and the reaction mixture was stirred at 75° C. for 18 h in in steel bomb. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (2×200 mL). The combined organic extracts were dried over Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure to afford 2-(dimethylamino)-N-(2,6-dimethylphenyl) acetamide (4.1 g). .sup.1H NMR (400 MHz, CDCl.sub.3-d) δ ppm 8.63 (1H, br s), 7.02-7.15 (3H, m), 3.15 (2H, s), 2.45 (6H, s), 2.24 (6H, s).

Synthesis of N-benzyl-2-((2, 6-dimethylphenyl) amino)-N, N-dimethyl-2-oxoethan-1-aminium bromide

[0226] To a stirred solution of 2-(dimethylamino)-N-(2, 6-dimethylphenyl) acetamide (0.2 g, 0.969 mmol, 1.0 eq) in ACN (3 mL) was added benzyl bromide (0.23 mL, 1.936 mmol, 2.0 eq) and the reaction mixture was stirred at 90° C. for 16 h 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 to afford crude product, which was triturated with EtOAc (5 mL) to afford product N-benzyl-2-((2,6-dimethylphenyl)amino)-N,N-dimethyl-2-oxoethan-1-aminium bromide (0.14 g). MS (ESI): m/z 297.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.95 (1H, s), 7.49-7.66 (5H, m), 7.06-7.19 (3H, m), 4.81 (2H, s), 4.30 (2H, s), 3.26 (6H, s), 2.19 (6H, s).

3. Synthesis of 1-benzyl-1-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl) azepan-1-ium bromide ##STR01448##

Synthesis of intermediate 2-(azepan-1-yl)-N-(2, 6-dimethylphenyl) acetamide [0227] Synthesis of intermediate 2-bromo-N-(2,6-dimethylphenyl) acetamide was as described above for Compound 2. To a stirred solution of 2-bromo-N-(2, 6-dimethylphenyl)acetamide (0.5 g, 1.9 mmol, 1.0 eq) in ACN (5.0 mL) was added K.sub.2CO.sub.3 (0.639 g, 4.6 mmol, 2.5 eq) and azepane (0.4 mL, 4.0 mmol, 2.0 eq), and the mixture was stirred for 20 h at 90° C. as progress of the reaction was monitored by TLC (mobile phase: 5% MeOH in DCM, visualization by UV). The crude reaction was concentrated under reduced pressure and the resulting residue was partitioned between water and EtOAc (2×50 mL). The combined organic extracts were washed with brine solution, dried over Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure to afford crude product, which was triturated with EtOAc (20 mL) to afford 2-(azepan-1-yl)-N-(2, 6-dimethylphenyl) acetamide (0.47 g). MS (ESI): m/z 261.57 [M+H].sup.+. .sup.1H NMR (400 MHz, CHLOROFORM-d) δ 8.83 (br s, 1H), 7.09 (s, 3H), 3.32 (s, 2H), 2.93-2.73 (m, 4H), 2.24 (s, 6H), 1.87-1.52 (m, 9H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) azepan-1-ium bromide [0228] To a stirred solution of 2-(azepan-1-yl)-N-(2, 6-dimethylphenyl) acetamide (0.2 g, 0.8 mmol, 1.0 eq) in ACN (1.0 mL) was added benzyl bromide (0.1 mL, 0.6 mmol, 2.0 eq), and the reaction was heated to reflux for 16 has progress of the reaction was monitored by TLC (mobile phase: 10% MeOH in DCM, visualization by UV). The crude reaction mixture was concentrated under reduced pressure and the product was triturated with EtOAc (15 mL) to afford product 1-benzyl-1-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl) azepan-1-ium bromide (0.12 g). MS (ESI): m/z 351.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 10.04 (s, 1H), 7.71-7.62 (m, 2H), 7.60-7.48 (m, 3H), 7.20-7.03 (m, 3H), 4.93 (s, 2H), 4.15 (s, 2H), 3.86-3.70 (m, 2H), 3.66-3.42 (m, 2H), 2.23 (s, 6H), 1.98 (br d, J=4.8 Hz, 4H), 1.67 (br s, 4H).

4. Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidin-1-ium bromide ##STR01449##

Synthesis of intermediate N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) acetamide [0229] Synthesis of intermediate 2-bromo-N-(2,6-dimethylphenyl) acetamide was as described above for Compound 2. To a stirred solution of 2-bromo-N-(2,6-dimethylphenyl) acetamide (1.2 g, 5.0 mmol, 1.0 eq) in EtOAc (40 mL) was added piperidine (0.851 g, 10.0 mmol, 2.0 eq), and the reaction mixture was stirred for 16 h at 75° C. as the progress of the reaction was monitored by TLC (mobile phase: 50% EtOAc in petrolium ether, visualization by UV). The reaction mixture was diluted with EtOAc (20 mL) and washed with water (2×50 ml). The organic extracts were combined, dried over Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure to afford crude product, which was triturated with n-pentane (25 mL) and dried under vacuo to afford product N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) acetamide (1.05 g). MS (ESI): m/z 247.36 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3-d) δ ppm 8.81 (1H, br s), 7.04-7.11 (3H, m), 3.14 (2H, s), 2.62 (4H, br s), 2.24 (6H, s), 1.65 (4H, quin, J=5.61 Hz), 1.44-1.54 (2H, m).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidin-1-ium bromide [0230] To a stirred solution of N-(2,6-dimethylphenyl)-2-(piperidin-1-yl) acetamide (0.15 g, 0.6 mmol, 1.0 eq) in ACN (3 mL) was added benzyl bromide (0.205 g, 1.2 mmol, 2.0 eq), and the reaction mixture was stirred for 16 h at 80° C. 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 allowed to cool to room temperature and concentrated under reduced pressure to afford crude product, which was triturated with EtOAc (15 mL) and dried under vacuo to afford product 1-benzyl-1-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)piperidin-1-ium bromide (0.15 g). MS (ESI): m/z 337.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.07 (1H, s), 7.49-7.66 (5H, m), 7.07-7.21 (3H, m), 4.96 (2H, s), 4.21 (2H, s), 3.65 (2H, br d, J=12.50 Hz), 3.50 (2H, dt, J=12.93, 6.69 Hz), 2.21 (6H, s), 1.91-2.05 (4H, m), 1.64-1.76 (1H, m), 1.55 (1H, dt, J=13.76, 7.04 Hz).

5. Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) pyrrolidin-1-ium bromide ##STR01450##

Synthesis of intermediate N-(2, 6-dimethylphenyl)-2-(pyrrolidin-1-yl) acetamide [0231] Synthesis of intermediate 2-bromo-N-(2,6-dimethylphenyl) acetamide was as described above for Compound 2. To a stirred solution of 2-bromo-N-(2,6-dimethylphenyl)acetamide (1.2 g, 5.0 mmol, 1.0) in EtOAc (40 mL) was added pyrrolidine (0.533 g, 7.5 mmol, 1.5 eq), and the reaction mixture was stirred for 3 h at 75° C. as the progress of the reaction was monitored by TLC (mobile phase: 50% EtOAc in petrolium ether, visualization by UV). The reaction mixture was diluted with EtOAc (25 mL), washed with water (50 mL), dried over NaSO4, filtered and concentrated under reduced pressure to afford N-(2, 6-dimethylphenyl)-2-(pyrrolidin-1-yl) acetamide (1.0 g). MS (ESI): m/z 233.44 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3-d) δ ppm 8.63 (1H, br s), 7.00-7.15 (3H, m), 3.35 (2H, s), 2.69-2.84 (4H, m), 2.24 (6H, s), 1.80-1.93 (4H, m). Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) pyrrolidin-1-ium bromide [0232] To a stirred solution of N-(2, 6-dimethylphenyl)-2-(pyrrolidin-1-yl) acetamide (0.15 g, 0.6 mmol, 1.0 eq) in ACN (5 mL) added benzyl bromide (0.205 g, 1.2 mmol, 2.0 eq), and the reaction mixture was stirred for 16 h at 80° C. in a sealed tube as progress of the reaction was monitored by TLC (mobile phase: 10% MeOH in DCM, visualization by UV). The reaction cooled to room temperature and was concentrated under reduced pressure to afford crude product, which was triturated with EtOAc (15 mL) and dried under vacuo to afford 1-benzyl-1-(2-((2, 6dimethylphenyl)amino)-2-oxoethyl) pyrrolidin-1-ium bromide (0.14 g). MS (ESI): m/z 323.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 2.11-2.29 (10H, m), 3.60-3.74 (2H, m), 3.76-3.88 (2H, m), 4.20 (2H, s), 4.83 (2H, s), 7.08-7.18 (3H, m), 7.50-7.66 (5H, m), 9.97 (1H,

6. Synthesis of 1-benzyl-1-(1-((2,6-dimethylphenyl)amino)-1-oxobutan-2-yl)piperidin-1-ium bromide

##STR01451##

Synthesis of intermediate 2-bromobutanoyl chloride

[0233] Thionyl chloride (150 mL) was added to 2-bromobutanoic acid (25 g, 149.7 mmol, 1.0 eq) at 0° C. and the resulting solution was subsequently stirred at 80° C. for 2 h. The reaction mixture was cooled to RT and concentrated under reduced pressure to afford crude 2-bromobutanoyl chloride (27.7 g, 99.5%) as a brown residue which was taken to next step immediately without further purification. .sup.1H NMR (400 MHz, CDCl.sub.3) δ 4.52-4.44 (m, 1H), 2.29-2.16 (m, 1H), 2.15-2.02 (m, 1H), 1.10 (t, J=7.3 Hz, 3H).

Synthesis of intermediate 2-bromo-N-(2, 6-dimethylphenyl) butanamide

[0234] A solution of 2, 6-dimethylaniline (15 g, 121.18 mmol, 1.0 eq) and pyridine (15 mL, 189.6 mmol, 1.5 eq) in DCM (400 mL) was cooled in an ice bath to 0° C. To this mixture was slowly added a solution of 2-bromobutanoyl chloride (27.5 g, 148.6 mmol, 1.2 eq) in DCM (50 mL) and the resulting mixture was allowed to warm to room temperature while stirring for 2 h. The reaction

solution was adjusted to pH $^{\sim}5$ to 6 with 2 N HCl and extracted with DCM (2×200 mL). The combined organic extracts were washed with water (250 mL) and brine (200 mL), dried over Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure. The resulting crude product was triturated with n-pentane (150 mL) to afford 2-bromo-N-(2,6-dimethylphenyl)butanamide (30 g). MS (ESI): m/z 272.13 [M+2].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 9.69 (s, 1H), 7.15-7.02 (m, 3H), 4.51 (t, J=7.3 Hz, 1H), 2.22-2.04 (m, 7H), 2.03-1.91 (m, 1H), 0.98 (t, J=7.3 Hz, 3H).

Synthesis of intermediate N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) butanamide [0235] To a stirred solution of 2-bromo-N-(2,6-dimethylphenyl)butanamide (50 g, 259.1 mmol, 1.0 eq) in toluene (1 L) was added piperidine (54 mL, 544.1 mmol, 2.1 eq) at RT. The reaction mixture was stirred at 110° C. for 16 h as progress of the reaction was monitored by TLC (mobile phase: 30% EtOAc in hexane, visualization by UV). The reaction mixture was concentrated under reduced pressure to afford crude product, which was triturated with n-pentane (500 mL) to afford N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) butanamide (55 g) MS (ESI): m/z 275.27 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.16 (s, 1H), 7.06 (s, 3H), 3.06 (dd, J=5.7, 8.6 Hz, 1H), 2.60 (br t, J=4.8 Hz, 4H), 2.16 (s, 6H), 1.79-1.59 (m, 2H), 1.51 (br s, 4H), 1.44-1.35 (m, 2H), 0.93 (t, J=7.5 Hz, 3H). Synthesis of 1-benzyl-1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl) piperidin-1-ium bromide

[0236] To a stirred solution of N-(2,6-dimethylphenyl)-2-(piperidin-1-yl) butanamide (1.5 g, 5.5 mmol, 1.0 eq) in ACN (25.0 mL) was added benzyl bromide (1.872 g, 10.9 mmol, 2.0 eq) and the 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 by UV). The reaction mixture was concentrated under reduced pressure and the crude product was triturated with EtOAc (3×10 mL) to afford 1-benzyl-1-(1-((2,6-dimethylphenyl)amino)-1-oxobutan-2-yl)piperidin-1-ium bromide (1.2 g) MS (ESI): m/z 365.4 [M]. +. 1H NMR (400 MHz, DMSO-d6) δ 10.36 (s, 1H), 7.57-7.54 (m, 5H), 7.17-7.11 (m, 3H), 5.41 (d, 1H), 4.62 (d, 1H), 4.39 (bs, 1H), 3.72 (bs, 2H), 3.22 (bs, 2H), 2.43-2.39 (m, 1H), 2.15-2.07 (m, 9H), 1.96-1.95 (m, 2H), 1.61-1.45 (m, 2H), 1.18 (t, 3H).

7. Synthesis of Compounds 7A-27A: Table 5

[0237] Table 5 provides additional representative examples of the invention which were prepared from intermediate N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) butanamide and the appropriate alkyl halide according to the described methods for the synthesis of compound 6.

TABLE-US-00009 TABLE 5 Compound # Structure MS (ESI): m/z 1H NMR (400 MHz, DMSO-D6) δ 7A [01452] embedded image 383.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.17 (3 H, br t, J = 6.80 Hz, 1.35-1.69 (2H, m), 1.81-2.03 (3 H, m) 2.05-2.27 (8 H, m), 2.31-2.47 (1 H, m), 3.10-3.25 (2 H, m), 3.57-3.89 (2 H, m), 4.33-4.55 (1H, m), 4.63 (1 H, br d, J = 13.59 Hz), 5.40 (1 H, br d, J = 13.59 Hz), 7.04-7.22 (3 H, m), 7.38 (2 H, br t, J = 8.66 Hz), 7.61 (2 H, dd, J = 8.33, 5.48 Hz), 10.36 (1 H, br s) 8A [01453] embedded image 383.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.18 (3 H, br t, J = 7.02 Hz), 1.47 (1 H, br s), 1.59 (1 H, br s), 1.80-2.04 (3 H, m), 2.08-2.16 (1 H, m), 2.21 (8 H, s), 3.23 (2 H, br d, J = 16.66 Hz), 3.64-3.85 (2 H, m), 4.36-4.72(2 H, m), 5.42 (1 H, br d, J = 13.15 Hz), 7.06-7.23 (3 H, m), 7.33-7.51 (3 H, m), 7.51-7.65 (1 H, m)m), 10.39 (1 H, s) 9A [01454] embedded image 383.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.11-1.30 (3 H, m), 1.42 (1 H, br d, J = 1.75), 1.62 (1 H, br d, J = 11.40 Hz), 1.77-2.06 (3 H, m), 2.10-2.43 (9 H, m), 3.03-3.24 (2 H, m), 3.61-3.90 (2 H, m), 4.54-4.80 (2 H, m), 5.63 (1 H, br d, J = 12.93 Hz), 7.03-7.25 (3 H, m), 7.32-7.50 (2 H, m), 7.58-7.72 (2 H, m), 10.43 (1 H, s) 10A [01455] embedded image 399.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.11-1.23 (3 H, m), 1.42-1.67 (2 H, m), 1.80-2.03 (3 H, m), 2.10-2.29 (8 H, m), 2.31-2.46 (1 H, m), 3.21 (2 H, br s), 3.57-3.88 (2 H, m), 4.27-4.52 (1 H, m), 4.63 (1 H, br d, J = 13.59 Hz), 5.40 (1 H, br d, J = 13.59Hz), 7.04-7.22 (3 H, m), 7.50-7.67 (4 H, m), 10.35 (1 H, s) 11A [01456] embedded image 399.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.18 (3 H, br t, J = 6.91 Hz), 1.38-1.65 (2 H, m), 1.79-2.01 (2 H, m), 2.03-2.28 (8 H, m), 2.40 (1 H, br dd, J = 12.93, 7.02 Hz), 3.05-3.26 (2 H, m),

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3.76 (2 H, br d, J = 6.14 Hz), 4.31 - 4.57 (1 H, m), 4.63 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 5.41 (1 H, br d, J = 13.37 Hz), 
= 13.37 Hz), 7.06-7.23 (3 H, m), 7.44-7.61 (2 H, m), 7.62-7.71 (2 H, m), 10.36 (1 H, s) 12A
[01457] embedded image 399.1 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.24 (3 H, br t, J =
6.91 \text{ Hz}), 1.29-1.41 (1 H, m), 1.65 (1 H, br d, J = 12.50 \text{ Hz}), 1.81 (2 H, br s), 1.92-2.10 (1 H, m),
2.11-2.29 (7 H, m), 2.31-2.46 (2 H, m), 3.03 (1 H, br t, J = 12.28 Hz), 3.14-3.26 (1 H, m), 3.77 (1
H, br d, J = 13.15 \text{ Hz}), 3.98 (1 H, br d, J = 12.93 \text{ Hz}), 4.65 (1 H, br d, J = 13.37 \text{ Hz}), 4.84 (1 H, br
d, J = 9.65 \text{ Hz}), 5.82 (1 H, br d, J = 13.15 \text{ Hz}), 7.16 (3 H, s), 7.46- 7.55 (1 H, m), 7.59 (1 H, br t, J = 13.15 \text{ Hz}), 7.16 (3 H, s), 7.46- 7.55 (1 H, m), 7.59 (1 H, br t, J = 13.15 \text{ Hz})
= 7.23 Hz), 7.62-7.71 (1 H, m), 7.76 (1 H, br d, J = 7.23 Hz), 10.41 (1 H, br s) 13A [01458]
Rembedded image 390.3 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.17 (3 H, br t, J = 6.58
Hz), 1.39-1.68 (2 H, m), 1.79-2.04 (3 H, m), 2.08-2.28 (8 H, m), 2.35-2.46 (1 H, m), 3.09-3.26 (2
H, m), 3.64-3.88 (2 H, m), 4.30-4.60 (1 H, m), 4.72 (1 H, br d, J = 13.37 Hz), 5.49 (1 H, br d, J =
13.37 Hz), 7.04-7.25 (3 H, m), 7.76 (2 H, d, J = 8.11 Hz), 8.03 (2 H, d, J = 8.11 Hz), 10.35 (1 H, s)
14A [01459] embedded image 390.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.20 (3 H, br
t, J = 6.80 Hz), 1.36-1.52 (1 H, m), 1.59 (1 H, br s), 1.77-2.03 (3 H, m), 2.07-2.17 (1 H, m), 2.22 (6
H, s), 2.28- 2.45 (2 H, m), 3.04-3.26 (2 H, m), 3.77 (2 H, br s), 4.39-4.76 (2 H, m), 5.46 (1 H, br d,
J = 13.15 \text{ Hz}), 7.06- 7.25 (3 H, m), 7.67-7.81 (1 H, m), 7.90 (1 H, br d, J = 7.89 \text{ Hz}), 7.99-8.13 (2
H, m), 10.39 (1 H, br s) 15A [01460] embedded image 390.2 [M]+ 1H NMR (400 MHz, DMSO-
d6) \delta ppm 1.18-1.48 (4 H, m), 1.65 (1 H, br d, J = 11.40 Hz), 1.82 (2 H, br d, J = 14.03 Hz), 1.94-
2.11 (1 H, m), 2.25 (7 H, s), 2.33-2.47 (2 H, m), 3.07-3.24 (2 H, m), 3.76 (1 H, br d, J = 11.18 Hz),
3.97 (1 \text{ H, br d, J} = 11.40 \text{ Hz}), 4.76 (1 \text{ H, br d, J} = 13.81 \text{ Hz}), 4.88 (1 \text{ H, br d, J} = 5.26 \text{ Hz}), 5.75 (1 \text{ Hz})
H, br d, J = 13.59 Hz), 7.16 (3 H, br s), 7.78 (1 H, br d, J = 5.26 Hz), 7.88 (s, H, br s), 8.05 (1 H, br
d, J = 7.45 Hz), 10.45 (1 H, br s) 16A [01461] embedded image 379.2 [M]+ 1H NMR (400 MHz,
DMSO-d6) \delta ppm 1.17 (3 H, br t, J = 6.80 Hz), 1.32-1.66 (2 H, m), 1.82-2.03 (3 H, m), 2.06-2.27
(8 H, m), 2.38 (4 H, s), 3.05-3.27 (2 H, m), 3.57-3.89 (2 H, m), 4.25-4.47 (1 H, m), 4.57 (1 H, br d,
J = 13.37 \text{ Hz}), 5.37 (1 H, br d, J = 13.37 \text{ Hz}), 7.00- 7.24 (3 H, m), 7.28-7.51 (4 H, m), 10.38 (1 H,
s) 17A [01462] embedded image 379.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.18 (3 H,
br t, J = 6.80 Hz), 1.43 (1 H, br d, J = 1.32 Hz), 1.58 (1 H, br s), 1.83-2.03 (3 H, m), 2.05-2.29 (8 H,
m), 2.33-2.43 (4 H, m), 3.05-3.27 (2 H, m), 3.74 (2 H, br d, J = 7.02 Hz), 4.31-4.62 (2 H, m), 5.38
(1 \text{ H, br d, } J = 12.93 \text{ Hz}), 7.06-7.20 (3 \text{ H, m}), 7.28-7.49 (4 \text{ H, m}), 10.38 (1 \text{ H, s}) 18A [01463]
Rembedded image 379.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.25 (4 H, br t, J = 7.23
Hz), 1.66 (1 H, br d, J = 12.28 Hz), 1.79 (2 H, br t, J = 12.72 Hz), 1.93-2.10 (1 H, m), 2.11-2.30 (7
H, m), 2.30-2.48 (5 H, m), 2.85 (1 H, br t, J = 12.50 Hz), 3.12-3.28 (1 H, m), 3.49-3.65 (1 H, m),
3.97 (1 \text{ H, br d, } J = 12.72 \text{ Hz}), 4.52 (1 \text{ H, br d, } J = 13.37 \text{ Hz}), 4.83 (1 \text{ H, br d, } J = 10.08 \text{ Hz}), 5.74 (1 \text{ Hz})
H, br d, J = 13.37 Hz), 7.09-7.27 (3 H, m), 7.27-7.40 (2 H, m), 7.40-7.47 (1 H, m), 7.52 (1 H, br d,
J = 7.45 \text{ Hz}), 10.43 (1 H, s) 19A [01464] embedded image 393.3 [M]+ 1H NMR (400 MHz,
DMSO-d6) δ ppm 1.08-1.31 (6 H, s), 1.36-1.67 (2 H, m), 1.81-2.06 (3 H, m), 2.06-2.32 (8 H, m),
2.33-2.44 (1 H, m), 2.68 (2 H, br d, J = 7.23 Hz), 2.99-3.26 (2 H, m), 3.58-3.88 (2 H, m), 4.29-4.69
(2 \text{ H, m}), 5.37 (1 \text{ H, br d}, J = 12.93 \text{ Hz}), 7.14 (3 \text{ H, br s}), 7.29- 7.54 (4 \text{ H, m}), 10.39 (1 \text{ H, br s}) 20A
[01465] embedded image 393.3 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.08-1.29 (6 H, m),
1.35-1.52 (1 H, m), 1.59 (1 H, br d, J = 3.73 Hz), 1.82-2.04 (3 H, m), 2.07-2.27 (8 H, m), 2.40 (1 H,
br dd, J = 12.93, 7.67 Hz), 2.68 (2 H, q, J = 7.45 Hz), 3.08- 3.27 (2 H, m), 3.61-3.86 (2 H, m), 4.30-
4.52 (1 \text{ H, m}), 4.58 (1 \text{ H, br d}, J = 13.37 \text{ Hz}), 5.39 (1 \text{ H, br d}, J = 13.15 \text{ Hz}), 7.03-7.24 (3 \text{ H, m}),
7.27-7.51 (4 H, m), 10.36 (1 H, s) 21A [01466] embedded image 393.2 [M]+ 1H NMR (400
MHz, DMSO-d6) \delta ppm 1.14 (3 H, t, J = 7.45 Hz), 1.26 (4 H, br t, J = 7.34 Hz), 1.66 (1 H, br d, J =
12.50 Hz), 1.78 (2 H, br t, J = 15.13 Hz), 1.95-2.12 (1 H, m), 2.13-2.29 (7 H, m), 2.30-2.48 (2 H,
m), 2.60- 2.90 (3 H, m), 3.16-3.27 (1 H, m), 3.53 (1 H, br d, J = 13.15 Hz), 3.98 (1 H, br d, J =
12.72 Hz), 4.50 (1 H, br d, J = 13.37 Hz), 4.87 (1 H, br d, J = 10.52 Hz), 5.81 (1 H, br d, J = 13.37
Hz), 7.10-7.25 (3 H, m), 7.28-7.39 (1H, m), 7.40-7.58 (2 H, m), 10.45 (1 H, br s) 22A [01467]
Dembedded image 395.4 [M]+ 1H NMR (500 MHz, DMSO-d6) δ ppm 1.15 (3 H, br s), 1.36-1.66
(2 H, m), 1.85-2.26 (11 H, m), 2.31-2.45 (1 H, m), 3.08-3.25 (2 H, m), 3.82 (3 H, s), 4.56 (1 H, br
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d, J = 13.43 Hz), 5.33 (1 H, d, J = 13.73 Hz), 7.02- 7.20 (5 H, d), 7.45 (2 H, d, J = 8.85 Hz),
10.33 (1 H, s) 23A [01468] embedded image 395.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm
1.18 (3 \text{ H, br s}), 1.35-1.69 (2 \text{ H, m}), 1.77-2.29 (11 \text{ H, m}), 2.41 (1 \text{ H, br dd}, J = 11.84, 7.45 \text{ Hz}),
3.06-3.28 (2 H, m), 3.62-3.91 (5 H, m), 4.32-4.66 (2 H, m), 5.37 (1 H, br d, J = 13.15 Hz), 7.03-
7.22 (6 H, m), 7.46 (1 H, br t, J = 7.89 Hz), 10.40 (1 H, s) 24A [01469] embedded image 395.2
[M]+ 1H NMR (400 MHz, DMSO-d6) \delta ppm 1.18 (3 H, br t, J = 7.02 Hz), 1.36 (1 H, br d, J = 3.95
Hz), 1.62 (1 H, br d, J = 13.15 Hz), 1.75-2.01 (3 H, m), 2.04-2.43 (9 H, m), 2.94-3.23 (2 H, m),
3.61-3.91 (5 H, m), 4.47 (1 H, br d, J = 13.15 Hz), 4.54-4.69 (1 H, m), 5.51 (1 H, br d, J = 12.06
Hz), 7.00-7.27 (5 H, m), 7.42-7.61 (2 H, m), 10.34 (1 H, s) 25A [01470] embedded image 386.4
[M]+ 1H NMR (500 MHz, DMSO-d6) \delta ppm 1.12 (4 H, br t, J = 7.17 Hz), 1.38-1.71 (3H, m),
1.82-2.33 (16 H, m), 2.73 (4 H, br s), 2.91-3.08 (1 H, m), 3.74-4.33 (3 H, m), 4.60-5.04 (2 H, m),
5.44-5.71 (1 H, m), 6.40-6.65 (1 H, m), 6.69-6.91 (1 H, m), 6.97-7.22 (3 H, m), 7.92 (1 H, br s),
10.38-10.68 (1 H, m) 26A [01471] embedded image 371.2 [M]+ 1H NMR (400 MHz, DMSO-d6)
\delta ppm 1.15 (3 H, br t, J = 7.23 Hz), 1.56 (2 H, br s), 1.96 (2 H, br s), 2.02-2.27 (9 H, m), 2.29-2.46
(1 \text{ H, m}), 3.30 (2 \text{ H, s}), 3.59 (1 \text{ H, br s}), 3.84 (1 \text{ H, br s}), 4.31 (1 \text{ H, br d}), 4.65 (1 \text{ H, br d})
d, J = 13.81 Hz), 5.34 (1 H, d), J = 13.81 Hz), 7.05-7.20 (3 H, d), 7.22-7.33 (1 H, d), 7.76 (1 H, d)
br dd, J = 4.82, 2.85 Hz), 7.93 (1 H, d, J = 1.75 Hz), 10.39 (1 H, s) 27A [01472] embedded image
370.2 [M]+ 1H NMR (400 MHz, DMSO-d6) δ ppm 1.00-1.27 (3 H, m), 1.42-1.74 (2 H, m), 1.81-
2.28 (12 H, m), 2.28- 2.42 (2 H, m), 3.38-3.67 (3 H, m), 3.84-4.10 (1 H, m), 4.22 (1 H, br dd, J =
5.70, 2.85 Hz), 4.78 (1 H, br d, J = 13.81 Hz), 5.41 (1 H, br d, J = 14.03 Hz), 6.60 (1 H, br s), 7.13
(3 H, br s), 10.39 (1 H, br s).
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28. Synthesis of 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-(2-hydroxybenzyl) piperidin-1-ium 2, 2, 2-trifluoroacetate ##STR01473##

[0238] To a stirred solution of 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-(2-methoxybenzyl) piperidin-1-ium bromide (compound 24, 0.1 g, 0.21 mmol, 1.0 eq) in DMC (2 mL) was added boron tribromide (1M in DCM) (4 mL, 4.0 mmol, 20 eq) at 0° C., and the reaction mixture was stirred for 16 h at room temperature as progress of the reaction was monitored by TLC (mobile phase: 10% MeOH in DCM, visualization by UV). The reaction mixture was concentrated under reduced pressure to afford crude product which was purified by preparative HPLC (mobile phase A: 0.1% TFA (aq.); mobile phase B: ACN; column: Synergy Polar 250×21 mm, 4.7 u (Phenomenex Inc.); flow: 18 mL/min, method: 0/15, 2/15, 10/50, 15/80, 15.2/98, 18/98, 18.2/15, 22/15; temperature: ambient) Pure fractions were lyophilized to afford product 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-(2-hydroxybenzyl) piperidin-1-ium 2, 2, 2-trifluoroacetate (0.056 g). MS (ESI): m/z 381.4[M]+. 1H NMR (500 MHz, DMSO-d6) δ ppm 1.17 (3H, br t, J=7.02 Hz), 1.32-1.47 (1H, m), 1.55-1.67 (1H, m), 1.76-2.01 (3H, m), 2.05-2.19 (2H, m), 2.25-2.3 (6H, m), 2.30-2.41 (1H, m), 2.99-3.26 (1H, m), 3.64-3.85 (2H, m), 4.35-4.61 (2H, m), 5.41-5.50 (1H, m), 6.88-6.95 (1H, m), 6.99 (1H, d, J=8.24 Hz), 7.10-7.19 (3H, m), 7.31-7.45 (2H, m), 10.34 (2H, br d, J=10.07 Hz).

29. Synthesis of 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-(3-hydroxybenzyl) piperidin-1-ium carbonate ##STR01474##

[0239] To a stirred solution of 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-(3-methoxybenzyl) piperidin-1-ium bromide (compound 23, 0.06 g, 0.1 mmol, 1 eq) in DCM (2 mL) was added boron tribromide (1 M in DCM) (2 mL) at 0° C., and the reaction mixture was stirred for 16 h at room temperature as progress was monitored by TLC (mobile phase: 10% MeOH in DCM, visualization by UV). The reaction mixture was concentrated under reduced pressure to afford crude product, which was purified by reverse phase preparative-HPLC (mobile phase (A): 10 mM ammonium bicarbonate (aq.); mobile phase (B): 100% CAN; column: X-select C18 (19*250) 5 u, method: 0/35, 2/40, 20/40; flow: 18 ml/min. The combined pure fractions were

lyophilized to afford product 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-(3-hydroxybenzyl) piperidin-1-ium carbonate (0.02 g). MS (ESI): m/z 381.38 [M].sup.+. .sup.1H NMR (500 MHz, DMSO-d6) δ ppm 1.11 (3H, br s), 1.31-1.62 (2H, m), 1.76-2.25 (12H, m), 2.93-3.13 (1H, m), 3.43-3.54 (3H, m), 3.60-3.76 (1H, m), 3.92-4.17 (2H, m), 4.21-4.39 (1H, m), 5.29-5.63 (1H, m), 6.67-6.85 (4H, m), 6.91 (2H, br s), 7.19 (1H, br t, J=7.78 Hz). 30. Synthesis of 1-benzyl-1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl) azepan-1-ium

##STR01475##

bromide

Synthesis of intermediate 2-(azepan-1-yl)-N-(2, 6-dimethylphenyl) butanamide [0240] Synthesis of intermediate 2-bromo-N-(2, 6-dimethylphenyl) butanamide was as described above for Compound 6. To a stirred solution of 2-bromo-N-(2, 6-dimethylphenyl) butanamide (0.5 g, 1.9 mmol, 1.0 eq) in ACN (10 mL) was added K.sub.2CO.sub.3 (0.393 g, 2.85 mmol, 1.5 eq) and azepane (0.376 g, 3.8 mmol, 2.0 eq), and the reaction mixture was stirred for 16 h at 75° C. as progress of the reaction was monitored by TLC (mobile phase: 10% MeOH in DCM, visualization by UV). The crude reaction mixture was quenched with water (10 mL) and extracted EtOAc (2×15 mL). The combined organic extracts were dried over Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure to afford intermediate 2-(azepan-1-yl)-N-(2, 6-dimethylphenyl) butanamide (0.20 g). MS (ESI): m/z 289.33 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3-d) δ ppm 1.00-1.16 (3H, m), 1.57-1.86 (12H, m), 1.95-2.13 (2H, m), 2.18-2.29 (8H, m), 2.72-2.97 (4H, m), 3.24 (1H, br t, J=6.72 Hz), 3.46-3.55 (2H, m), 7.03-7.15 (4H, m), 8.75 (1H, br s). Synthesis of 1-benzyl-1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl) azepan-1-ium bromide [0241] To a stirred solution of 2-(azepan-1-yl)-N-(2, 6-dimethylphenyl) butanamide (0.2 g, 0.7 mmol, 1.0 eq) in ACN (5 mL) was added benzyl bromide (0.459 g, 2.85 mmol, 1.5 eq) and the reaction was stirred for 16 h at 75° C. as progress 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 to afford crude product, which was triturated with EtOAc (20 mL) and dried under vacuo to afford 1-benzyl-1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2yl) azepan-1-ium bromide (0.118 g). MS (ESI): m/z 379.52 [M]+. 1H NMR (500 MHz, DMSO-d6) δ ppm 1.16 (3H, t, J=7.32 Hz), 1.26-1.51 (4H, m), 1.60 (2H, br s), 1.77-1.94 (2H, m), 2.10-2.31 (7H, m), 2.34-2.48 (1H, m), 3.56-3.81 (4H, m), 4.26 (1H, br d, J=10.68 Hz), 4.66 (1H, d, J=13.12 Hz), 5.21 (1H, d, J=13.12 Hz), 7.06-7.22 (3H, m), 7.45-7.61 (3H, m), 7.61-7.69 (2H, m), 10.42 (1H, s).

31. Synthesis of 1-benzyl-1-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)azocan-1-ium bromide ##STR01476##

Synthesis of intermediate 2-(azocan-1-yl)-N-(2, 6-dimethylphenyl) acetamide [0242] To a stirred solution of 2-bromo-N-(2, 6-dimethylphenyl) acetamide (500 mg, 2.065 mmol) in ACN (5.0 mL) was added K.sub.2CO.sub.3 (713 mg, 5.159 mmol) followed by azocane (467 mg, 4.125 mmol) and the resulting reaction mixture was stirred for 16 h at 80° C. as progress of the reaction was monitored by TLC (5% MeOH in DCM, visualization by UV). The crude reaction mixture was poured into ice-cold water (40 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine solution (50 mL), dried over anhydrous Na.sub.2SO.sub.4, and subsequently concentrated under reduced pressure to afford 2-(azocan-1-yl)-N-(2,6-dimethylphenyl) acetamide (480 mg) as an off white solid. Mass (ESI): m/z 275.1 [M+H]+. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.74 (br s, 1H), 7.02-7.16 (m, 3H), 3.34 (s, 2H), 2.74-2.88 (m, 4H), 2.25 (s, 6H), 1.53-1.80 (m, 10H). Synthesis of 1-benzyl-1-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)azocan-1-ium bromide

[0243] To a stirred solution of 2-(azocan-1-yl)-N-(2, 6-dimethylphenyl) acetamide (200 mg, 0.728 mmol) in ACN (2.0 mL) was added benzyl bromide (240 mg, 1.403 mmol) and the resulting reaction mixture was stirred for 16 h at 90° C. as progress of the reaction was monitored by TLC (5% MeOH in DCM, visualization by UV). The reaction mixture was concentrated under reduced

pressure to afford crude product which was triturated with a 1:1 mixture of EtOAc: Et2O (3×50 mL) to afford 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) azocan-1-ium bromide as a pale brown solid. Mass (ESI): m/z 365.54 [M]+. 1H NMR (400 MHz, DMSO-d6) δ ppm 10.02 (s, 1H), 7.46-7.70 (m, 5H), 7.05-7.22 (m, 3H), 4.89 (s, 2H), 4.07 (s, 2H), 3.64-3.76 (m, 2H), 3.48-3.62 (m, 2H), 2.23 (s, 6H), 1.94-2.14 (m, 4H), 1.50-1.83 (m, 6H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3, 3-difluoropiperidin-1-ium bromide

##STR01477##

Synthesis of 2-(3, 3-difluoropiperidin-1-yl)-N-(2, 6-dimethylphenyl) acetamide [0244] To a stirred solution of 3, 3-difluoropiperidine hydrochloride salt (0.371 g, 0.309 mmol) in ACN (25 mL) at 0° C. was added TEA (0.626 g, 6.195 mmol) at 0° C. After stirring for 10 minutes at 0° C., 2-bromo-N-(2, 6-dimethylphenyl) acetamide (0.5 g, 2.065 mmol) was added at 0° C. The resulting reaction mixture was stirred for 16 h at room temperature as progress of the reaction was monitored by TLC (30% EtOAc in Pet Ether, visualization by UV). The reaction mixture was diluted with water (10 mL) and extracted with ETOAc (2×25 mL).

[0245] The combined organic layers were concentrated under reduced pressure to afford crude product which was purified by normal phase flash chromatography (5% MeOH in DCM) to afford 2-(3, 3-difluoropiperidin-1-yl)-N-(2, 6-dimethylphenyl) acetamide (0.4 g) as a white solid. MS (ESI): m/z 283.24 [M+H].sup.+. .sup.1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.58 (s, 1H), 7.07-7.13 (m, 3H), 3.27 (s, 2H), 2.86 (t, 2H), 2.50 (d, 2H), 2.23 (s, 6H), 1.86-2.04 (m, 4H). Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3, 3-difluoropiperidin-1-ium bromide

[0246] To a solution of 2-(3, 3-difluoropiperidin-1-yl)-N-(2, 6-dimethylphenyl) acetamide (0.2 g, 0.708 mmol) in ACN (10 mL) was added benzyl bromide (0.145 g, 0.850 mmol) at room temperature in a sealed tube. The resulting reaction mixture was heated to 75° C. for 16 h as progress of the reaction was monitored by TLC (5% MeOH in DCM, visualization by UV). The reaction mixture was diluted with water (25 mL) and extracted with 10% methanol in DCM (2×100 mL). The combined organic layers were concentrated under reduced pressure to afford crude product which was triturated with ethyl acetate (10 mL) to afford 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3, 3-difluoropiperidin-1-ium bromide (0.060 g) as an off white solid. MS (ESI): m/z 373.1 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.10 (s, 1H), 7.56-7.62 (m, 5H), 7.07-7.18 (m, 3H), 5.16 (d, 1H), 5.01 (d, 1H), 4.31-4.40 (m, 2H), 3.98-4.18 (m, 2H), 3.61-3.68 (m, 2H), 2.11-2.48 (m, 10H).

Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-((phenyl-d5) methyl) azepan-1-ium chloride

##STR01478##

chloride

Synthesis of 1-(chloromethyl) benzene-2, 3, 4, 5, 6-d5

[0247] To a stirred solution of benzene-d6 (5 g, 59.41 mmol) in Conc. HCl (15 mL) was added paraformaldehyde (5.3522 g, 178.23 mmol) at room temperature, and the reaction mixture was stirred for 48 h at 80° C. in sealed tube as progress of the reaction was monitored by 1H NMR The reaction mixture was extracted with Et.sub.2O (2×25 mL) and the combined organic extracts washed with saturated sodium bicarbonate solution (50 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure at 25° C. to afford 1-(chloromethyl) benzene-2, 3, 4, 5, 6-d5 (1.6 g) as a colourless liquid. .sup.1H NMR (400 MHz, CDCl3) δ ppm 4.6 (s, 2H). Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-((phenyl-d5) methyl) azepan-1-ium

[0248] To a stirred solution of 2-(azepan-1-yl)-N-(2,6-dimethylphenyl) acetamide (1.5 g, 5.76 mmol) in ACN (15 mL) was added 1-(chloromethyl) benzene-2, 3, 4, 5, 6-d5 (1.592 g, 12.1 mmol) and the resulting reaction mixture was stirred at 80° C. for 16 h in a sealed tube as progress of the reaction was monitored by TLC (10% MeOH in DCM, Visualization by UV). The reaction mixture

was cooled to room temperature, was filtered and the precipitated solid was washed with EtOAc to afford 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-((phenyl-d5) methyl) azepan-1-ium chloride (1.67 g) as a white solid. MS (ESI): m/z 356.36 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.55 (s, 1H), 7.1-7.18 (m, 3H), 4.95 (s, 2H), 4.2 (s, 2H), 3.72-3.81 (m, 1H), 3.5-3.6 (m, 1H), 2.25 (s, 6H), 1.9-2.1 (m, 4H), 1.1-1.2 (m, 4H).

Synthesis of 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-((1-methyl-1H-pyrazol-4-yl) methyl) piperidin-1-ium bromide

##STR01479##

Synthesis of 4-(bromomethyl)-1-methyl-1H-pyrazole hydrogen bromide

[0249] To a stirred solution of (1-methyl-1H-pyrazol-4-yl) methanol (1.0 g, 8.918 mmol) in AcOH (5 mL) was added 33% HBr in AcOH (12 mL) at rt. The reaction mixture was heated at 100° C. for 16 h as progress of the reaction was monitored by TLC (10% MeOH in DCM, visualization by UV). The reaction mixture was concentrated under reduced pressure to afford 4-(bromomethyl)-1-methyl-1H-pyrazole hydrogen bromide (1.5 g) as pale brown solid. .sup.1H NMR (400 MHz, DMSO-d6) δ ppm 8.01 (s, 1H), 7.50 (s, 1H), 5.51 (s, 2H), 3.81 (s, 3H).

Synthesis of 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-((1-methyl-1H-pyrazol-4-yl) methyl) piperidin-1-ium bromide

[0250] To a solution of 4-(bromomethyl)-1-methyl-1H-pyrazole.Math.hydrogenbromide (0.5 g, 1.953 mmol) in DMF (5 mL) was added N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) butanamide (0.783 g, 2.853 mmol) and potassium carbonate (0.473 g, 3.427 mmol). The resulting reaction mixture was heated at 100° C. for 24 h in a sealed tube as progress of the reaction was monitored by TLC (5% MeOH in DCM, visualization by UV). The reaction mixture was diluted with water (25 mL) and extracted with 10% methanol in DCM (2×100 ml). The combined organic layer was concentrated under reduced pressure to afford crude product which was purified by normal phase flash chromatography (5% MeOH in DCM) to afford 1-(1-((2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)-1-((1-methyl-1H-pyrazol-4-yl) methyl) piperidin-1-ium bromide (0.120 g) as an off white solid. MS (ESI): m/z 369.48 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.4 (s, 1H), 8.01 (s, 1H), 7.64 (s, 1H), 7.10-7.14 (m, 3H), 5.17 (d, 1H), 4.48 (d, 1H), 4.1-4.3 (m, 1H), 3.90 (s, 3H), 3.8-3.9 (m, 1H), 3.20-3.45 (m, 2H), 2.30-2.36 (m, 1H), 2.16 (s, 6H), 1.92-2.08 (m, 6H), 1.54 (d, 2H), 1.11-1.17 (m, 3H).

Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(3-(methoxycarbonyl) benzyl) piperidin-1-ium bromide

##STR01480##

Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(3-(methoxycarbonyl) benzyl) piperidin-1-ium bromide

[0251] To a solution of N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) acetamide (200 mg, 0.812 mmol) in ACN (3 mL) was added methyl 3-(bromomethyl)benzoate (241.6 mg, 1.055 mmol) at room temperature. The resulting reaction mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (5% MeOH in DCM, Visualization: UV). The reaction mixture was cooled to room temperature and was concentrated under reduced pressure to afford crude product which was triturated with EtOAc (3×10 mL) to afford pure 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(3-(methoxycarbonyl) benzyl) piperidin-1-ium bromide (57.5 mg) as an off white solid. MS (ESI): m/z 395.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.09 (s, 1H), 8.18 (s, 1H), 8.13 (d, 1H), 7.83-7.85 (m, 1H), 7.69-7.72 (m, 1H), 7.12-7.17 (m, 3H), 5.06 (s, 2H), 4.22 (s, 2H), 3.88 (s, 3H), 3.52-3.65 (m, 2H), 3.47-3.50 (m, 2H), 2.21 (s, 6H), 1.90-1.96 (m, 4H), 1.71-1.74 (m, 1H), 1.56-1.57 (m, 1H).

Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(4-(methoxycarbonyl) benzyl) piperidin-1-ium bromide

##STR01481##

Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(4-(methoxycarbonyl) benzyl)

piperidin-1-ium bromide

[0252] To a stirred solution of N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) acetamide (0.4 g, 1.623 mmol) in ACN (5 mL) was added methyl 4-(bromomethyl)benzoate (0.743 g, 3.247 mmol) and the resulting reaction mixture was stirred for 16 h at 80° C. as progress of the reaction was monitored by TLC (10% Methanol in DCM, visualisation: UV). The reaction mixture was allowed cool to room temperature and was concentrated under reduced pressure to afford crude product which was purified by reflux with EtOAc (30 mLl) for 2 h at 70° C. Refluxed product was filtered and washed with hot ethyl acetate (30 mL) to afford the (1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(4-(methoxycarbonyl) benzyl) piperidin-1-ium bromide (43 mg) as white solid. Mass (ESI): m/z 395.3 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.06 (s, 1H), 8.09 (d, 2H), 7.72 (d, 2H), 7.17-7.12 (m, 3H), 5.03 (s, 2H), 4.22 (s, 2H), 3.89 (s, 3H), 3.67-3.64 (m, 2H), 3.54-3.49 (m, 2H), 2.20 (s, 6H), 2.0-1.97 (m, 4H), 1.72-1.69 (m, 1H), 1.58-1.53 (m, 1H). Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(2-(methoxycarbonyl) benzyl)

##STR01482##

piperidin-1-ium bromide

Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(2-(methoxycarbonyl) benzyl) piperidin-1-ium bromide

[0253] To a solution of N-(2, 6-dimethylphenyl)-2-(piperidin-1-yl) acetamide (0.500 g, 2.0296 mmol) in ACN (5.0 mL) was added methyl 2-(bromomethyl) benzoate (0.929 g, 4.0592 mmol) and the resulting reaction mixture was heated to 80° C. for 16 h as progress of the reaction was monitored by TLC (10% MeOH, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude compound which was triturated with 3×10 mL of ethyl acetate followed by 2×10 mL of diethyl ether to afford pure 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1-(2-(methoxycarbonyl) benzyl) piperidin-1-ium bromide (250 mg) as an off white soli. MS (ESI): m/z 395.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d6) δ ppm 10.11 (s, 1H), 8.01 (d, 1H), 7.69-7.76 (m, 3H), 7.11-7.17 (m, 3H), 5.37 (s, 2H), 4.43-4.46 (m, 2H), 3.85 (s, 3H), 3.75 (d, 2H), 3.17 (t, 2H), 2.20 (s, 6H), 1.96-2.07 (m, 2H), 1.79-1.83 (m, 2H), 1.66-1.70 (m, 1H), 1.37-1.40 (m, 1H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) (methyl) amino)-2-oxoethyl) azepan-1-ium formate

##STR01483##

Synthesis of 2-Iodo-N-(2, 6-dimethylphenyl)-N-methyl acetamide

[0254] To a stirred solution of 2-chloro-N-(2, 6-dimethylphenyl) acetamide (2.0 g, 10.118 mmol) in THF (16 mL) was added NaH (60%) (0.607 g, 25.295 mmol) at 0° C. and the mixture was stirred for 20 min at 0° C. Methyl iodide (0.5 ml, 8.031 mmol) was added at 0° C. and resulting reaction mixture was stirred at room temperature 16 h as progress of the reaction was monitored by TLC (10% EtOAc in Pet, Visualisation by UV). The reaction mixture was poured into ice water (50 mL) and extracted with ethyl acetate (2×50 mL). The combined organic extracts were washed with brine solution (25 mL), dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford the crude product which was purified by column chromatography (eluted with 20-30% of ethyl acetate in pet ether). The collected pure fractions were concentrated under reduced pressure to afford N-(2,6-dimethylphenyl)-2-iodo-N-methylacetamide (0.55 g) as yellow liquid. Mass (ESI): m/z 304.03 [M+H].sup.+.

 $Synthesis\ of\ 2\hbox{--}(azepan-1\hbox{--}yl)\hbox{--}N\hbox{--}(2,6\hbox{--}dimethylphenyl)\hbox{--}N\hbox{--}methylacetamide}$

[0255] To a stirred solution of N-(2, 6-dimethylphenyl)-2-iodo-N-methylacetamide (0.5 g, 1.649 mmol) in ACN (5.0 mL) was added K.sub.2CO.sub.3 (0.569 g, 4.123 mmol) and azepane (0.327 ml, 3.298 mmol) at room temperature. The resulting reaction mixture was stirred for 16 h at 90° C. as progress of the reaction was monitored by TLC (50% EtOAc in pet ether, visualization by UV). The reaction mixture was poured into ice water (25 mL) and extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed with brine solution (25 mL), dried over

Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford the crude compound which was purified by normal phase flash chromatography (eluted with 10%-50% EtOAc in pet ether) The collected pure fractions were concentrated under reduced pressure to afford 2-(azepan-1-yl)-N-(2, 6-dimethylphenyl)-N-methyl acetamide (0.23 g). MS (ESI): m/z 275.49 [M+H].sup.+. Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) (methyl) amino)-2-oxoethyl) azepan-1-ium formate

[0256] To a stirred solution of 2-(azepan-1-yl)-N-(2,6-dimethylphenyl)-N-methylacetamide (0.1 g, 0.364 mmol) in Acetonitrile (1.0 mL) was added (bromomethyl)benzene (0.124 g, 0.728 mmol). The resulting reaction mixture was stirred for 16 h at 90° C. as progress of the reaction was monitored by TLC (10% MeOH in DCM, Visualisation: UV). The reaction mixture was concentrated under reduced pressure to afford the crude product which was purified by reverse phase Prep HPLC. (Column: X-select C18 (250*19) mm, 5 u, Mobile phase A: 0.1% FA in water, [0257] Mobile phase B: ACN: MeOH, Flow: 13 ml/min, Solubility: Water+THF+ACN, Method (T% of B): 0/10, 2/10, 10/50, 13/50, 13.2/98, 17/98, 17.2/10, 20/10, Temperature: Ambient). The collected pure fractions were lyophilized to afford the product (1-benzyl-1-(2-((2, 6-dimethylphenyl) (methyl) amino)-2-oxoethyl) azepan-1-ium formate (70 mg) as white gum. MS (ESI): m/z 365.3 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 8.43 (s, 1H), 7.56-7.42 (m, 5H), 7.26-7.17 (m, 3H), 4.95 (s, 2H), 4.41 (s, 1H), 3.91-3.85 (m, 1H), 3.62-3.50 (m, 3H), 3.36 (s, 1H), 3.14 (d, 3H), 2.32-2.05 (s, 7H), 1.95-1.65 (m, 2H), 1.46-1.23 (m, 5H). Synthesis of: Synthesis of 1-benzyl-1-(1-(mesityl amino)-1-oxobutan-2-yl) piperidin-1-ium bromide

##STR01484##

Synthesis of 2-bromo-N-mesitylbutanamide

[0258] To a stirred solution of 2,4,6-tri methyl aniline (2.0 g, 14.791 mmol) in DCM (20 mL) was added DIPEA (5.735 g, 44.373 mmol) at room temperature, followed by drop-wise addition of 2-bromo butanoyl chloride (3.291 g, 17.749 mmol) at 0° C. and the resulting reaction mixture was stirred for 3 h as progress of the reaction was monitored by TLC (20% Ethyl acetate in Pet ether. Visualization: UV). The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2×100 mL). The combined organic extracts were washed with brine solution, dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product which was purified by column chromatography (eluted with 10%-50% of ethyl acetate in pet ether). Pure fractions were combined and concentrated to afford desired product 2-bromo-N-mesitylbutanamide (1.5 g). MS (ESI): m/z 286.11 [M+2].sup.+. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.60 (s, 1H), 6.95 (s, 2H), 4.45 (t, 1H), 2.25 (s, 3H), 2.2 (s, 6H), 1.60-1.40 (m, 2H), 1.10 (t, 3H). Synthesis of N-mesityl-2-(piperidin-1-yl) butanamide

[0259] To a stirred solution of 2-bromo-N-mesityl butanamide (1.5 g, 5.278 mmol) in Acetonitrile (30 ml) was added Potassium carbonate (2.18 g, 15.834 mmol) and piperdine (0.943 g, 11.083 mmol) at room temperature. The resulting reaction was reflux for 16 h as progress of the reaction was monitored by TLC (50% EtOAc/Hexane, Visualization: UV). The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine solution, dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product which was triturated with ethyl acetate (40 mL) to afford pure N-mesityl-2-(piperidin-1-yl) butanamide (760 mg). MS (ESI): m/z 289.43 [M+H].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.07 (s, 1H), 6.86 (s, 2H), 3.06-3.01 (t, 1H), 2.60-2.48 (m, 4H), 2.21 (s, 3H), 2.06 (s, 6H), 1.80-1.25 (t, 8H), 0.95 (t, 3H).

Synthesis of 1-benzyl-1-(1-(mesitylamino)-1-oxobutan-2-yl) piperidin-1-ium bromide [0260] To a stirred solution of N-mesityl-2-(piperidin-1-yl) butanamide (0.15 g, 0.52 mmol) in Acetonitrile (1 mL) was added benzyl bromide (0.177 g, 1.04 mmol). The resulting reaction mixture was stirred for 20 h at 80° C. as progress of the reaction was monitored by TLC (10% Methanol in DCM, Visualization: UV). The reaction mixture was concentrated under reduced

pressure to afford crude product which was triturated with EtOAc (20 mL) to deliver desired product 1-benzyl-1-(1-(mesitylamino)-1-oxobutan-2-yl) piperidin-1-ium bromide (194 mg) as a white solid. Mass (ESI): m/z 379.3 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.31 (s, 1H), 7.62-7.50 (m, 5H), 6.93 (s, 2H), 5.42-5.39 (m, 1H), 4.63-4.20 (m, 2H), 4.05-3.55 (m, 2H), 3.30-3.10 (m, 2H), 2.41-2.31 (m, 1H), 2.23 (s, 9H), 2.15-2.06 (m, 2H), 2.05-1.80 (m, 3H), 1.57-1.43 (m, 2H), 1.23-1.07 (m, 3H).

Synthesis of 1-benzyl-1-(2-((4-((tert-butoxycarbonyl) (butyl) amino) phenyl) amino)-2-oxoethyl) azepan-1-ium bromide

##STR01485##

Synthesis of 2-bromo-N-(4-nitrophenyl) acetamide

[0261] To a stirred suspension of 4-nitro aniline (10 g, 72.395 mmol) in H.sub.2O (100 mL) was added bromo acetyl bromide (29.226 g, 144.790 mmol) at 0° C., and the reaction mixture was stirred at room temperature for 16 h as progress of the reaction was monitored by TLC (50% EtOAc in Pet-ether, Visualization: UV). The reaction mixture was basified with sat. Na.sub.2CO.sub.3 solution (100 mL) and the precipitated solid was filtered and dried. Crude product was triturated with diethyl ether (2×100 mL) to afford 2-bromo-N-(4-nitrophenyl) acetamide (8 g) as a yellow solid. Mass (ESI): m/z 259.17 [M+1].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.97 (s, 1H), 8.25 (d, 2H), 7.83 (d, 2H), 4.11 (s, 2H).

Synthesis of 2-(azepan-1-yl)-N-(4-nitrophenyl) acetamide

[0262] To a stirred solution of 2-bromo-N-(4-nitrophenyl) acetamide (5 g, 19.300 mmol) in ACN (50 ml) was added K.sub.2CO.sub.3 (8 g, 57.900 mmol) followed by Azepane (3.8 g, 38.600 mmol, 2 eq), and the reaction mixture was heated to 90° C. for 16 h in a sealed tube as progress of the reaction was monitored by TLC (50% EtOAc in Pet ether, Visualization: UV). The reaction mixture was allowed to cool to room temperature, and was then diluted with water (200 mL) and extracted with EtOAc (2×200 mL). The combined organic extracts were washed with brine solution (100 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure to afford crude product. The crude product was triturated with diethyl ether (2×50 mL) to afford pure 2-(azepan-1-yl)-N-(4-nitrophenyl) acetamide (2.5 g,). Mass (ESI): m/z 278.27 [M+1].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.26 (s, 1H), 8.21 (d, 1H), 7.91 (d, 2H), 3.33-3.4 (m, 2H), 2.72-2.81 (m, 4H), 1.56-1.62 (m, 8H).

Synthesis of N-(4-aminophenyl)-2-(azepan-1-yl) acetamide

[0263] To a stirred solution of 2-(azepan-1-yl)-N-(4-nitrophenyl) acetamide (2.5 g, 9.014 mmol) in MeOH (25 mL) was added 10% Pd/C (2.5 g) at room temperature, and the reaction mixture was stirred at RT for 16 h under H.sub.2 gas (Balloon pressure) as progress of the reaction was monitored by TLC (50% EtOAc/pet-ether, Visualization: UV). The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford pure N-(4-aminophenyl)-2-(azepan-1-yl) acetamide (1.5 g). Mass (ESI): m/z 248.30 [M+H]. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.20 (s, 1H), 7.22 (d, 2H), 6.49 (d, 2H), 4.85 (s, 1H), 3.16-3.19 (m, 2H), 2.68-2.72 (m, 4H), 1.57-1.62 (m, 8H).

Synthesis of 2-(azepan-1-yl)-N-(4-(butylamino) phenyl) acetamide

[0264] To a stirred solution of N-(4-aminophenyl)-2-(azepan-1-yl) acetamide (1.8 g, 7.277 mmol) and butyronitrile (2.51 g, 36.385 mmol) in methanol (20 mL) was added 10% Pd/C (1.8 g), and the reaction mixture was stirred for 16 h at room temperature under H.sub.2 gas atmosphere (balloon) as progress of the reaction was monitored by TLC (50% EtOAc in Pet ether, Visualization: UV). The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford desired product 2-(azepan-1-yl)-N-(4-(butylamino) phenyl) acetamide (1 g). Mass (ESI): m/z 304.43[M+1].sup.+.

Synthesis of tert-butyl (4-(2-(azepan-1-yl) acetamido) phenyl) (butyl) carbamate [0265] To a stirred solution of 2-(azepan-1-yl)-N-(4-(butylamino) phenyl) acetamide (1.4 g, 4.613 mmol) in ACN (20 mL) was added triethyl amine (1.39 g, 13.839 mmol) followed by di-tert-butyl

dicarbonate (1.5 g, 6.919 mmol) and the reaction mixture was stirred at rt for 16 h as progress of the reaction was monitored by TLC (50% EtOAc in Pet-ether, Visualization: UV). After completion of starting material on TLC, the crude compound was diluted with water (100 mL), extracted with EtOAc (2×120 mL) and the combined organic extracts were washed with brine solution (70 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (eluted with 10%-20% EtOAc in pet-ether) to afford product tert-butyl (4-(2-(azepan-1-yl) acetamido) phenyl) (butyl) carbamate (1 g,). Mass (ESI): m/z 404.58 [M+H]. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.65 (s, 1H), 7.59 (d, 2H), 7.13 (d, 2H), 3.53 (t, 2H), 3.24 (s, 2H), 2.70-2.75 (m, 4H), 1.61-1.86 (m, 8H), 1.35-1.44 (m, 9H), 1.24-1.32 (m, 3H), 1.17-1.22 (m, 3H).

Synthesis of 1-benzyl-1-(2-((4-((tert-butoxycarbonyl) (butyl) amino) phenyl) amino)-2-oxoethyl) azepan-1-ium bromide

[0266] To a stirred solution of tert-butyl (4-(2-(azepan-1-yl) acetamido) phenyl) (butyl) carbamate (200 mg, 0.495 mmol) in ACN (2 mL) was added benzyl bromide (127 mg, 0.742 mmol) at room temperature, and the reaction mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (10% MeOH in DCM, Visualization: UV). The reaction was concentrated under reduced pressure and crude compound was triturated with diethyl ether (2×20 mL) and EtOAc (2×20 mL) to afford 1-benzyl-1-(2-((4-((tert-butoxycarbonyl) (butyl) amino) phenyl) amino)-2-oxoethyl) azepan-1-ium bromide (80 mg). Mass (ESI): m/z 494.56 [M].sup.+. .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ ppm 10.63 (s, 1H), 7.66 (d, 2H), 7.50-7.60 (m, 5H), 7.24 (d, 2H), 4.91 (s, 2H), 4.00 (s, 2H), 3.52-3.76 (m, 6H), 1.90-1.98 (m, 4H), 1.63-1.76 (m, 4H), 1.37-1.41 (m, 13H), 0.85 (t, 3H).

Synthesis of 1-benzyl-1-(2-((4-(butylamino) phenyl) amino)-2-oxoethyl) azepan-1-ium formate ##STR01486##

Synthesis of 1-benzyl-1-(2-((4-(butylamino) phenyl) amino)-2-oxoethyl) azepan-1-ium formate [0267] A reaction mixture of 1-benzyl-1-(2-((4-((tert-butoxycarbonyl) (butyl) amino) phenyl) amino)-2-oxoethyl) azepan-1-ium bromide (50 mg, 0.087 mmol) in 47% Aq. HBr (1 mL) was stirred at 80° C. for 16 h as progress of the reaction was monitored by LCMS. The reaction mixture was concentrated under reduced pressure to afford crude product which was purified by reverse phase Prep.HPLC (Column: X-Select C18 (19×250) mm 5 u, Mobile phase: 0.1% Formic Acid in H.sub.2O: CAN, Flow: 18 ml/min, Gradient method: 0/51, 7.1/50, 7.2/99, 9.2/99, 9.3/5, 12/5). Pure fractions were collected and lyophilized to afford 1-benzyl-1-(2-((4-(butylamino) phenyl) amino)-2-oxoethyl) azepan-1-ium formate (25 mg). Mass (ESI): m/z 394.53 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.95 (s, 1H), 8.56 (s, 1H), 7.68 (d, 2H), 7.49-7.54 (m, 3H), 7.36 (d, 2H), 6.54 (d, 2H), 5.52 (t, 1H), 4.89 (s, 2H), 4.01 (s, 2H), 3.67-3.69 (m, 2H), 3.51-3.53 (m, 2H), 2.97 (t, 2H), 1.91-2.01 (m, 4H), 1.49-1.62 (m, 2H), 1.35-1.40 (m, 2H), 1.36 (t, 3H). Synthesis of 1-benzyl-1-(2-((4-(butylamino) phenyl) amino)-2-oxoethyl) piperidin-1-ium carbonate ##STR01487##

Synthesis of N-(4-nitrophenyl)-2-(piperidin-1-yl) acetamide

[0268] To a stirred solution of 2-bromo-N-(4-nitrophenyl) acetamide (3.0 g, 11.580 mmol) in ACN (30.0 mL) was added potassium carbonate (4.801 g, 34.74 mmol) and piperidine (1.972 g, 23.16 mmol) and the resulting reaction mixture was stirred at 85° C. for 1 h as progress of the reaction was monitored by TLC (50% ethyl acetate in Pet ether, visualization by UV). The reaction mixture was cooled to rt and concentrated under reduced pressure to afford crude reside. The crude residue was diluted with water (150 mL), extracted with EtOAc (3×100 mL), and the combined organic extracts were was washed with brine solution (1×100 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude product which was purified by column chromatography (eluted with 5% EtOAc in Pet ethe) to afford product N-(4-nitrophenyl)-2-(piperidin-1-yl) acetamide (1.40 g) as a pale yellow solid. MS (ESI): m/z 264.26 [M+H.sup.+].sup.· 1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.28 (s, 1H), 8.20-8.23 (m, 2H),

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Synthesis of N-(4-aminophenyl)-2-(piperidin-1-yl) acetamide
[0269] To a solution of N-(4-nitrophenyl)-2-(piperidin-1-yl) acetamide (1.4 g, 5.3171 mmol) in
MeOH (15.0 ml) was added 10% Pd/C (1.4 g) and the resulting reaction mixture was stirred at
R.sup.T for 16 h under hydrogen gas atmosphere (balloon pressure) as progress of the reaction was
monitored by TLC (50% EtOAc in Pet ether, Visualization: UV). The reaction mixture was filtered
through celite washed with an excess of methanol (2×20 ml) and the combined filtrate was
concentrated under reduced pressure to afford crude product which was triturated with diethyl ether
(3×20 mL) to afford N-(4-aminophenyl)-2-(piperidin-1-yl) acetamide (1.20 g). MS (ESI): m/z
234.29 [M+].sup. · 1H NMR (500 MHz, DMSO-d.sub.6) δ ppm 10.25 (s, 1H), 8.22 (d, 2H), 7.92 (t,
2H), 3.32 (d, 2H), 2.72-2.85 (m, 4H), 1.52-1.62 (m, 8H). Analytical data enclosed.
Synthesis of N-(4-(butyl amino) phenyl)-2-(piperidin-1-yl) acetamide
[0270] To a solution of N-(4-aminophenyl)-2-(piperidin-1-yl) acetamide (1.2 g, 5.1431 mmol) in
methanol (15.0 mL) was added butyronitrile (1.777 g, 25.7157 mmol) and 10% Pd/C (1.2 g) under
nitrogen atmosphere. The resulting reaction mixture was stirred at rt for 16 h under hydrogen gas
atmosphere (balloon pressure) as progress of the reaction was monitored by TLC (ethyl acetate in
Pet ether, UV visualization). The reaction mixture was filtered through celite washed with excess of
methanol (2×20 mL) and concentrated to afford crude product which was purified by column
chromatography (eluted with 20% of EtOAc in Pet ether) to afford pure N-(4-(butyl amino)
phenyl)-2-(piperidin-1-yl) acetamide (1.10 g). MS (ESI): m/z 290.42 [M+H]· .sup.1H NMR (400
MHz, DMSO-d.sub.6) δ ppm 9.21 (s, 1H), 7.27 (d, 2H), 6.48 (d, 2H), 5.33 (t, 2H), 2.88-2.95 (m,
4H), 2.49-2.51 (m, 4H), 1.47-1.58 (m, 6H), 1.34-1.41 (m, 4H), 0.90 (t, 3H).
Synthesis of tert-butyl butyl (4-(2-(piperidin-1-yl) acetamido) phenyl) carbamate
[0271] To a stirred solution of N-(4-(butylamino) phenyl)-2-(piperidin-1-yl) acetamide (0.956 g,
3.30 mmol) in DCM (10.0 mL) at 0° C. was added TEA (1.672 g, 16.527 mmol) and di-tert-butyl
dicarbonate (1.803 g, 8.2635 mmol) and the resulting reaction mixture was allowed to stir at rt for
16 h as progress of the reaction was monitored by TLC (100% EtOAc, Visualization: UV). The
reaction mixture was concentrated under reduced pressure, diluted with water (50 mL) and
extracted with DCM (3×50 mL). The combined organic extracts were washed with brine solution
(1×50 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced
pressure to afford crude product which was purified by normal phase flash chromatography (eluted
with 30% in Pet ether). The collected pure fractions were concentrated under reduced pressure to
afford product tert-butyl butyl (4-(2-(piperidin-1-yl) acetamido) phenyl) carbamate (1.15 g). MS
(ESI): m/z 390.57 [M+H].sup.+.
Synthesis of 1-benzyl-1-(2-((4-((tert-butoxycarbonyl) (butyl) amino) phenyl) amino)-2-oxoethyl)
piperidin-1-ium bromide
[0272] To a stirred solution of tert-butyl butyl (4-(2-(piperidin-1-yl) acetamido) phenyl) carbamate
(0.225 g, 0.5776 mmol) in Acetonitrile (3 mL) was added benzyl bromide (0.197 g, 1.1552 mmol)
in microwave vial. The reaction mixture was stirred at 100° C. for 1 h in a microwave (CEM
instrument) as progress of the reaction was monitored by LCMS and TLC (5% MeOH in DCM,
Detection: UV). The reaction mixture was allowed to cool to rt and concentrated under reduced
pressure to afford crude product which was triturated with diethyl ether (5×5 ml) to afford product
1-benzyl-1-(2-((4-((tert-butoxycarbonyl)(butyl)amino)phenyl) amino)-2-oxoethyl) piperidin-1-ium
bromide (110 mg). MS (ESI): m/z 480.58 [M]+·.
Synthesis of 1-benzyl-1-(2-((4-(butyl amino) phenyl) amino)-2-oxoethyl) piperidin-1-ium
carbonate
[0273] A reaction mixture of 1-benzyl-1-(2-((4-((tert-butoxy carbonyl) (butyl) amino) phenyl)
amino)-2-oxoethyl) piperidin-1-ium bromide (105 mg, 0.2184 mmol) in aqueous hydrogen
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bromide (48%) (1 mL) was stirred at rt for 16 h as progress of the reaction was monitored by LCMS and TLC (80% Ethyl acetate in pet ether, Detection: UV). The reaction mixture was

7.89-7.93 (m, 2H), 3.14 (s, 2H), 2.44-2.51 (m, 4H), 1.53-1.59 (m, 4H), 1.40 (t, 2H).

lyophilized to afford crude product which was purified by reverse phase Prep. HPLC (Column: X-select C18 (19*250) 5 u, Mobile Phase (A): 10 mM ammonium bicarbonate, Mobile Phase (B): 100% ACN Method: 0/3, 2/40, 20/40, 20.50/100, 30/35, Flow Rate: 18 ml/min, Solubility: CAN+THF+MeOH). Pure fractions were combined and lyophilized to afford 1-benzyl-1-(2-((4-(butyl amino) phenyl) amino)-2-oxoethyl) piperidin-1-ium carbonate (15.1 mg). MS (ESI): m/z 380.2 [M]+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 11.10 (br s, 1H), 7.54-7.72 (m, 5H), 7.34 (d, 2H), 6.52 (d, 2H), 5.44 (t, 1H), 4.94 (s, 2H), 4.09 (s, 2H), 3.65 (d, 2H), 3.33-3.5 (m, 2H), 2.97-3.01 (m, 2H), 1.92-1.97 (m, 4H), 1.63 (q, 1H), 1.48-1.55 (m, 3H), 1.34-1.42 (m, 2H), 0.91 (t, 3H).

Synthesis of 1-benzyl-1-(1-((4-(butylamino)-2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl) piperidin-1-ium carbonate

##STR01488##

Synthesis of N-(2, 6-dimethylphenyl)-4-methylbenzenesulfonamide

[0274] To a stirred solution of 2, 6-dimethyl aniline (50 g, 413 mmol) in pyridine (1.2 L) was added Tosyl chloride (94.396 g, 495.131 mmol) and the mixture was heated to reflux at 115° C. for 4 h as progress of the reaction mixture monitored by TLC (30% Ethyl acetate in pet ether, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude residue which was diluted with water (500 mL), adjusted pH to 6 with 2N HCl (500 mL) and extracted with ethyl acetate (2×1 L). The combined organic extracts were washed with brine solution (1.0 L), dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product which was triturated with pet ether to provide N-(2, 6-dimethylphenyl)-4-

methylbenzenesulfonamide (90 g) as an off white solid. MS (ESI): m/z 276.23 [M+H].sup.+. sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.231 (s, 1H), 7.530-7.551 (d, 2H), 7.354-7.375 (d, 2H), 6.985-7.069 (m, 3H), 2.384 (s, 3H), 1.940 (s, 6H).

Synthesis of N-(2, 6-dimethyl-4-nitrophenyl)-4-methylbenzenesulfonamide

[0275] To a solution of N-(2, 6-dimethylphenyl)-4-methylbenzenesulfonamide (90 g, 326.8 mmol) in AcOH (675 mL) and water (450 mL) was added NaNO.sub.2 (45.103 g, 653.666 mmol) followed by the drop-wise addition of Conc.Math.HNO.sub.3 (41.181 g, 653.666 mmol) over a period of 15 min at room temperature. The resulting reaction mixture was heated to 110° C. for 5 h as progress of the reaction mixture was monitored by TLC (30% ethyl acetate in pet ether, Visualization: UV). The reaction mixture was diluted with ice cold water (500 mL), basified with 1N NaOH solution (800 mL) and extracted with ethyl acetate (2×1 L). The combined organic extracts were washed with brine solution (1 L), dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product which was triturated with pet ether (500 mL) to provide product N-(2, 6-dimethyl-4-nitrophenyl)-4-methylbenzenesulfonamide (40 g) as an off white solid. MS (ESI): m/z 321.18 [M+H].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.72 (s, 1H), 7.925 (s, 2H), 7.562-7.583 (d, 2H), 7.390-7.409 (d, 2H), 2.400 (s, 3H), 2.073 (s, 6H).

Synthesis of 2, 6-dimethyl-4-nitroaniline

[0276] To a stirred solution of N-(2, 6-dimethyl-4-nitrophenyl)-4-methylbenzenesulfonamide (25 g, 78.037 mmol) in AcOH (125 ml) was added HClO.sub.4 (250 ml) at rt and the mixture was heated to 100° C. for 3 h. as progress of the reaction mixture was monitored by TLC (30% Ethyl acetate in pet ether, Visualization: UV). The reaction mixture was poured into crushed ice, basified (pH $^{\sim}$ 11) with aqueous ammonia solution and extracted with ethyl acetate (2×1 L). The combined organic extracts were washed with brine solution (300 mL), dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product which was purified by column chromatography (eluted with 20% ethyl acetate in pet ether) to afford 2, 6-dimethyl-4-nitroaniline (10 g) as a yellow solid. MS (ESI): m/z 167.03 [M+H].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 7.787 (s, 2H), 6.142 (s, 2H), 2.155 (s, 6H).

Synthesis of 2-bromo-N-(2, 6-dimethyl-4-nitrophenyl) butanamide

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[0277] To a cooled solution (0° C.) of 2, 6-dimethyl-4-nitroaniline (3 g, 18.05 mmol) in DCM (45
mL) was added pyridine (1.713 g, 21.66 mmol) followed by 2-bromobutanoyl chloride (4.017 g,
21.66 mmol). The resulting reaction mixture was allowed to stir at rt for 16 h as progress of the
reaction mixture was monitored by TLC (50% ethyl acetate in pet ether, Visualization: UV). The
reaction mixture was filtered and the isolated solid was washed with DCM (20 mL) and dried under
high vacuum to afford 2-bromo-N-(2,6-dimethyl-4-nitrophenyl) butanamide (2 g) as an off white
solid. MS (ESI): m/z 315.26 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.05 (s,
1H), 8.0 (s, 2H), 4.55 (t, 1H), 2.279 (s, 6H), 1.940-2.143 (m, 2H), 0.99 (t, 3H).
Synthesis of N-(2, 6-dimethyl-4-nitrophenyl)-2-(piperidin-1-yl) butanamide
[0278] To a stirred solution of 2-bromo-N-(2, 6-dimethyl-4-nitrophenyl) butanamide (2 g, 6.345
mmol) in ACN (30 mL) was added K.sub.2CO.sub.3 (2.627 g, 19.03 mmol) and piperidine (1.080
g, 12.690 mmol). The resulting mixture was heated to 80° C. for 16 h as progress of the reaction
mixture was monitored by TLC (50% ethyl acetate in pet ether, Visualization: UV). The reaction
mixture was concentrated, diluted with Ethyl acetate (150 mL) and washed with water (50 mL×3)
and brine solution (60 mL). The combined organic extracts were dried over anhydrous
Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product which was
purified by by column chromatography (eluted with 50% ethyl acetate in pet ether) to afford N-(2,
6-dimethyl-4-nitrophenyl)-2-(piperidin-1-yl) butanamide (1.70 g). MS (ESI): m/z 320.42
[M+H].sup.+. .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ ppm 9.578 (s, 1H), 7.992 (s, 2H), 3.12
(t, 1H), 2.55-2.62 (m, 4H), 2.28 (s, 6H), 1.60-1.81 (m, 2H), 1.35-1.56 (m, 6H), 0.93 (t, 3H).
Synthesis of N-(4-amino-2, 6-dimethylphenyl)-2-(piperidin-1-yl) butanamide
[0279] To a stirred solution of N-(2, 6-dimethyl-4-nitrophenyl)-2-(piperidin-1-yl) butanamide (1.7
g, 5.322 mmol) in EtOH (40 mL) was added 10% Pd—C (0.900 g) and the mixture was stirred for
16 h at rt under H.sub.2 gas (balloon pressure) as progress of the reaction mixture was monitored
by TLC (100% Ethyl acetate, Visualization: UV). The mixture was filtered through celite, the filter
bed was washed with MeOH (200 ml) and the filtrate was concentrated under reduced pressure to
afford crude product which was purified by normal phase flash chromatography (eluted with
EtOAc) to afford N-(4-amino-2, 6-dimethylphenyl)-2-(piperidin-1-yl) butanamide (1.0 g). MS
(ESI): m/z 290.46 [M+H].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 8.78 (s, 1H),
6.23 (s, 2H), 4.82 (s, 2H), 2.95 (t, 1H), 2.45-2.6 (m, 4H), 1.2-1.6 (m, 8H), 0.910 (t, 3H).
Synthesis of N-(4-(butylamino)-2, 6-dimethylphenyl)-2-(piperidin-1-yl) butanamide
[0280] To a solution of N-(4-amino-2,6-dimethylphenyl)-2-(piperidin-1-yl) butanamide (1.0 g,
3.455 mmol) in MeOH (20 mL) was added butyronitrile (2.387 g, 34.551 mmol) and 10% Pd/C (1
g) at and the mixture was stirred for 16 h at rt under H.sub.2 gas (balloon pressure) as progress of
the reaction mixture was monitored by TLC (Ethyl acetate, Visualization: UV). The reaction
mixture was filtered through a bed of celite, the filter bed was washed with MeOH (150 ml) and the
filtrate was concentrated under reduced pressure to afford crude product which was purified by
normal phase flash chromatography (eluted with ethyl acetate) to afford N-(4-(butylamino)-2, 6-
dimethyl phenyl)-2-(piperidin-1-yl) butanamide (0.500 g). MS (ESI): m/z 346.51 [M+H].sup.+.
.sup.1H NMR (500 MHz, DMSO-d.sub.6) δ ppm 8.789 (s, 1H), 6.242 (s, 2H), 2.96 (t, 3H), 2.50-
2.57 (m, 3H), 2.027 (s, 6H), 1.498-1.518 (m, 2H), 1.475-1.488 (m, 6H), 1.22-1.387 (m, 6H), 0.885-
0.918 (m, 6H).
Synthesis of tert-butyl butyl (3, 5-dimethyl-4-(2-(piperidin-1-yl) butanamido) phenyl) carbamate
[0281] To a stirred solution of N-(4-(butylamino)-2, 6-dimethylphenyl)-2-(piperidin-1-yl)
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[0281] To a stirred solution of N-(4-(butylamino)-2, 6-dimethylphenyl)-2-(piperidin-1-yl) butanamide (0.400 g, 1.157 mmol) in EtOH (10 mL) was added DIPEA (0.179 g, 1.389 mmol) and di-tert-butyl dicarbonate (0.758 g, 3.473 mmol) at 0° C. The reaction mixture was stirred at rt for 16 h as progress of the reaction mixture was monitored by TLC (50% Ethyl acetate in pet ether, Visualization: UV). The mixture was concentrated under vacuum to afford crude reside which was diluted with ethyl acetate (80 ml) and washed with water (40 ml), brine solution (40 ml). The organic layer was dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure

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to afford crude product which was purified by normal phase flash chromatography (eluted with
40% ethyl acetate in pet ether) to afford tert-butyl butyl (3, 5-dimethyl-4-(2-(piperidin-1-yl)
butanamido) phenyl) carbamate (0.300 g). MS (ESI): m/z 446.66 [M+H].sup.+. .sup.1H NMR data
shows product along with aliphatic impurities. Analytical data enclosed.
Synthesis of 1-benzyl-1-(1-((4-((tert-butoxycarbonyl) (butyl) amino)-2, 6-dimethylphenyl)
amino)-1-oxobutan-2-yl) piperidin-1-ium bromide
[0282] To a stirred solution of tert-butyl butyl (3, 5-dimethyl-4-(2-(piperidin-1-yl) butanamido)
phenyl) carbamate (0.250 g, 0.561 mmol) in ACN (5 mL) was added benzyl bromide (0.191 g,
1.116 mmol) and the mixture was heated to 85° C. for 24 h as progress of the reaction mixture was
monitored by TLC (10% Methanol in DCM, Visualization: UV). The reaction mixture was
concentrated under vacuum to afford crude product which was triturated with mixture of diethyl
ether (20 ml) and ethyl acetate (10 ml) to afford 1-benzyl-1-(1-((4-((tert-butoxycarbonyl) (butyl)
amino)-2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)piperidin-1-ium bromide (0.200 g). MS
(ESI): m/z 536.61 [M].sup.+. .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ ppm 10.317 (s, 1H),
7.547 (s, 5H), 7.002 (s, 2H), 5.41 (d, 1H), 4.62 (d, 1H), 3.6-3.9 (m, 3H), 3.1-3.4 (m, 2H), 2.4-2.5
(m, 2H), 1.953-2.184 (m, 12H), 1.163-1.620 (m, 18H), 0.857 (s, 3H).
Synthesis of 1-benzyl-1-(1-((4-(butylamino)-2, 6-dimethylphenyl) amino)-1-oxobutan-2-yl)
piperidin-1-ium carbonate
[0283] An Aqueous 47% HBr solution (8 ml) was added to 1-benzyl-1-(1-((4-((tert-
butoxycarbonyl) (butyl)amino)-2,6-dimethylphenyl)amino)-1-oxobutan-2-yl) piperidin-1-ium
bromide (0.150 g, 0.243 mmol) at 0° C. and the resulting mixture was allowed to stir at rt for 16 h
as progress of the reaction mixture was monitored by TLC. (10% Methanol in DCM, Visualization:
UV). The reaction mixture was concentrated under reduced pressure and the residue was washed
with diethyl ether (5 ml) to afford crude product which was purified by reverse phase prep-HPLC
(Column: kromasil C18 (25×150) mm 10 u, Mobile phase-10 mM Ammonium Bicarbonate in
H.sub.2O: CAN, Flow: 25 ml/min, Gradient method: 0/40, 10/82, 10.1/99, 12/99, 12.1/40, 14/40).
The pure fractions were collected and lyophilized to afford 1-benzyl-1-(1-((4-(butyl amino)-2, 6-
dimethylphenyl) amino)-1-oxobutan-2-yl) piperidin-1-ium carbonate salt (0.050 g). MS (ESI): m/z
436.61 [M].sup.+. .sup.1H NMR (500 MHz, DMSO-d.sub.6) δ ppm 10.826 (s, 1H), 7.54 (t, 5H),
6.271 (s, 2H), 5.44 (t, 2H), 4.60 (d, 2H), 3.708 (s, 2H), 2.96 (q, 2H), 2.362 (s, 2H). 2.027-2.066 (m,
8H), 1.838-1.99 (m, 2H), 1.492-1.549 (m, 6H), 1.32-1.45 (m, 3H), 1.12-1.25 (m, 3H), 0.922 (t,
3H).
Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-4-(methoxy carbonyl)
piperidin-1-ium bromide
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##STR01489##

Synthesis of methyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-4-carboxylate [0284] To a stirred solution of 2-bromo-N-(2, 6-dimethylphenyl) acetamide (0.500 g, 2.065 mmol) and methyl piperidine-4-carboxylate (0.443 g, 3.097 mmol) in ACN (10 ml) was added K.sub.2CO.sub.3 (0.712 g, 5.162 mmol). The mixture was heated to 90° C. for 16 h as progress of the reaction mixture was monitored by TLC (50% Ethyl acetate in pet ether, Visualization: UV). The reaction mixture was concentrated under reduced pressure, diluted EtOAc (100 ml) and washed with water (50 ml×3) and brine solution (50 ml). The organic extract was dried over anhydrous Na.sub.2SO.sub.4 and concentrated to afford crude product which was purified by normal phase flash chromatography (eluted with 10%-30% of Ethyl acetate in Pet ether gradient). The collected pure fractions were concentrated under reduced pressure to afford the desired product methyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-4-carboxylate (0.400 g). MS (ESI): m/z 305.36 [M+H].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.171 (s, 1H), 7.060-7.09 (m, 3H), 3.607 (s, 3H), 3.089 (s, 2H), 2.879-2.908 (m, 2H), 2.316-2.371 (m, 1H), 2.198-2.261 (m, 2H), 2.129 (s, 6H), 1.816-1.856 (m, 2H). 1.680-1.778 (m, 2H). Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-4-(methoxy carbonyl)

piperidin-1-ium bromide

[0285] To a stirred solution of methyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-4-carboxylate (0.200 g, 0.657 mmol) in ACN (5 ml) was added benzyl bromide (0.224 g, 1.314 mmol) and the mixture was heated to 90° C. for 24 h as progress of the reaction was monitored by TLC (10% MeOH in DCM, Visualization: UV). The reaction mixture was concentrated to afford crude product which was triturated ethyl acetate (30 ml) and n-pentane (20 ml) to afford pure 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-4-(methoxy carbonyl) piperidin-1-ium bromide (0.080 g) as white solid. MS (ESI): m/z 395.3 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.048 (s, 1H), 7.551-7.591 (m, 5H), 7.144-7.159 (m, 3H), 4.947 (s, 2H), 4.237 (s, 2H), 3.671-3.766 (m, 5H), 3.541-3.549 (m, 2H), 2.732-2.788 (m, 1H), 2.128-2.212 (m, 10H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(ethoxycarbonyl) piperidin-1-ium bromide

##STR01490##

Synthesis of ethyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate [0286] To a stirred solution of 2-chloro-N-(2, 6-dimethylphenyl) acetamide (5 g, 25.295 mmol) in ACN (100 ml) was added K.sub.2CO.sub.3 (8.726 g, 63.237 mmol) and ethyl piperidine-3-carboxylate (5.964 g, 37.942 mmol) at RT. The resulting reaction mixture was stirred at RT for 16 h as progress of the reaction mixture was monitored by TLC (30% Ethyl acetate in pet ether, Visualization: UV). The reaction mixture was filtered to remove inorganic salts and the filtrate was concentrated under reduced pressure to afford crude product which was diluted with ethyl acetate (250 ml) and washed with water (80 ml×3) and brine solution (80 ml). The organic phase was dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford ethyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate (6.5 g). MS (ESI): m/z 319.01 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3) δ ppm 8.751 (s, 1H), 7.066-7.101 (m, 3H), 4.075-4.168 (m, 2H), 3.154-3.249 (m, 2H), 2.927-2.949 (m, 1H), 2.761-2.817 (m, 2H), 2.613-2.664 (m, 1H), 2.45-2.49 (m, 1H), 2.23 (s, 6H), 1.506-2.045 (m, 4H), 1.209-1.277 (m, 3H). Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(ethoxycarbonyl) piperidin-1-ium bromide

[0287] To a stirred solution of ethyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate (0.300 g, 0.942 mmol) in ACN (10 ml) was added benzyl bromide (0.322 g, 1.884 mmol) and the mixture was heated to 90° C. for 16 h in sealed tube as progress of the reaction was monitored by TLC (10% MeOH in DCM, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude product which was purified by normal phase flash chromatography (eluted with 2% Methanol in DCM). The collected pure fractions were concentrated under reduced pressure to afford the desired product as a colourless gum (LCMS-85%), This compound was diluted with ethyl acetate (15 ml) and stirred for 1 h, and then filtered and washed with ethyl acetate (15 ml×3) to afford pure 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(ethoxycarbonyl) piperidin-1-ium bromide (70 mg) as an off white solid. MS (ESI): m/z 409.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.05 (s, 1H), 7.545-7.585 (m, 5H), 7.125-7.178 (m, 3H), 4.945-5.060 (m, 2H), 4.109-4.342 (m, 4H), 3.904-3.934 (m, 1H), 3.644-3.677 (m, 1H), 3.433-3.569 (m, 2H), 3.230-3.262 (m, 1H), 2.213 (s, 6H), 1.948-2.195 (m, 3H), 1.553-1.620 (m, 1H), 1.24 (t, 3H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(isopropoxycarbonyl) piperidin-1-ium trifluoroacetate salt ##STR01491##

Synthesis of 1-(2-((2,6-dimethylphenyl) amino)-2-oxoethyl)piperidine-3-carboxylic acid [0288] A mixture of ethyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate (5 g, 15.702 mmol) in Conc.Math.HCl (100 ml) was heated to 100° C. for 16 h as progress of the reaction was monitored by TLC (50% EtOAc in pet ether, Visualization: UV). The reaction mixture

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was concentrated under reduced pressure to afford 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)
piperidine-3-carboxylic acid (4.2 g) MS (ESI): m/z 291.13 [M+H].sup.+.
Synthesis of isopropyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate
[0289] To a stirred solution of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-
carboxylic acid (0.5 g, 1.722 mmol) in isopropanol (10 mL) was added thionyl chloride (5 mL)
drop wise at 0° C. The resulting reaction mixture was allowed to stir at 90° C. for 16 h as progress
of the reaction was monitored by TLC (50% EtOAc in pet ether, Visualization: UV). The reaction
mixture was cooled to room temperature and concentrated under reduced pressure to afford crude
residue which was quenched with ice cold saturated sodium bicarbonate solution (20 mL) and
extracted with EtOAc (2×50 mL). The combined organic extracts were dried over anhydrous
sodium sulphate and concentrated under reduced pressure to afford crude product which was
purified by normal phase flash chromatography (eluted with 20%-30% of EtOAc/Pet ether). The
collected pure fractions were concentrated under reduced pressure to afford 1-(2-((2, 6-
dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate (0.54 g) as a pale yellow solid. MS
(ESI): m/z 332.27 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3) δ ppm 8.5 (br s, 1H), 7.06-7.11
(m, 3H), 4.97-5.03 (m, 1H), 3.19-3.24 (m, 2H), 2.93-2.95 (m, 1H), 2.59-2.48 (m, 2H), 2.48-2.40
(m, 2H), 2.18-2.20 (m, 5H), 1.41-1.65 (m, 3H), 1.18-1.24 (m, 6H).
Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl)amino)-2-oxoethyl)-3-(isopropoxy carbonyl)
piperidin-1-ium trifluoroacetate salt
[0290] To a stirred solution of isopropyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)
piperidine-3-carboxylate (0.4 g, 1.203 mmol) in ACN (10 mL) was added benzyl bromide (0.6173
g, 3.609 mmol) at room temperature. The resulting reaction mixture was stirred at 90° C. for 16 h
in a sealed tube as progress of the reaction was monitored by TLC (50% EtOAc in Pet ether,
Visualization: UV). The reaction mixture was allowed to cool to room temperature and was
concentrated under reduced pressure to afford 430 mg (LCMS 51%) of crude compound which was
further purified by reverse phase Prep.HPLC (Column: X-select csh C18 (250*19) mm, 5 u;
Mobile Phase A: 0.1% TFA (Aq.) in Water, Mobile Phase B: Acetonitrile, Flow: 22 ml/min, Method
(T/% of B): 0/10, 2/10, 10/50, 13/50, 13.1/100, 16/100, 16.1/10, 19/20, Solubility:
ACN+H.sub.2O+THF, Temperature: Ambient). Combined pure fractions were lyophilized to afford
pure 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(isopropoxycarbonyl) piperidin-1-
ium trifluoroacetate salt (168 mg). LCMS: 99.37% (77.95%+21.42%, mixture of isomers), MS
(ESI): m/z 423.2, [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.01-10.05 (m,
1H), 7.57-7.61 (m, 5H), 7.12-7.17 (m, 3H), 4.92-5.06 (m, 3H), 4.14-4.22 (m, 2H), 3.87-3.67 (dd,
1H), 3.46-3.55 (m, 3H), 3.15-3.21 (m, 1H), 2.208 (d, 6H), 1.85-2.07 (m, 3H), 1.19-1.23 (m, 6H).
Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(propoxycarbonyl)
piperidin-1-ium bromide
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##STR01492##

Synthesis of propyl piperidine-3-carboxylate

[0291] To a stirred solution of piperidine-3-carboxylic acid (2.0 g, 15.484 m.Math.mol) in propan-1-ol (20.0 ml) was added SOCl.sub.2 (11.05 g, 92.908 mmol) at 0-5° C. The resulting reaction mixture was stirred for 16 h at 80° C. as progress of the reaction was monitored by TLC (30% ethyl acetate/pet ether. Visualisation: ninhydrin). The reaction mixture was concentrated under reduced pressure to afford the crude compound which was dissolved into ethyl acetate (100 ml) and wash with saturated bicarbonate solution (1×100 ml) and brine solution (1×50 ml). The organic layer was dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford the propyl piperidine-3-carboxylate (2.0 g) as a colourless liquid. This crude product carry forwarded to next step without purification and analysis.

Synthesis of propyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate [0292] To a stirred solution of 2-chloro-N-(2, 6-dimethylphenyl) acetamide (2.0 g, 10.15 mmol) in ACN (20 ml) was added K.sub.2CO.sub.3 (4.14 g, 29.95 mmol) and propyl piperidine-3-

carboxylate (3.47 g, 20.28 mmol) at room temperature. The resulting reaction mixture was stirred for 16 h at 80° C. as progress of the reaction was monitored by TLC (50% ethyl acetate/pet ether, Visualization: UV active). After completion of reaction on TLC, the reaction mixture was concentrated under reduced pressure to afford the crude compound which was diluted with water (30 ml) and extracted with ethyl acetate (2×100 ml). The combined organic extracts were washed with brine (50.0 ml), dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford the crude compound which was purified by column chromatography (eluted with 20%-80% of ethyl acetate/pet ether). The collected pure fractions were concentrated under reduced pressure to afford the propyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate (1.0 g) as a gummy compound. MS (ESI): m/z 333.10 [M+H].sup.+. Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(propoxy carbonyl) piperidin-1-ium bromide

[0293] To a solution of propyl 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxylate (0.3 g, 0.9030 mmol) in Acetonitrile (10 ml) was added benzyl bromide (0.3113 g, 1.806 mmol) at room temperature. The resulting reaction mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (10% MeOH/DCM, Visualization: UV). After consumption of the starting material on TLC, the reaction mixture was directly concentrated under reduced pressure to afford crude compound as pale yellow semi solid which was purified by normal phase flash chromatography (eluted with 0%-30% of MeOH/DCM). The collected pure fractions were concentrated under reduced pressure to afford 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(propoxycarbonyl) piperidin-1-ium bromide (70 mg) as an off-white solid. MS (ESI): m/z 423.3 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d6) δ ppm 10.30 (s, 1H), 7.55-7.60 (m, 5H), 7.11-7.18 (m, 3H), 4.97-5.15 (m, 2H), 4.33 (dd, 2H) 4.05 (t, 2H), 3.88 (d, 1H), 3.66 (d, 1H), 3.31-3.54 (m, 3H), 2.09-2.21 (m, 8H), 1.96 (d, 2H), 1.55-1.64 (m, 3H), 0.87-0.93 (m, 3H). [0294] The following examples were prepared from piperidine-3-carboxylic acid, 2-chloro-N-(2, 6-dimethylphenyl) acetamide and benzyl bromide following procedures described for the synthesis of compound 47A.

TABLE-US-00010 Compound # Structure MS (ESI): m/z 48A [01493] embedded image 437.2 [M]+ 49A [01494] embedded image 437.3 [M]+ 50A [01495] embedded image 449.2 [M]+ 51A [01496] embedded image 463.3 [M]+.

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(propionyloxy) piperidin-1-ium bromide

##STR01497##

Synthesis of tert-butyl 3-(propionyloxy) piperidine-1-carboxylate

[0295] To a stirred solution of tert-butyl 3-hydroxypiperidine-1-carboxylate (2 g, 9.936 mmol) and pyridine (2.357 g, 29.808 mmol) in DCM (30 ml) was added propionyl chloride (1.103 g, 11.923 mmol) at 0° C. and the resulting reaction mixture was stirred for 24 h at room temperature as progress of the reaction was monitored by TLC (20% EtOAc in Pet ether, Visualization: UV). The reaction mass was diluted with DCM (120 mL) and washed twice with water (50 mL), dried over sodium sulphate and concentrated under reduced pressure to afford tert-butyl 3-(propionyloxy) piperidine-1-carboxylate (1.34 g) as an off-white solid. sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 4.85-4.75 (m, 1H), 3.51-3.43 (m, 3H), 3.3-3.29 (m, 1H), 2.41-2.39 (m, 2H), 1.85-1.72 (m, 3H), 1.45 (s, 9H), 1.18-1.12 (m, 4H).

Synthesis of piperidin-3-yl propionate

[0296] To a stirred solution of tert-butyl 3-(propionyloxy) piperidine-1-carboxylate (1.3 g, 5.05 mmol) in DCM (20 ml) was added TFA (5 ml) at 0° C. and the resulting reaction mixture was stirred at room temperature for 16 h as progress of the reaction was monitored by TLC (50% EtOAc in Pet ether, Visualization: ninhydrin). The reaction mixture was concentrated under reduced pressure to afford crude product which was co-distilled with toluene (2×15 mL) to afford piperidin-3-yl propionate TFA salt (1.34 g) as a light yellow oil. .sup.1H NMR (400 MHz,

CDCl.sub.3) δ ppm 5.16 (s, 1H), 3.41 (d, 2H), 3.24 (t, 1H), 3.10 (d, 1H), 2.42-2.36 (m, 2H), 2.13-2.10 (m, 2H), 2.02-2.01 (m, 2H), 1.88-1.84 (m, 3H).

Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidin-3-yl propionate [0297] To a stirred solution of 2-chloro-N-(2,6-dimethylphenyl)acetamide (0.3 g, 1.517 mmol) in Acetonitrile (15 mL) was added DIPEA (0.5884 g, 4.551 mmol) and piperidin-3-yl propionate TFA salt (0.4937 g, 1.8204 mmol) at room temperature. The resulting reaction mixture was stirred at 80° C. for 16 h in a sealed tube as progress of the reaction was monitored by TLC (50% EtOAc in pet ether. Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford residue which was diluted with water (50 ml) and extracted with ethyl acetate (2×25 ml). The combined organic extracts were dried over sodium sulphate and concentrated under reduced pressure to afford crude product which was purified by normal phase flash chromatography (eluted with 25%-30% of EtOAc/Pet ether). The collected pure fractions were concentrated under reduced pressure to afford 2-(azepan-1-yl)-N-(3-methyl-[1, 1'-biphenyl]-2-yl) acetamide (310 mg). Mass (ESI): 319.26 m/z, [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 8.67 (s, 1H), 7.12-7.06 (m, 3H), 4.95-4.92 (m, 1H), 3.20 (s, 2H), 2.95-2.89 (m, 1H), 2.73-2.56 (m, 1H), 2.59-2.54 (m, 2H), 2.31-2.23 (m, 8H), 1.88-1.84 (m, 2H), 1.68-1.56 (m, 3H), 1.09 (t, 3H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(propionyloxy) piperdin-1-ium bromide

[0298] To a stirred solution 1-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)piperidin-3-yl propionate (0.2 g, 0.6281 mmol) in Acetonitrile (15 ml) was added Benzyl bromide (0.4297 g, 2.5124 mmol) in a sealed tube at room temperature and the resulting reaction mixture was stirred at room temperature for 16 h as progress of the reaction was monitored by TLC (10% Methanol in DCM. Visualization: UV). The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure to afford crude product, which was triturated with 1:1 EtOAc:Et.sub.2O (30:30 ml) to afford 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(propionyloxy) piperidin-1-ium bromide (90 mg) (mixture of isomers, Peak-1: 35.75%+Peak-2: 63.34%). Mass (ESI): m/z 409.03 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.05 (d, 1H), 7.60-7.56 (m, 5H), 7.15-7.13 (m, 3H), 5.45-5.25 (m, 1H), 5.05-4.97 (m, 1H), 4.35-4.18 (m, 2H), 4.29 (d, 2H), 3.87-3.52 (m, 4H), 2.44-2.35 (m, 2H), 2.21 (m, 6H), 2.20-1.98 (m, 3H), 1.80-1.6 (m, 1H), 1.04 (t, 3H).

Synthesis of 1-benzyl-3-carbamoyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidin-1-ium bromide

##STR01498##

Synthesis of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxamide [0299] To a stirred solution of 2-chloro-N-(2, 6-dimethylphenyl) acetamide (2.0 g, 10.1183 mmol) in ACN (20.0 ml) was added potassium carbonate (4.195 g, 30.3551 mmol) and the resulting mixture was stirred for 10 min at RT. The reaction mixture was treated with piperidine-3-carboxamide (2.6081 g, 20.2366 mmol) at room temperature, and then heated at 90° C. while stirring for 16 h as progress of the reaction was monitored by TLC (10% MeOH in DCM. Visualization: UV). The reaction mixture was allowed to cool to room temperature, diluted with 70 ml of ethyl acetate and washed with 2×50 ml of water followed by 1×30 ml of brine solution. The organic phase was dried over anhydrous Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure to afford 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-carboxamide (2.5 g) as an off white solid. MS (ESI): m/z 290.25 [M+H].sup.+. .sup.1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.57 (s, 1H), 7.06-7.09 (m, 3H), 5.95 (br s, 1H), 5.45 (br s, 1H), 3.15-3.30 (m, 2H), 2.70-2.90 (m, 3H), 2.45-2.60 (m, 2H), 2.15-2.30 (m, 6), 1.81-1.86 (m, 2H), 1.60-1.72 (m, 2H).

Synthesis of 1-benzyl-3-carbamoyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidin-1-ium bromide

[0300] To a stirred solution of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidine-3-

carboxamide (0.250 g, 0.865 mmol) in ACN (3.0 ml) was added benzyl bromide (0.295 g, 1.730 mmol) and the resulting reaction mixture was heated at 90° C. for 16 h as progress of the reaction was monitored by TLC (10% MeOH in DCM, Visualization: UV). The reaction mixture was directly concentrated under reduced pressure to afford crude compound which was triturated with 3×10 ml of ethyl acetate to afford 1-benzyl-3-carbamoyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl) piperidin-1-ium bromide (130 mg) as an off white solid (33.18%+65.55%, mixture of isomers). MS (ESI): m/z 380.2 [M].sup.+. .sup.1H NMR (400 MH-DMSO-d6) δ ppm 9.92-10.15 (m, 1H), 7.45-7.60 (m, 6H), 7.16-7.22 (m, 4H), 4.94-5.06 (m, 2H), 4.05-4.29 (m, 2H), 3.41-3.83 (m, 4H), 2.92 (t, 1H), 2.19-2.21 (m, 6H), 1.98-2.08 (m, 3H), 1.50-1.54 (m, 1H). Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(ethyl carbamoyl) piperidin-1-ium bromide

##STR01499##

Synthesis of 3-(ethylcarbamoyl) piperidine-1-carboxylate

[0301] To a stirred solution of 1-(tert-butoxycarbonyl) piperidine-3-carboxylic acid (2 g, 8.722 mmol) in THF (20 mL) was added Et.sub.3N (2.64 g, 26.166 mmol) and ethanamine hydrochloride (1.42 g, 17.444 mmol) followed by HATU (4.97 g, 13.083 mmol) and the reaction mixture was stirred at room temperature for 16 h as progress of the reaction was monitored by TLC (50% EtOAc-Pet-ether, Visualization: Ninhydrine). Upon completion, the reaction mixture was concentrated under reduced pressure, quenched with 2N HCl and extracted with EtOAc (2×200 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated under reduced pressured to afford crude compound (2.2 g) which was purified by column chromatography (eluted with 40% of EtOAc in pet-ether) to afford pure tert-butyl 3-(ethylcarbamoyl) piperidine-1-carboxylate (2.1 g) as a light brown liquid. sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 6.12 (br s, 1H), 3.83 (br s, 2H), 2.80 (S, 5H), 2.26-2.28 (m, 1H), 2.04-1.05 (m, 2H), 1.84-1.85 (m, 1H), 1.46-1.48 (m, 11H), 1.13 (t, 3H). Synthesis of N-ethylpiperidine-3-carboxamide

[0302] To a stirred solution of tert-butyl 3-(ethylcarbamoyl) piperidine-1-carboxylate (2.5 g, 9.752 mmol) in DCM (20 mL) was added TFA (10 mL) at 0° C., and the reaction mixture was stirred at room temperature for 3 h as progress of the reaction was monitored by TLC (10% MeOH-DCM, Visualization: Ninhydrine). The reaction mixture was concentrated under reduced pressure to afford pure N-ethylpiperidine-3-carboxamide TFA salt (2.4 g) as a light brown liquid. LCMS purity: 99.89%, Mass (ESI): m/z 157.09 [M+H].sup.+.

Synthesis 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-N-ethylpiperidine-3-carboxamide [0303] To a solution of N-ethylpiperidine-3-carboxamide TFA salt (1 g, 3.96 mmol) in ACN (10 mL) was added DIPEA (1.53 g, 11.89 mmol) followed by 2-bromo-N-(2, 6-dimethylphenyl) acetamide (960 mg, 3.96 mmol) and the reaction mixture was stirred at 90° C. for 16 h in a sealed tube as progress of the reaction was monitored by TLC (10% MeOH-DCM, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude compound (1.5 g) which was purified by column chromatography (eluted with 2% of MeOH in DCM) to afford product 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-N-ethylpiperidine-3-carboxamide (1 g,) as a semi solid. LCMS purity: 39%, Mass (ESI): m/z 318.12 [M+H].sup.+. This product carry forwarded to next step without further purification.

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-(ethylcarbamoyl) piperidin-1-ium bromide

[0304] To a stirred solution of 1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-N-ethylpiperidine-3-carboxamide (0.3 g, 0.945 mmol) in acetonitile (2 ml) was added benzyl bromide (0.808 g, 4.724 mmol) and the resulting reaction mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (10% Methanol in DCM. Visualization: UV). The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure to afford crude product which was purified by normal phase flash chromatography (eluted with 10%-15% of

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MeOH in DCM) to afford 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-3-
(ethylcarbamoyl) piperidin-1-ium bromide (100 mg) as a white solid. MS (ESI): m/z 408.19
[M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.15 (s, 1H), 7.98 (t, 1H), 7.60-7.53
(m, 5H), 7.18-7.12 (m, 3H), 5.01-5.00 (m, 2H), 4.22 (s, 2H), 3.73-3.66 (m, 2H), 3.51-3.42 (m, 2H),
3.13-3.04 (m, 2H), 2.9-2.78 (m, 1H), 2.21 (s, 6H), 2.02-1.98 (m, 3H), 1.54-1.51 (m, 1H), 0.99 (t,
3H).
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[0305] The following examples were prepared from 1-(tert-butoxycarbonyl) piperidine-3carboxylic acid, 2-bromo-N-(2, 6-dimethylphenyl) acetamide and benzyl bromide following procedures described for the synthesis of compound 54A. Products were purified by normal phase flash chromatography or reverse phase prep. HPLC.

TABLE-US-00011 Compound # Structure MS (ESI): m/z 55A [01500] embedded image 394.35 [M].sup.+ 56A [01501] embedded image 422.2 [M].sup.+ 57A [01502] embedded image 422.2 [M].sup.+ 58A [01503] embedded image 436.24 [M].sup.+ 59A [01504] embedded image 436.3 [M].sup.+ 60A [01505] embedded image 448.3 [M].sup.+ 61A [01506] embedded image 462.3 [M].sup.+ 62A [01507] embedded image 434.3 [M].sup.+ 63A [01508] embedded image 448.3 [M].sup.+ 64A [01509] embedded image 462.3 [M].sup.+ 65A [01510] embedded image 408.2 [M].sup.+ 66A [01511] embedded image 436.3 [M].sup.+. 67A [01512] embedded image 464.3 [M].sup.+ Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-4-(propoxycarbonyl)-1, 4diazepan-1-ium bromide ##STR01513##

Synthesis of 1-(tert-butyl) 4-propyl 1, 4-diazepane-1, 4-dicarboxylate

[0306] To a stirred solution of tert-butyl 1,4-diazepane-1-carboxylate (0.5 g, 2.496 mmol) in THF (5 ml) was added carbonyl diimidazole (1.21 g, 7.488 mmol, 3.0 eq) and TEA (0.758 g, 7.488 mmol) followed by 1-propanol (0.449 g, 7.488 mmol) at 0° C. The resulting reaction mixture was stirred at 80° C. for 16 h as progress of the reaction was monitored by TLC (30% EtOAc-Hexane, Visualization: PMA,). The reaction mixture was concentrated under reduced pressure to afford crude product which was diluted with EtOAc (150 ml) and washed with water (3×30 ml). The organic phase was dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford 1-(tert-butyl) 4-propyl 1, 4-diazepane-1, 4-dicarboxylate (0.655 g). MS (ESI): m/z 287.19 [M+H].sup.+.

Synthesis of propyl 1, 4-diazepane-1-carboxylate

[0307] A solution of 4M Dioxane.Math.HCl (10 ml) was added to 1-(tert-butyl) 4-propyl 1, 4diazepane-1, 4-dicarboxylate (0.65 g, 2.269 mmol, 1.0 eq) at 0° C. and the resulting reaction mixture was stirred at room temperature for 16 h as progress of the reaction was monitored by TLC (10% Methanol in DCM, Visualization: PMA). The reaction mixture was concentrated under reduced pressure to afford propyl 1, 4-diazepane-1-carboxylate hydrochloride salt (0.41 g) as pale yellow gummy solid. MS (ESI): m/z 187.12 [M+H].sup.+.

Synthesis of propyl 4-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1, 4-diazepane-1-carboxylate [0308] To a stirred solution of 2-chloro-N-(2,6-dimethylphenyl) acetamide (0.4 g, 2.023 mmol) in ACN (10 ml) was added and DIPEA (0.522 g, 4.046 mmol) and propyl 1,4-diazepane-1carboxylate hydrochloride salt (0.376 g, 2.023 mmol) at 0° C. The resulting reaction mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (50% EtOAc-Hexane, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford residue which was diluted with EtOAc (100 ml) and washed with water (60 ml), dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure. The resulting crude product was purified by normal phase flash chromatography (eluted with 10%-50% of EtOAc in Pet ether) to afford propyl 4-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-1, 4-diazepane-1-carboxylate (0.25) g) as a white solid. MS (ESI): m/z 348.69 [M+H].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.19 (s, 1H), 7.00 (s, 3H), 3.96-3.91 (m, 2H), 3.50-3.43 (m, 4H), 3.25 (s, 2H), 2.80-2.65 (m,

4H), 2.13 (s, 6H), 1.84-1.81 (m, 2H), 1.60-1.53 (m, 2H), 0.90-0.85 (m, 3H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-4-(propoxycarbonyl)-1, 4-diazepan-1-ium bromide

[0309] To a stirred solution of propyl 4-(2-((2,6-dimethylphenyl) amino)-2-oxoethyl)-1,4-diazepane-1-carboxylate (0.25 g, 0.719 mmol) in ACN (5 ml) was added benzyl bromide (0.419 g, 2.876 mmol) at room temperature and the resulting reaction mass was stirred at 90° C. for 16 h ase progress of the reaction was monitored by TLC (10% Methanol in DCM, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude product, which was triturated with Ethyl acetate (40 ml) to afford 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-4-(propoxycarbonyl)-1, 4-diazepan-1-ium bromide (122.1 mg) as a white solid. Mass (ESI): m/z 438.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.99 (s, 1H), 7.61-7.53 (m, 5H), 7.18-7.11 (m, 3H), 5.00 (s, 2H), 4.29-4.16 (m, 2H), 4.01-3.56 (m, 10H), 2.32-2.30 (m, 2H), 2.21 (s, 6H), 1.62-1.57 (m, 2H), 0.92-0.88 (m, 3H).

Synthesis of 1-benzyl-1-(2-((2-fluoro-6-methylphenyl)amino)-2-oxoethyl)azepan-1-ium bromide ##STR01514##

Synthesis of 2-bromo-N-(2-fluoro-6-methylphenyl)acetamide

[0310] To a solution of 2-flouro 6-methyl aniline (3.0 g, 23.980 mmol) in water (30.0 ml) was cooled to 0° C. and bromo acetyl bromide (29 g, 143.884 mmol) was added. The resulting reaction mixture was stirred for 16 h at rt as progress of the reaction was monitored by TLC (50% EtOAc in petether, Visualization: UV). The reaction mixture was basified with NaCO.sub.3, stirred for 20 min, filtered, washed with water (100 ml) followed by pet ether (50 mL) and dried to afford crude compound 2-bromo-N-(2-fluoro-6-methylphenyl)acetamide (2.8 g) as an off white solid MS (ESI): m/z 246.08 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d6) δ ppm 9.95 (s, 1H), 7.18 (d, 3H), 4.15 (s, 2H), 2.20 (s, 3H).

Synthesis of 2-(azepan-1-yl)-N-(2-fluoro-6-methylphenyl)acetamide

[0311] To a stirred solution of 2-bromo-N-(2-fluoro-6-methylphenyl) acetamide (4.0 g, 16.254 mmol) in ACN (40 ml) was added potassium carbonate (2.243 g, 48.762 mmol) at room temperature and the mixture stirred for 10 min. Next, azepane (3.225 g, 32.509 mmol) was added and the reaction mixture was stirred for 16 h at room temperature as progress of the reaction was monitored by TLC (50% EtOAc in petether, Visualization: UV). The reaction mixture was diluted with ethyl acetate (100 ml), washed with water (2×50 ml), dried over sodium sulphate, filtered and concentrated under reduced pressure. Crude compound was triturated with n-pentane (3×30 ml) to afford 2-(azepan-1-yl)-N-(2-fluoro-6-methylphenyl) acetamide (2.2 g) as an off-white solid. MS (ESI): m/z 264.34 [M].sup.+. .sup.1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.88 (s, 1H), 7.26 (s, 1H), 7.10-7.16 (m, 1H), 6.93-7.03 (m, 1H), 3.31 (s, 2H), 2.82 (t, 4H), 2.27 (s, 3H), 1.58-1.73 (m, 8H).

Synthesis of 1-benzyl-1-(2-((2-fluoro-6-methylphenyl)amino)-2-oxoethyl)azepan-1-ium bromide [0312] To a stirred solution of 2-(azepan-1-yl)-N-(2-fluoro-6-methylphenyl)acetamide (0.50 g, 1.89 mmol) in ACN (5.0 mL) was added benzyl bromide (1.9411 g, 11.35 mmol) at room temperature and the resulting reaction mixture was heated to 80° C. for 16 h as progress of the reaction was monitored by TLC (10% MeOH in DCM, Visualization: UV). The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford crude compound which was triturated with a solution of 1:1 EtOAc/pet ether (3×10 mL) to afford product 1-benzyl-1-(2-((2-fluoro-6-methylphenyl)amino)-2-oxoethyl)azepan-1-ium bromide (200 mg). MS (ESI): m/z 355.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d6) δ ppm 10.19 (s, 1H), 7.64 (t, 2H), 7.51-7.57 (m, 3H), 7.27-7.32 (m, 1H), 7.17 (t, 2H), 4.88 (s, 2H), 4.11 (s, 2H), 3.78 (q, 2H), 3.51-3.56 (m, 2H), 2.27 (s, 3H), 1.96 (s, 4H), 1.66 (s, 4H).

[0313] The following examples were prepared from bromo acetyl bromide, benzyl bromide, azepane and the appropriate aniline following procedures described for the synthesis of compound 69A.

TABLE-US-00012 MS Compound (ESI): # Structure m/z 70A [01515] embedded image 365.2 [M].sup.+ 71A [01516] embedded image 367.3 [M].sup.+ 72A [01517] embedded image 362.2 [M].sup.+ 73A [01518] embedded image 405.2 [M].sup.+ 74A [01519] embedded image 379.2 [M].sup.+ 75A [01520] embedded image 379.2 [M].sup.+ 76A [01521] embedded image 413.2 [M].sup.+ 77A [01522] embedded image 381.3 [M].sup.+ 78A [01523] embedded image 408.2 [M].sup.+

Synthesis of 1-benzyl-1-(2-((2-hydroxy-6-methylphenyl) amino)-2-oxoethyl) azepan-1-ium formate

##STR01524##

1-benzyl-1-(2-((2-hydroxy-6-methylphenyl) amino)-2-oxoethyl) azepan-1-ium [0314] To a stirred solution of 1-benzyl-1-(2-((2-methoxy-6-methylphenyl) amino)-2-oxoethyl) azepan-1-ium bromide (1 g, 2.235 mmol) in DCM (25 ml) was added BBr.sub.3 (2.239 g, 8.94 mmol) at 0° C. The resulting reaction mixture was stirred for 16 h at room temperature as progress of the reaction mixture was monitored by TLC (10% MeOH in DCM, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude product which was purified by normal phase flash chromatography (eluted with 6% MeOH in DCM). gradient. Pure fractions were concentrated under reduced pressure to afford 1-benzyl-1-(2-((2-hydroxy-6-methylphenyl) amino)-2-oxoethyl) azepan-1-ium bromide (0.9 g) as an off white solid. MS (ESI): m/z 353.21 [M].sup.+. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ ppm 9.82 (s, 1H), 9.59 (s, 1H), 7.73-7.71 (m, 2H), 7.59-7.49 (m, 3H), 7.07-7.02 (t, 1H), 6.77-6.70 (m, 2H), 4.88 (s, 2H), 4.06 (s, 2H), 3.77-3.72 (m, 2H), 3.58-3.53 (m, 2H), 2.17 (s, 3H), 2.05-1.9 (m, 4H), 1.66-1.45 (m, 4H). Synthesis of 1-benzyl-1-(2-((2-methyl-6-(propionyloxy) phenyl) amino)-2-oxoethyl) azepan-1-ium bromide

##STR01525##

Synthesis of 1-benzyl-1-(2-((2-methyl-6-(propionyloxy) phenyl) amino)-2-oxoethyl) azepan-1-ium bromide

[0315] Propionic anhydride (5 ml) was added to 1-benzyl-1-(2-((2-hydroxy-6-methylphenyl) amino)-2-oxoethyl) azepan-1-ium bromide (0.4 g, 0.922 mmol) at room temperature and the resulting reaction mixture was heated to 80° C. for 16 h as progress of the reaction mixture was monitored by TLC (10% MeOH in DCM, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude product which was purified by normal phase flash chromatography (eluted with 15% MeOH in DCM). Pure fractions were concentrated under reduced pressure to afford product which was again triturated with diethyl ether (45 ml) to afford 1-benzyl-1-(2-((2-methyl-6-(propionyloxy) phenyl) amino)-2-oxoethyl) azepan-1-ium bromide (95.6 mg) as an off white solid. MS (ESI): m/z 409.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d6) δ ppm 10.16 (s, 1H), 7.66-7.64 (m, 2H), 7.57-7.51 (m, 3H), 7.31-7.27 (t, 1H), 7.22-7.21 (d, 1H), 7.09-7.07 (m, 1H), 4.89 (s, 2H), 4.08 (s, 2H), 3.75-3.71 (m, 2H), 3.51-3.47 (m, 2H), 2.58 (q, 2H), 2.27 (s, 3H), 2.05-1.85 (m, 4H), 1.75-1.55 (m, 4H), 1.12 (t, 3H).

Synthesis of 1-benzyl-1-(2-((2-carbamoyl-6-methylphenyl) amino)-2-oxoethyl) azepan-1-ium bromide

##STR01526##

Synthesis of N, N, 3-trimethyl-2-nitrobenzamide

[0316] To a stirred solution of 3-methyl-2-nitrobenzoic acid (3.0 g, 16.56 mmol) in DMF (30 ml) was added DIPEA (6.42 g, 49.68 mmol) and HATU (9.44 g, 24.84 mmol) followed by dimethyl amine (2 M in THF) (16.56 ml, 33.12 mmol). The resulting reaction mixture was stirred for 16 h at room temperature as progress of the reaction was monitored by TLC (30% EtOAc/pet ether, visualisation: UV). The reaction mixture was poured into ice water and extracted with EtOAc (2×50 ml). The combined extracts were washed with brine (30 ml), dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford the crude product which purified by normal phase flash chromatography (eluted with 20%-80% of EtOAc in pet ether) to afford N, N, 3-

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trimethyl-2-nitrobenzamide (2.2 g) as black liquid. Mass (ESI): m/z 209.09 [M+H].sup.+. .sup.1H
NMR (400 MHz, CDCl.sub.3) δ ppm 7.47-7.43 (m, 1H), 7.36-7.33 (m, 1H), 7.22-7.19 (m, 1H),
3.09 (s, 3H), 2.93 (s, 3H), 2.80 (s, 6H), 2.33 (s, 3H).
Synthesis of 2-amino-N, N, 3-trimethylbenzamide
[0317] To a stirred solution of N, N, 3-trimethyl-2-nitrobenzamide (2 g, 9.605 mmol) in Ethanol
(20 ml) and H.sub.2O (20 ml) was added Fe (3.75 g, 67.235 mmol) and NH.sub.4Cl (3.59 g,
67.235 mmol) at room temperature. The resulting reaction mixture was stirred for 8 h at 80° C. as
progress of the reaction was monitored by TLC (10% EtOAc in pet ether, visualization: UV). The
reaction mixture was filtered through a celite pad and washed with EtOH (2×50 ml) twice. Filtrate
was concentrated under reduced pressure to afford residue which was diluted with water (50 ml)
and extracted with EtOAc (2×50 ml). The combined organic extracts were washed with brine (50
ml), dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product
which was purified by column chromatography (eluted with 10%-40% of EtOAc in pet) to afford
2-amino-N, N, 3-trimethylbenzamide (600 mg). LCMS purity: 98.02%, Mass (ESI): m/z 179.12
[M+H].sup.+. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.26 (s, 1H), 7.06 (s, 1H), 6.97 (d,
1H), 6.66-6.63 (m, 1H), 4.33 (bs, 2H), 3.05 (s, 6H), 2.17 (s, 3H).
Synthesis of 2-(2-bromoacetamido)-N, N, 3-trimethylbenzamide
[0318] To a stirred solution of isopropyl 2-amino-N, N, 3-trimethylbenzamide (0.6 g, 3.366 mmol)
in H.sub.2O (6 ml) was added 2-bromoacetyl bromide (5.34 g, 26.928 mmol) at 0° C. The resulting
reaction mixture was stirred for 16 h at room temperature as progress of the reaction was monitored
by TLC (10% MeOH in DCM, Visualization: UV). The reaction mixture was basified with
saturated Na.sub.2CO.sub.3 at 0° C. to afford precipitated solid which was filtered, washed with
water and dried to afford (2-(2-bromoacetamido)-N, N, 3-trimethylbenzamide (650 mg) as white
solid. LCMS purity: 93.98%, Mass (ESI): m/z 301.12 [M+2].sup.+. .sup.1H NMR (400 MHz,
CDCl.sub.3) δ ppm 8.84 (s, 1H), 7.26-7.07 (m, 3H), 3.93 (s, 2H) 3.09 (s, 3H), 2.93 (s, 3H), 2.21 (s,
3H).
Synthesis of 2-(2-(azepan-1-yl) acetamide)-N, N, 3-trimethylbenzamide
[0319] To a stirred solution of 2-(2-bromoacetamido)-N, N, 3-trimethylbenzamide (0.6 g, 2.005)
mmol) in Acetonitrile (6 ml) was added K.sub.2CO.sub.3 (0.692 g, 5.012 mmol) and Azepane
(0.397 g, 4.01 mmol) at room temperature. The resulting reaction mixture was stirred for 16 h at
80° C. as progress of the reaction was monitored by TLC (10% MeOH in DCM, Visualization:
UV). After completion of reaction on TLC, the reaction mixture was concentrated under reduced
pressure to afford residue which was poured into ice water and extracted with EtOAc (2×25 ml).
The combined organic extracts were washed with brine (50 ml), dried over Na.sub.2SO.sub.4 and
concentrated under reduced pressure to afford (2-(2-(azepan-1-yl) acetamido)-N, N,3-
trimethylbenzamide (600 mg). MS (ESI): m/z 318.27 [M+H].sup.+. .sup.1H NMR (400 MHz,
CDCl.sub.3) δ ppm 9.19 (s, 1H) 7.27-7.25 (m, 1H), 7.20-7.17 (m, 1H), 7.09-7.07 (m, 1H), 3.24 (s,
2H) 3.04 (s, 3H), 2.91 (s, 3H), 2.79-2.76 (t, 4H), 2.26 (s, 3H) 1.71-1.62 (m, 8H).
Synthesis of 1-benzyl-1-(2-((2-(dimethylcarbamoyl)-6-methylphenyl) amino)-2-oxoethyl) azepan-
1-ium bromide
[0320] To a stirred solution of 2-(2-(azepan-1-yl)acetamido)-N,N,3-trimethylbenzamide (0.5 g,
1.575 mmol) in acetonitrile (5 ml) was added benzyl bromide (0.538 g, 3.15 mmol) at room
temperature. The resulting reaction mixture was stirred for 48 h at 80° C. as progress of the
reaction was monitored by TLC (Mobile phase: -10% MeOH in DCM, Rf: 0.47, Visualization:
UV). After consumption of starting material on TLC, the reaction mixture was concentrated under
reduced pressure to afford crude product which was purified by column chromatography (eluted
with 4%-8% of MeOH in DCM) to afford the (1-benzyl-1-(2-((2-(dimethylcarbamoyl)-6-
methylphenyl) amino)-2-oxoethyl) azepan-1-ium bromide (100 mg) as a brown solid. Mass (ESI):
m/z 408.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 10.31 (s, 1H), 7.70-7.68
(m, 2H), 7.56-7.51 (m, 3H), 7.38-7.36 (m, 1H), 7.32-7.28 (m, 1H), 7.19-7.16 (m, 1H), 4.85 (s, 2H),
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4.03 (s, 2H), 3.70-3.66 (m, 2H), 3.47-3.43 (m, 2H), 2.95 (s, 3H), 2.87 (s, 3H), 2.27 (s, 3H), 1.94-1.90 (s, 4H), 1.70-1.65 (s, 4H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylbenzoyl) oxy) ethyl) azepan-1-ium bromide ##STR01527##

Synthesis of intermediate 2-bromoethyl 2, 6-dimethylbenzoate

[0321] To a stirred solution of 2, 6-dimethylbenzoic acid (5 g, 33.29 mmol) in toluene (40 mL) was added 2-bromoethan-1-ol (4.16 g, 33.29 mmol) and a catalytic amount of concentrated H.sub.2SO.sub.4 (0.2 ml). The resulting reaction mixture was refluxed for 16 h using a Dean-Stark condenser as progress of the reaction was monitored by TLC (30% EtOAc in Pet Ether, visualization: UV). After completion reaction, the mixture was cooled to room temperature and concentrated under reduced pressure to afford residue which was diluted with ice water (250 ml) and extracted with EtOAc (3×150 ml). The combined organic extracts were washed with saturated sodium bicarbonate solution (50 ml) and brine (100 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 2-bromoethyl 2, 6-dimethylbenzoate (5.52 g). MS (ESI): m/z 258.82 [M+H+2].sup.+· 1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.22-7.18 (m, 1H), 7.0-7.02 (m, 2H), 4.64 (t, 2H), 3.63 (t, 2H), 2.33 (s, 6H).

Synthesis of intermediate 2-(azepan-1-yl) ethyl 2, 6-dimethylbenzoate

[0322] To a stirred solution of 2-bromoethyl 2, 6-dimethylbenzoate (2.0 g, 7.778 mmol) in ACN (30 ml) was added K.sub.2CO.sub.3 (3.224 g, 23.334 mmol) and azepane (1.157 g, 11.667 mmol). The resulting mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (30% EtOAc in pet ether, Visualization: UV.) The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to afford residue which was diluted with cold water (100 ml) and extracted with EtOAc (3×50 ml). The combined organic extracts were was washed with brine (50 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 2-(azepan-1-yl)ethyl 2,6-dimethylbenzoate (1.80 g) as a brown liquid. MS (ESI): m/z 276.35 [M+H].sup.+· 1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.19-7.15 (m, 1H), 7.03-7.01 (m, 2H), 4.41 (t, 2H), 2.86 (t, 2H), 2.72-2.69 (mt, 4H), 2.33 (s, 6H), 1.65-1.56 (m, 8H). Synthesis of 1-benzyl-1-(2-((2, 6-dimethylbenzoyl) oxy) ethyl) azepan-1-ium bromide [0323] To a stirred solution of 2-(azepan-1-yl) ethyl 2, 6-dimethylbenzoate (300 mg, 1.089 mmol) in ACN (5 ml) was added benzyl bromide (279.3 mg, 1.633 mmol) and the resulting mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (MeOH in DCM, visualization: UV). After consumption of starting material, the reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure to afford crude product, which was triturated with a 1:2 mixture of Et.sub.2O & EtOAc (60 ml) to afford 1-benzyl-1-(2-((2, 6-dimethylbenzoyl) oxy) ethyl) azepan-1-ium bromide (117.4 mg,) as an off white solid. Mass (ESI): m/z 366.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 7.61-7.59 (m, 2H), 7.54-7.48 (m, 3H), 7.29-7.26 (m, 1H), 7.13-7.11 (d, 2H), 4.89 (t, 2H), 4.67 (s, 2H), 3.65-3.45 (m, 6H), 2.28 (s, 6H), 1.83-1.77 (d, 4H), 1.6-1.5 (m, 4H).

Synthesis of 1-benzyl-1-(2-(2, 6-dimethylphenoxy)-2-oxoethyl) azepan-1-ium 2, 2, 2-trifluoroacetate

##STR01528##

Synthesis of intermediate 2, 6-dimethylphenyl 2-bromoacetate

[0324] To a stirred solution of 2, 6-dimethyl phenol (0.5 g, 4.092 mmol) in ACN (5 ml) was added pyridine (0.647 g, 8.184 mmol) and 2-bromoacetyl bromide (1.23 g, 6.138 mmol) at 0° C. and the resulting reaction mixture was stirred at 0° C. for 15 min as progress of the reaction was monitored by TLC (10% EtOAc in Pet ether, Visualization: UV). After consumption of starting, the reaction mixture was diluted with water (20 ml) and extracted with EtOAc (2×25 ml). The combined organic extracts were washed with brine (30 ml), dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford product 2, 6-dimethylphenyl 2-bromoacetate (500 mg) as a pale yellow liquid. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.07 (s, 3H), 4.07 (s, 2H), 2.18 (s,

6H).

Synthesis of intermediate 2,6-dimethylphenyl 2-(azepan-1-yl) acetate

[0325] To a stirred solution of 2, 6-dimethylphenyl 2-bromoacetate (0.5 g, 2.056 mmol) in ACN (5 ml) was added K.sub.2CO.sub.3 (0.71 g, 5.14 mmol) and azepane (0.407 g, 4.112 mmol) at room temperature. The resulting reaction mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (Mobile phase: Ethyl acetate, Visualization: UV). After completion of reaction, the mixture was concentrated under reduced pressure to afford residue which was diluted with ice water (25 ml) and extracted with ethyl acetate (2×100 ml). The combined organic extracts were washed with brine (50 ml), dried over Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford 2, 6-dimethylphenyl 2-(azepan-1-yl) acetate (500 mg) as red liquid. Mass (ESI): m/z 262.09 [M+H].sup.+.

Synthesis of 1-benzyl-1-(2-(2, 6-dimethylphenoxy)-2-oxoethyl) azepan-1-ium 2, 2, 2-trifluoroacetate

[0326] To a stirred solution of 2, 6-dimethylphenyl 2-(azepan-1-yl) acetate (0.45 g, 1.721 mmol) in ACN (4.5 ml) was added benzyl bromide (0.588 g, 3.442 mmol) and the resulting reaction mixture was stirred at 90° C. for 16 h as progress of the reaction was monitored by TLC (Mobile phase: 10% MeOH in DCM, Visualization: UV). After completion of reaction, the reaction mixture was concentrated under reduced pressure to afford the crude product which was purified by the reverse phase Prep HPLC (Column: X select phenyl hexyl C18 (19*250), 5 um; Mobile phase A: 0.1% TFA (Aq); Mobile phase B-Acetonitrile; Flow: 15 ml/min; Method: 0/20, 2/20, 10/50, 15/75, 15.2/98, 19/98, 19.2/20, 23/20; Solubility: ACN+Water+THF; Temperature: ambient). [0327] The collected pure fractions were lyophilized to afford 1-benzyl-1-(2-(2, 6-dimethylphenoxy)-2-oxoethyl) azepan-1-ium 2, 2, 2-trifluoroacetate (56 mg) as pale yellow solid. MS (ESI): m/z 352.2 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 7.60-7.53 (m, 5H), 7.21-7.16 (m, 3H), 4.87 (s, 2H), 4.71 (s, 2H), 3.90-3.84 (m, 2H), 3.66-3.60 (m, 3H), 2.19 (s, 6H), 2.07-1.91 (m, 4H), 1.40-1.20 (s, 4H).

Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino) ethyl) azepan-1-ium trifluoroacetate ##STR01529##

Synthesis of intermediate 1-(azepan-1-yl)-2-chloroethan-1-one

[0328] To a cooled solution of azepane (10 g, 100.826 mmol) (0° C.) in ACN (100 mL) was added TEA (30.6 g, 302.478 mmol) followed by 2-chloroacetyl chloride (13.6 g, 120.98 mmol). The reaction mixture was stirred at room temperature for 3 h as progress of the reaction was monitored by TLC (Mobile phase: EtOAc, visualization by UV and ninhydrin). The reaction was guenched with saturated aq. NaHCO.sub.3 and extracted with EtOAc (2×250 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered, and concentrated under reduced pressure to afford crude product which was purified by column chromatography (eluted with 30% EtOAc in pet ether) to afford 1-(azepan-1-yl)-2-chloroethan-1one (8.5 g) as a brown liquid. Mass (ESI): m/z 175.89 [M+1].sup.+. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 4.08 (s, 2H), 3.49-3.55 (m, 4H), 1.72-1.79 (m, 4H), 1.58-1.63 (d, 4H). Synthesis of intermediate 1-(azepan-1-yl)-2-((2, 6-dimethylphenyl) amino) ethan-1-one [0329] To a stirred solution of 1-(azepan-1-yl)-2-chloroethan-1-one (5 g, 28.464 mmol) in ACN (40 mL) was added DIPEA (11.03 g, 85.392 mmol) followed by 2, 6-dimethylaniline (5.17 g, 42.696 mmol) and the resulting reaction mixture was stirred at 90° C. for 3 days as progress of the reaction was monitored by TLC (Mobile phase: 30% EtOAc in pet-ether, Visualization: UV). The reaction mixture was quenched with saturated aq. NaHCO.sub.3 (20 ml) and extracted with EtOAc (2×250 ml). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure to afford crude product (8.5 g) which was purified by column chromatography (eluted with 30% of EtOAc in pet-ether) to afford 1-(azepan-1-yl)-2-((2, 6-dimethylphenyl) amino) ethan-1-one (2.7 g, 36%) as a brown solid. Mass (ESI): m/z 261.18 [M+1].sup.+. .sup.1H NMR (400 MHz, cdcl3) δ ppm 6.97-7.99 (m, 2H), 6.76-

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1.73 (m, 4H), 1.55-1.59 (m, 5H).
Synthesis of intermediate N-(2-(azepan-1-yl) ethyl)-2, 6-dimethylaniline
[0330] A solution of 1-(azepan-1-yl)-2-((2, 6-dimethylphenyl) amino) ethan-1-one (1.5 g, 5.760
mmol) in THF (15 mL) was cooled to 0° C. and LAH (2 M in THF, 5.76 mL, 11.521 mmol) was
added drop-wise with stirring. The resulting mixture was then stirred at room temperature for 15 h
as progress of the reaction was monitored by TLC (Mobile phase: 30% EtOAc in pet-ether,
Visualization: UV). The reaction mixture was guenched with saturated ag. NH.sub.4Cl solution at
0° C., and then allowed to stir at R.sup.T for 1 h. The precipitated solid was removed by filtration
and the filtrate was concentrated under reduced pressure to afford N-(2-(azepan-1-yl) ethyl)-2, 6-
dimethylaniline (1.4 g) as a pale yellow liquid. Mass (ESI): m/z 247.23 [M+1].sup.+.
Synthesis of intermediate t-butyl (2-(azepan-1-yl) ethyl) (2, 6-dimethylphenyl) carbamate
[0331] To a stirred solution of N-(2-(azepan-1-yl) ethyl)-2, 6-dimethylaniline (800 mg, 3.247)
mmol) in a 1:1 mixture of 1, 4-dioxane and H.sub.2O (10 ml) was added NaOH (260 mg, 6.494
mmol) followed by (Boc).sub.2O (2.12 g, 9.741 mmol) and the resulting mixture was stirred at rt
for 24 h as progress of the reaction was monitored by TLC (Mobile phase: 30% EtOAc in pet-ether,
detection: ninhydrin). The reaction mixture was diluted with water (75 mL), extracted with EtOAc
(2×75 mL) and the combined organic extracts were washed with brine (70 mL), dried over
anhydrous Na.sub.2SO.sub.4, filtered, and concentrated under reduced pressure. The crude product
was purified by column chromatography (eluted with 15% of EtOAc in pet-ether) to afford tert-
butyl (2-(azepan-1-yl) ethyl) (2, 6-dimethylphenyl) carbamate (600 mg) as a colour less liquid.
Mass (ESI): m/z 347.24 [M+1].sup.+. .sup.1H NMR (400 MHz, DMSO-d6) δ ppm 7.00-7.26 (m,
3H), 3.47-3.57 (m, 2H), 2.60-2.73 (m, 6H), 2.30 (s, 6H), 2.22 (t, 11H), 1.57 (s, 6H).
Synthesis of intermediate 1-benzyl-1-(2-((tert-butoxycarbonyl) (2, 6-dimethylphenyl) amino) ethyl)
azepan-1-ium chloride
[0332] To a stirred solution of tert-butyl (2-(azepan-1-yl) ethyl)(2, 6-dimethylphenyl) carbamate
(300 mg, 0.865 mmol) in ACN (4 mL) was added benzyl chloride (328 mg, 2.595 mmol) and the
resulting reaction mixture was stirred at 90° C. for 15 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 1-benzyl-1-(2-((tert-butoxycarbonyl) (2, 6-
dimethylphenyl) amino) ethyl) azepan-1-ium chloride salt (400 mg) as a colour less gum. Mass
(ESI): m/z 437.30 [M+1].sup.+.
Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) amino) ethyl) azepan-1-ium trifluoro acetate
[0333] To a stirred solution of 1-benzyl-1-(2-((tert-butoxycarbonyl) (2, 6-dimethylphenyl) amino)
ethyl) azepan-1-ium chloride (360 mg, 0.634 mmol) was added 4 M HCl in 1, 4-dioxane (3.17 mL,
12.680) at 0° C. The resulting reaction mixture was stirred at rt for 15 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-Bridge C18 (150*25) mm, 10 u; Mobile phase A: 0.1% TFA
in Water (Ag); Mobile phase B: Acetonitrile; Flow: 14 ml/min; Method (T/% of B): 0/20, 2/30,
10/40, 19/40, 19.2/98, 22/98, 22.2/20, 26/20; Solubility: ACN+WATER+THF; Temperature:
Ambient). Pure fractions collected and lyophilized to afford 1-benzyl-1-(2-((2, 6-dimethylphenyl)
amino) ethyl) azepan-1-ium trifluoro acetate (165 mg) as a pale brown solid. Mass (ESI): m/z
337.30 [M].sup.+· LCMS: 99.72%. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 7.41-7.53 (m,
5H), 6.96-7.21 (m, 2H), 6.83 (t, 1H), 4.56 (s, 2H), 3.31-3.53 (m, 8H), 2.27 (s, 6H), 1.82-1.83 (m,
4H), 1.58-1.59 (m, 4H).
Synthesis of 1-benzyl-1-(2-(2, 6-dimethylphenoxy) ethyl) azepan-1-ium bromide
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[0334] To a stirred solution of 2, 6-dimethylphenol (0.500 g, 4.096 mmol) in acetonitrile (8.0 mL)

##STR01530##

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

6.80 (m, 1H), 4.78 (s, 1H), 3.81 (s, 2H), 3.33-3.58 (m, 2H), 3.30-3.32 (m, 2H), 2.34 (s, 6H), 1.72-

was added potassium carbonate (1.698 g, 12.288 mmol) and 1, 2-dibromoethane (3.847 g, 20.480 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 ther, Visualization: UV). The reaction mixture was cooled to RT and concentrated under reduced pressure, diluted with water (100 mL) and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine solution (1×50 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. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.00-7.25 (m, 2H), 6.91-6.95 (m, 1H), 4.01-4.10 (m, 2H), 3.65-3.68 (m, 2H), 2.30 (s, 6H).

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

[0335] To a solution of 2-(2-bromoethoxy)-1, 3-dimethylbenzene (200 mg, 0.87 mmol) in acetonitrile (3.0 mL) was added DIPEA (451.2 mg, 3.49 mmol) and azepane (120.2 mg, 1.22 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 (3×20 mL). The combined organic extracts were washed with brine solution (1×20 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 1-(2-(2, 6-dimethylphenoxy) ethyl) azepane (210 mg). .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 6.98-7.00 (m, 2H), 6.88-6.92 (m, 1H), 3.85-3.88 (m, 2H), 2.93-2.96 (m, 2H), 2.75-2.77 (m, 4H), 2.28 (s, 6H), 1.59-1.68 (m, 8H).

Synthesis of 1-benzyl-1-(2-(2, 6-dimethylphenoxy) ethyl) azepan-1-ium bromide [0336] To a solution of 1-(2-(2, 6-dimethylphenoxy) ethyl) azepane (100 mg, 0.404 mmol) in acetonitrile (1.5 mL) was added benzyl bromide (0.072 ml, 0.606 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 gummy which was triturated with ethyl acetate (3×5 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].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 7.63-7.65 (m, 2H), 7.49-7.57 (m, 3H), 7.04-7.08 (m, 2H), 6.96-6.98 (m, 1H), 4.72 (s, 2H), 4.29 (t, 2H), 3.52-3.69 (m, 6H), 2.29 (s, 6H), 1.88-1.92 (m, 4H), 1.59-1.62 (m, 4H).

Synthesis of N-(2-(2, 6-dimethylphenyl) amino)-2-oxoethyl)-N, N-diethyl-3-phenylpropan-1-aminium bromide ##STR01531##

Synthesis of intermediate N, N-diethyl-3-phenylpropan-1-amine

[0337] To a stirred solution of (3-bromopropyl) benzene (2 g, 10.04 mmol) in acetonitrile (5 ml) was added diethylamine (1.46 g, 19.96 mmol) at room temperature. The resulting reaction mixture stirred for 16 h at 75° C. as progress of the reaction was monitored by TLC (Mobile phase: 50% EtOAc in pet ether, Visualization by UV). The reaction mixture was allowed to cool to room temperature, quenched with water and extracted with ethyl acetate (2×15 ml). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford N, N-diethyl-3-phenylpropan-1-amine (1.3 g). MS (ESI): m/z 192.25 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3) δ ppm 7.3-7.25 (m, 2H), 7.22-7.15 (m, 3H), 2.6-2.25 (m, 2H), 2.55-2.42 (m, 6H), 1.81-1.75 (m, 2H), 1.0 (t, 6H).

Synthesis of N-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-N, N-diethyl-3-phenylpropan-1-aminium bromide

[0338] To a solution of N, N-diethyl-3-phenylpropan-1-amine (0.2 g, 1.045 mmol) in toluene (5 ml) was added 2-bromo-N-(2, 6-dimethylphenyl) acetamide (0.328 g, 1.354 mmol) and the resulting mixture was heated to reflux for 16 h as progress of the reaction was monitored by TLC

(Mobile phase: 10% MeOH in DCM, visualization: UV). The reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford crude product which was triturated with EtOAc (20 ml) to afford N-(2-((2, 6-dimethylphenyl) amino)-2-oxoethyl)-N, N-diethyl-3-phenylpropan-1-aminium bromide (95 mg) as an off white solid. MS (ESI): m/z 353.45 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 9.9 (s, 1H), 7.45-7.3 (m, 5H), 7.15-7.09 (m, 3H), 4.28 (s, 2H), 3.58 (q, 4H), 3.51-3.45 (m, 2H), 2.68-2.51 (m, 2H), 2.15 (s, 6H), 2.08-2.0 (m, 2H), 1.28 (t, 6H).

Synthesis of N-benzyl-2-((2, 6-dimethylphenyl) sulfonyl)-N, N-diethylethan-1-aminium bromide ##STR01532##

Synthesis of intermediate (2-chloroethyl) (2, 6-dimethylphenyl) sulfane [0339] To a stirred solution of 2, 6-dimethylbenzenethiol (2 g, 14.468 mmol, 1 eq) in ethanol (30 ml) was added NaOH (1.736 g, 43.405 mmol) and 1-bromo-2-chloroethane (4.149 g, 28.937 mmol) at 0° C. The resulting reaction mixture was stirred at RT for 16 h as progress of the reaction mixture was monitored by TLC (Mobile phase: 100% Pet ether, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude residue which was diluted with ethyl acetate (80 ml), washed with water (50 ml×2) and brine, dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crud product. The crude product was purified by flash chromatography (eluted with Pet ether). The collected pure fractions were concentrated under reduced pressure to afford (2-chloroethyl) (2, 6-dimethylphenyl) sulfane (0.500 g) as a colourless liquid. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.085-7.163 (m, 3H), 3.502-3.542 (m, 2H), 2.963-3.003 (m, 2H), 2.544 (s, 6H).

Synthesis of intermediate 2-((2-chloroethyl) sulfonyl)-1, 3-dimethylbenzene [0340] To a stirred solution of (2-chloroethyl) (2, 6-dimethylphenyl) sulfane (0.500 g, 2.491 mmol) in acetic acid (10 ml) was added hydrogen peroxide (33% in H.sub.2O) (0.847 g, 24.910 mmol) at R.sup.T, and the reaction mixture was heated to 110° C. for 16 h as progress of the reaction was monitored by TLC (Mobile phase: 20% Ethyl acetate in pet ether, Visualization: UV). The reaction mixture was diluted with water (60 ml) and extracted with ethyl acetate (70 ml×3). The combined organic extracts were washed with aq. sodium thiosulfate (50 ml×2) and brine solution (50 ml), and then concentrated under reduced pressure to afford crude product which was purified by flash chromatography (eluted with 10% Ethyl acetate in Pet) The collected pure fractions were concentrated under reduced pressure to afford 2-((2-chloroethyl) sulfonyl)-1, 3-dimethylbenzene (0.350 g) as an off white solid. MS (ESI): m/z 232 [M].sup.+. .sup.1H NMR (400 MHz, CDCl3) δ ppm 7.345-7.383 (m, 1H), 7.176-7.195 (m, 2H), 3.815-3.854 (m, 2H), 3.531-3.569 (m, 2H), 2.714 (s, 6H).

Synthesis of intermediate 2-((2, 6-dimethylphenyl) sulfonyl)-N, N-diethylethan-1-amine [0341] To a stirred solution of 2-((2-chloroethyl) sulfonyl)-1, 3-dimethylbenzene (0.300 g, 1.289 mmol) in acetonitrile (10 ml) was added potassium iodide (0.428 g, 2.578 mmol) and diethylamine (0.283 g, 3.867 mmol) at RT. The resulting reaction mixture was heated to 90° C. for 16 h in a sealed tube as progress of the reaction mixture 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 product which was diluted with ethyl acetate (60 ml), washed with water (30 ml×3) and brine (30 ml), dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product which was purified by flash chromatography (eluted with 40% ethyl acetate in Pet ether) The collected pure fractions were concentrated under reduced pressure to afford the desired product 2-((2, 6-dimethylphenyl) sulfonyl)-N, N-diethylethan-1-amine (0.200 g) as an off white solid. MS (ESI): m/z 270.16 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3) δ ppm 7.308-7.346 (m, 1H), 7.153-7.172 (m, 2H), 3.244-3.283 (m, 2H), 2.947-2.985 (m, 2H), 2.716 (s, 6H), 2.437-2.490 (m, 4H), 0.937-0.973 (m, 6H).

Synthesis of N-benzyl-2-((2, 6-dimethylphenyl) sulfonyl)-N, N-diethylethan-1-aminium bromide [0342] To a stirred solution of 2-((2, 6-dimethylphenyl) sulfonyl)-N, N-diethylethan-1-amine

(0.100 g, 0.371 mmol) in acetonitrile (5 ml) was added benzyl bromide (0.127 g, 0.742 mmol) and the resulting reaction mixture was heated to 90° C. for 16 h as progress of the reaction mixture was monitored by TLC (Mobile phase: 10% MeOH in DCM, Visualization: UV). The reaction mixture was concentrated under reduced pressure to afford crude which was triturated with EtOAc (20 ml) and n-pentane (10 ml) to afford N-benzyl-2-((2, 6-dimethylphenyl) sulfonyl)-N, N-diethylethan-1aminium bromide (0.060 mg) as an off white solid. MS (ESI): m/z 360.0 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 7.475-7.552 (m, 6H), 7.347-7.366 (d, 2H), 4.604 (s, 2H), 3.925-3.965 (m, 2H), 3.520-3.560 (m, 2H), 3.243-3.288 (m, 4H), 2.676 (s, 6H), 1.235-1.312 (m, 6H). Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) sulfonyl) ethyl) azepan-1-ium bromide ##STR01533##

Synthesis of intermediate (2-((2, 6-dimethylphenyl) sulfonyl) ethyl)

[0343] To a stirred solution of 2-((2-chloroethyl)sulfonyl)-1, 3-dimethylbenzene (1.0 g, 4.2970 mmol) in ACN (10.0 ml) was added azepane (0.639 g, 6.4455 mmol) and potassium iodide (1.426 g, 8.5940 mmol). The resulting reaction mixture was heated to reflux for 16 h as progress of the reaction was monitored by TLC (Mobile phase: 30% EtOAc in pet ether, visualization: UV). The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (2×50 ml) and brine (1×50 mL). The organic phase was then, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford crude compound which was triturated with 2×10 ml of n-pentane to afford (2-((2, 6-dimethylphenyl) sulfonyl) ethyl) azepane (180 mg) as an off white solid. MS (ESI): m/z 295.44 [M+H]. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.34 (t, 1H), 7.17 (d, 2H), 3.1-3.8 (m. 6H), 2.71 (d, 6H), 1.57-1.82 (m, 10H), 2.71 (d, 6H). Synthesis of 1-benzyl-1-(2-((2, 6-dimethylphenyl) sulfonyl) ethyl) azepan-1-ium bromide [0344] To a stirred solution of 1-(2-((2, 6-dimethylphenyl) sulfonyl) ethyl) azepane (0.550 g, 1.864 mmol) in ACN (6.0 ml) was added benzyl bromide (0.637 g, 3.728 mmol) and the resulting reaction mixture was heated to reflux for 48 h 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 to afford crude compound which was triturated with 3×10 ml of ethyl acetate to afford 1-benzyl-1-(2-((2, 6-dimethylphenyl) sulfonyl) ethyl) azepan-1-ium bromide (80 mg) as an off white solid. MS (ESI): m/z 386.40 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 7.5-7.63 (m, 6H), 7.44 (d, 2H), 4.59-4.65 (d, 2H), 4.06-4.15 (m, 2H), 3.49-3.55 (m, 6H), 2.696 (s, 6H), 1.817-1.95 (m, 4H), 1.569-1.65 (m, 4H). Synthesis of 1-benzyl-1-(1-(2,6-dimethylphenyl)-2-oxopyrrolidin-3-yl)piperidin-1-ium bromide ##STR01534##

Synthesis of 3-bromo-1-(2, 6-dimethylphenyl) pyrrolidin-2-one

[0345] A stirred solution of 2, 6-dimethylaniline (1.0 g, 8.252 mmol) in ACN (20 ml) was treated with K.sub.3PO.sub.4 (1.751 g, 8.252 mmol) and 2, 4-dibromobutanoyl chloride (2.181 g, 8.252 mmol) at 0° C., and the reaction mixture was stirred at RT for 1 h. After 1 h, the resulting reaction mixture was treated with 50% NaOH aq. solution (1.650 g in 3.32 mL water) and the reaction mixture was stirred at R.sup.T for another 1 h as progress of the reaction mixture was monitored by TLC (Mobile phase: 50% Ethyl acetate in pet ether, Visualization: UV). After completion, the reaction mixture was filtered to remove inorganic salts and the filtrate was dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product as a colourless gummy. The crude product was triturated with n-pentane (30 ml) to afford 3-bromo-1-(2, 6dimethylphenyl) pyrrolidin-2-one (1.5 g). MS (ESI): m/z 268.03 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3) δ ppm 7.18-7.14 (m, 1H), 7.10-7.08 (m, 2H), 4.56-4.54 (m, 1H), 3.92-3.86 (m, 1H), 3.51-3.46 (m, 1H), 2.84-2.78 (m, 1H), 2.52-2.47 (m, 1H), 2.29 (s, 3H), 2.19 (s, 3H). Synthesis of 1-(2, 6-dimethylphenyl)-3-(piperidin-1-yl) pyrrolidin-2-one [0346] To a stirred solution of 3-bromo-1-(2, 6-dimethylphenyl) pyrrolidin-2-one (0.300 g, 1.118

mmol) in ACN (10 ml) was added piperidine (0.114 g, 1.342 mmol) and DIPEA (0.578 g, 4.475 mmol) at RT and the resulting mixture was heated to 90° C. for 16 h 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 concentrated under reduced pressure to afford crude product which was diluted with DCM (70 ml) and washed with water (40 ml×3) and brine (40 ml). The organic layer was dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford 1-(2, 6-dimethylphenyl)-3-(piperidin-1-yl) pyrrolidin-2-one (0.220 g). MS (ESI): m/z 273.35 [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl3) δ ppm 7.14-7.06 (m, 3H), 3.70-3.48 (m, 3H), 2.80-2.89 (m, 2H), 2.60-2.65 (m, 2H), 2.35-2.28 (m, 2H), 2.21 (s, 3H), 2.15 (s, 3H), 1.67-1.60 (m, 4H), 1.50-1.46 (m, 2H).

Synthesis of 1-benzyl-1-(1-(2, 6-dimethylphenyl)-2-oxopyrrolidin-3-yl) piperidin-1-ium bromide [0347] To a stirred solution of 1-(2, 6-dimethylphenyl)-3-(piperidin-1-yl) pyrrolidin-2-one (0.220 g, 0.807 mmol) in ACN (5 ml) was added benzyl bromide (0.276 g, 1.615 mmol) and the resulting mixture was heated at 90° C. for 16 h 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 cooled to RT, diluted with ethyl acetate (20 ml) and stirred for 2 h to afford solid which was filtered and washed with ethyl acetate (40 ml) followed by n-pentane (20 ml) and dried under high vacuum to afford 1-benzyl-1-(1-(2, 6-dimethylphenyl)-2-oxopyrrolidin-3-yl) piperidin-1-ium bromide (0.090 g) as an off white solid. MS (ESI): m/z 363.1 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d6) δ ppm 7.60-7.52 (m, 5H), 7.25-7.16 (m, 3H), 5.58-4.02 (m, 4H), 3.65-3.57 (m, 2H), 3.13-2.92 (m, 3H), 2.67-2.66 (m, 1H), 2.21-1.94 (m, 10H), 1.61-1.23 (m, 3H). [0348] The following example was prepared from 3-bromo-1-(2, 6-dimethylphenyl) pyrrolidin-2-one, azepane and benzyl bromide following procedures described for the synthesis of compound 89A.

TABLE-US-00013 Compound MS (ESI): # Structure m/z 90A [01535] embedded image 391.44 [M].sup.+

Synthesis of 1-benzyl-1-(1-(2, 6-dimethylphenyl)-2-oxopiperidin-3-yl) pyrrolidin-1-ium bromide ##STR01536##

Synthesis of 2, 5-dibromopentanoyl chloride

[0349] To a stirred suspension of 5-bromopentanoyl chloride (5 g, 25.066 mmol) was treated with bromine (2.56 ml, 50.132 mmol) at room temperature and the resulting reaction mixture was then stirred at 100° C. for 2 hours. After 2 h, the reaction was cooled to room temperature and concentrated under reduced pressure to afford crude 2, 5-dibromopentanoyl chloride (7.2 g) which was carry forwarded to next step without further purification.

Synthesis of 3-bromo-1-(2, 6-dimethylphenyl) piperidin-2-one

[0350] A stirred solution of 2, 6-dimethylaniline (2.0 g, 16.504 mmol) and potasium phosphate (3.503 g, 16.504 mmol) in acetonitrile (50 ml) was cooled to 0° C. and 2, 5-dibromopentanoyl chloride (4.594 g, 16.504 mmol) was added dropwise. The resulting reaction mixture was stirred at room temperature for 1 h. After 1 h, 50% NaOH aq. solution (3.3 g, 6.6 ml water) was added to the reaction mixture and the resulting reaction mixture was stirred at room temperature for 1 h as progress of the reaction was monitored by TLC (Mobile phase: 50% EtOAc:Pet ether, Visualization: UV). The reaction mixture was filtered to remove inorganic salts and the filtrate was dried over anhydrous Na.sub.2SO.sub.4 and concentrated under reduced pressure to afford crude product which was purified by column chromatography (eluted with 25%-30% of EtOAc in Pet ether) to afford 3-bromo-1-(2, 6-dimethylphenyl) piperidin-2-one (2.2 g) as an off-white solid. MS ESI): 282.25 m/z, [M+H].sup.+. .sup.1H NMR (400 MHz, CDCl.sub.3) δ ppm 7.15-7.08 (m, 3H), 4.87 (t, 1H), 3.54-3.49 (m, 1H), 3.37-3.34 (m, 1H), 2.51-2.45 (m, 1H), 2.27-2.21 (m, 2H), 2.22-2.10 (m, 6H), 1.94 (m, 1H).

Synthesis of 1-(2, 6-dimethylphenyl)-3-(pyrrolidin-1-yl) piperidin-2-one

[0351] To a solution of 3-bromo-1-(2, 6-dimethylphenyl) piperidin-2-one (0.2 g, 0.709 mmol) and DIPEA (0.366 g, 2.83 mmol) in acetonitrile (10 mL) was added pyrrolidine (0.0655 g, 0.921 mmol) and the resulting reaction mixture was stirred at 90° C. for 16 hours in a sealed tube as progress of

the reaction was monitored by TLC (Mobile phase: 50% EtOAc in pet ether, Visualization: UV). The reaction was concentrated under reduced pressure to afford crude residue which was diluted with water (20 mL) and extracted with ethyl acetate (2×50 mL). The combined organic extracts were dried over anhydrous Na.sub.2SO.sub.4 and concentrated to afford the crude product which was purified by normal phase flash chromatography (eluted with 25%-30% of EtOAc in Pet ether) to afford 1-(2, 6-dimethylphenyl)-3-(pyrrolidin-1-yl) piperidin-2-one (350 mg) as a pale yellow gummy oil. LCMS purity: 75.17%, MS (ESI): 273.43 m/z, [M+H].sup.+. Synthesis of 1-benzyl-1-(1-(2, 6-dimethylphenyl)-2-oxopiperidin-3-yl)pyrrolidin-1-ium bromide [0352] To a stirred solution 1-(2, 6-dimethylphenyl)-3-(pyrrolidin-1-yl) piperidin-2-one (250 mg, 0.9178 mmol) in acetonitrile (10 mL) was added with benzyl bromide (0.2041 g, 1.1931 mmol) and the resulting reaction mixture was stirred at 90° 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 to afford the crude product which was triturated with EtOAc (20 mL×2) to afford 1-benzyl-1-(1-(2, 6dimethylphenyl)-2-oxopiperidin-3-yl) pyrrolidin-1-ium bromide (105 mg) as an off white solid. MS (ESI): m/z 363.4 [M].sup.+. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ ppm 7.64-7.62 (m, 2H), 7.57-7.48 (m, 3H), 7.20-7.13 (m, 3H), 4.78 (m, 3H), 4.03-4.01 (m, 2H), 3.80-3.72 (m, 2H), 3.55-3.50 (m, 1H), 3.41-3.61 (m, 1H), 2.51-2.49 (m, 1H), 2.39-2.35 (m, 1H), 1.21-1.99 (m, 10H), 1.97-1.90 (m, 2H). [0353] The following examples were prepared from 3-bromo-1-(2, 6-dimethylphenyl) piperidin-2one, benzyl bromide and the appropriate azacycloalkane following procedures described for the synthesis of compound 91A. Products were purified by trituration or reverse phase prep. HPLC. TABLE-US-00014 Compound MS (ESI): # Structure m/z 92A [01537] embedded image 377.55 [M].sup.+ 93A [01538] embedded image 391.1 [M].sup.+ [0354] The following examples were prepared from bromo acetyl bromide, benzyl bromide and the

[0354] The following examples were prepared from bromo acetyl bromide, benzyl bromide and the appropriate azacycloalkane and substituted aniline following procedures to prepare compound 69A. TABLE-US-00015 Com- MS pound (ESI): # Structure m/z 94A [01539] embedded image 341.2 [M].sup.+ 95A [01540] embedded image 357.2 [M].sup.+ 96A [01541] embedded image 348.2 [M].sup.+ 97A [01542] embedded image 371.2 [M].sup.+ 98A [01543] embedded image 369.3 [M].sup.+ 99A [01544] embedded image 385.2 [M].sup.+ 100A [01545] embedded image 349.3 [M].sup.+ 101A [01546] embedded image 345.2 [M].sup.+ 102A [01547] embedded image 359.2 [M].sup.+ 103A [01548] embedded image 373.2 [M].sup.+ 104A [01549] embedded image 337.2 [M].sup.+ 105A [01550] embedded image 351.3 [M].sup.+ 106A [01551] embedded image 355.2 [M].sup.+ 107A [01552] embedded image 371.4 [M].sup.+

Example 2—Inhibition of Nav1.7 Current

[0355] Representative compounds of the invention were synthesized according to the described methods and tested for the ability to inhibit voltage-gated sodium channels.

Manual Patch Clamp:

Cell Culture

[0356] NaV1.7 was expressed in HEK293 cells 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.sub.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 μ g/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 μ g/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.sub.2 overnight.

Patch Clamp Solutions & Drugs

[0357] The intracellular solution contained the following (in mM) CsCl 135, NaCl 10, EGTA 10, HEPES 10, MgCl.sub.22, 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.sub.2 1.5, MgCl.sub.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

[0358] 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 M Ω 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 M Ω 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 ms.

Internal Block by Test Compounds

[0359] 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

[0360] 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.sub.baseline). The average peak inward current during the last 2 second of the last 5 Hz train was measured (I.sub.test). The control fraction current remaining was calculated by dividing I.sub.test by I.sub.baseline. On each recording day three cells were tested with control internal solution and the average fraction of current remaining calculated (Ctrl fraction current).

[0361] 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.sub.0% block). To correct for the current change under control conditions, I.sub.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.sub.unblocked). The % block was calculated using the following equation: (1–I.sub.unblocked/(I.sub.0% block*Ctrl fraction current remaining)×100).

[0362] Representative examples of the invention were tested for intracellular inhibition of NaV 1.7. Activity Range is % inhibition at 10 μ M test concentration: "++++" (>950%), "+++" 95-70%, "++" (70-40%) or "+" (<40%). The results are presented in the following Table. TABLE-US-00016 Nav1.7 Intracellular Compound Inhibition 1A +++ 2A ++ 3A ++++ 4A

TABLE-US-00016 Nav1.7 Intracellular Compound Inhibition 1A +++ 2A ++ 3A ++++ 4A +++ 5A +++ 6A +++ 7A +++ 8A +++ 9A ++++ 10A +++ 11A ++++ 12A ++++ 13A +++ 14A +++ 15A ++++ 16A ++++ 17A ++++ 18A +++ 19A ++ 20A ++++ 21A ++++ 22A +++ 23A +++ 24A ++++ 25A ++ 26A +++ 27A +++ 28A ++ 29A +++ 30A ++++ 31A ++++ 37A +++ 39A +++ 40 A ++ 41A +++ 43A +++ 59A +++ 86A ++++

[0363] Representative examples of the invention were tested for intracellular inhibition of NaV 1.7. Activity Range is % inhibition at 3 μ M test concentration: "++++" (>90%), "+++" 90-70%, "++" (70-40%) or "+" (<400%). The results are presented in following Table.

TABLE-US-00017 Nav1.7 Intracellular Compound Inhibition 3A ++++ 4A +++ 5A ++++ 6A +++ 9A +++ 20A ++++ 21A ++++ 22A +++ 24A ++++ 28A + 29A ++++ 30A ++++ 31A ++++ 32A ++++ 33A ++++ 34A +++ 35A ++++ 36A +++ 37A +++ 38A +++ 44A ++++ 45A +++ 46A ++++ 47A ++++ 52A ++++ 53A ++++ 55A ++++ 55A +++ 56A ++ 57A +++ 59A + 62A ++++ 63A ++++ 65A ++++ 66A ++++ 66A ++++ 69A ++++ 70A ++++ 71A +++ 72A ++++ 73A ++++ 74A +++ 75A ++++ 76A ++++ 77A +++ 80A ++++ 81A +++ 82A +++ 85A +++++ 86A ++++ 89A +++ 90A ++++ 91A ++ 93A +++

External Block by Test Compounds

[0364] 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

[0365] 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.sub.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.sub.0% block). To correct for the rundown, I.sub.0% block is subtracted by the (Rate.sub.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.sub.unblocked). The % block was then calculated using the following equation: Fraction current block=1–I.sub.unblocked/(I.sub.0% block–Rate.sub.rundown*5 min).

[0366] Representative examples of the invention were tested for extracellular inhibition of NaV 1.7. Activity Range is % inhibition at 10 μ M test concentration: "++++" (>90%), "+++" 90-70%, "++" (70-40%) or "+" (<40%). The results are presented below.

TABLE-US-00018 Nav1.7 Extracellular Compound Inhibition 3A ++ 4A + 6A + 9A + 33A ++ 35A + 38A + 44A + 46A ++ 47A ++ 53A + 69A + 70A ++ 76A ++ 80A + 81A + 86A + 90A +

Automated Patch Clamp:

Cell Culture

[0367] NaV1.7 was expressed in HEK293 cells 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.sub.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 $\mu g/mL$, IBI Scientific, Peosta, IA) the day before recording.

[0368] Before experiments, cells were washed with DPBS (VWR, Radnor, PA), digested with Detachin (VWR Radnor, PA) and then triturated 10 times in CHO Serum-Free Media (VWR Radnor, PA) to resuspend the cells and to break apart cell aggregates. Cells were counted and the final concentration was set at 2-5 million cells per mL.

Patch Clamp Solutions & Drugs

[0369] The intracellular solution contained the following: 140 mM CsF, 1 mM/5 mM EGTA/CsOH, 10 mM HEPES, 10 mM NaCl, adjusted to pH 7.3 with CsOH, and osmolality to 320 with OSM solution. The external solution contained the following: 145 mM NaCl, 4 mM KCl, 1 mM MgCl2, 2 mM CaCl.sub.2), 10 mM HEPES, 10 mM Glucose, adjusted to pH 7.4 with CsOH and osmolality to 305 with OSM solution. The OSM solution was a normal Ringer solution containing (in mM) NaCl 155, HEPES 10, sucrose, KCl 3.5, CaCl.sub.2) 1.5, MgCl2 1 adjusted to pH 7.4 with NaOH. All 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.

Automated Patch Clamp Protocol

[0370] Automated Patch Clamps were performed on Qube 384 (Sophion Bioscience, Woburn MA) with multihole Qchips at a temperature setting of 22 degrees. The whole cells configuration was formed with default Qube seal and break-in parameter. The membrane potential was held at -100 mV before the voltage protocol began. Two voltage protocols were followed.

[0371] Step 1: Cells were held at -100 mV with a depolarized pulse to -20 mV for 10 ms, the interval was set at 5 s. Currents were corrected by default leak subtraction from every pulse. The duration was set at 5 mins.

[0372] Step 2: Cells were held at -100 mV with a depolarized pulse to -20 mV for 10 ms. The frequency was 5 Hz. Currents were corrected by leak subtraction calculated before step 2. The duration was set at 4 mins.

Internal Block by Test Compounds

[0373] After Step 2, the Qchip was removed from the recording chamber. The internal solution was changed with solutions containing test compounds. Qchips were held at -100 mV without pulsing after being replaced in the recording chamber. The total solution switching time was 8 minutes. After the internal solution exchange, Cells were recorded and step 2 for repeated for 10 minutes. [0374] Data analysis was performed by Sophion Analyzer. Cells were filtered with minimum 50 MOhm seal resistance and minimum 5 nA starting current. The rundown of the currents was corrected with control cells (Non-Drug). The remaining was calculated by averaging last 3 points in the end of experiments. The base line was calculated as the average of last 3 points of Step 2. IC.sub.50 curves were plotted with DR-plots/Hill function (a dose-response plot with a Hill fit). Representative examples of the invention were tested for intracellular inhibition of NaV 1.7 in the automated patch clamp assay. Activity Range is reported as IC.sub.50: "++++" (<0.3 μ M), "+++"

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(0.3-1 \mu M), "++" (1-3 \mu M) or "+" (3-10 \mu M). The results are presented below.
TABLE-US-00019 Nav1.7 Intracellular Compound Inhibition 3 +++ 4 +++ 5 ++ 6 +++ 11
+++ 14 +++ 20 ++ 23 +++ 29 ++++ 30 ++++ 31 +++ 32A +++ 33A +++ 35A ++ 36A + 37A +++
38A ++ 41A + 44A ++++ 45A +++ 46A +++ 47A ++ 48A ++ 49A ++ 50A ++ 51A + 52A ++++
53A +++ 54A +++ 55A +++ 56A ++ 57A +++ 58A ++ 60A ++ 61A + 62A +++ 63A +++ 64A ++
65A +++ 66A ++ 67A ++ 68A +++ 69A +++ 70A +++ 71A +++ 72A +++ 73A +++ 74A +++ 75A
++ 76A ++ 77A +++ 78A + 79A ++ 80A +++ 81A +++ 82A +++ 83A +++ 84A + 85A ++ 86A ++
87A + 88A + 89A ++ 90A +++ 91A ++ 92A ++
External Block by Test Compounds
[0375] After Step 2, the external solution was changed with solutions containing test compounds.
Ochips were held at −100 mV without pulsing. The total solution switching time was 8 minutes.
After the external solution exchange, cells were recorded using the same procedure as step 2 for 10
minutes.
[0376] Data analysis was performed by Sophion Analyzer. Data were corrected with control cells
(Non-Drug). The IC.sub.50 data were plotted with DR-plots/Hill function (a dose-response plot
with a Hill fit). Representative examples of the invention were tested for extracellular inhibition of
NaV 1.7 in the automated patch clamp assay. Activity Range is reported as IC.sub.50: "++++" (<1
\muM, "+++" (1-3 \muM), "++" (3-10 \muM) or "+" (>10 \muM). The results are presented below.
TABLE-US-00020 Nav1.7 Extracellular Compound Inhibition 4 + 5 + 6 + 32A + 35A + 36A +
37A + 38A + 41A + 44A + 45A + 46A ++ 47A +++ 49A ++ 51A ++ 53A + 54A + 55A + 57A ++
58A ++ 62A + 63A ++ 64A ++ 66A + 68A + 69A ++ 75A ++ 77A +++ 80A + 81A + 82A ++ 83A
+++ 86A + 87A + 88A + 89A + 90A ++ 91A + 92A +
Example 3—Membrane Permeability
[0377] The PAMPA assay (pION, Inc., Woburn MA) was used to determine the ability of
compounds of the invention to cross an artificial lipid membrane by passive diffusion. Test
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[0377] The PAMPA assay (pION, Inc., Woburn MA) was used to determine the ability of compounds of the invention to cross an artificial lipid membrane by passive diffusion. Test compounds were dissolved in DMSO (10 mM) and diluted 200-fold in buffer (pION Inc., pH 7.4) to provide 50 uM stock solutions. Buffer (150 μ L) was added to a UV blank plate and stock solutions (150 μ L) were transferred to a UV reference plate. The blank and reference spectrum were read using a spectrophotometer. Stock solutions (200 μ L) were added to the donor plate of the PAMPA sandwich plate and an accept plate painted with GIT lipid (pION Pc, 5 μ L) was placed on top. Buffer (200 μ L) was added to the acceptor plate and the PAMPA sandwich plate was incubated for 4 hours. Aliquots (150 μ L) from the acceptor plate were added to a UV plate and read as acceptor spectrum. Aliquots (150 μ L) of the donor solutions were added to a UV analysis plate and read as donor spectrum. The permeability coefficient of test compounds was calculated using PAMPA ExplorerTM software (version 3.5.0.4) based on the AUC of the reference plate, the donor plate, and the acceptor plate.

[0378] The PAMPA permeability results (10.sup.-6 cm/s) of representative compounds are reported as "+" (<0.1 10.sup.-6 cm/s), "++" (0.1-2.010.sup.-6 cm/s), "+++" (2.0-10.010.sup.-6 cm/s) or "++++" (>10.0 10.sup.-6 cm/s).

TABLE-US-00021 PAMPA Compound (10.sup.-6 cm/s) 2A + 3A + 5A + 6A + 7A + 8A + 9A + 10A + 12A + 13A + 14A + 15A + 16A + 17A + 18A + 19A + 20A + 21A + 23A + 26A + 27A + 30A + 31A + 32A + 33A + 34A + 35A + 36A + 37A + 38A + 39A + 41A + 42A + 44A + 45A + 46A + 47A + 48A + 49A + 50A + 51A + 52A + 53A + 54A + 55A + ++ 56A + 57A + 58A + 59A + 60A + 61A + 62A + 63A + 64A + 65A + 66A + 68A + 69A + + 71A + 72A + 74A + 75A + 76A + 77A + 78A + 79A + 80A + 81A + 82A + 84A + 86A + 89A + + 90A + 91A + 93A + [0379] 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.

[0380] 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

- **1**. A compound represented by Formula (I) ##STR01553## wherein: Y.sup. is a pharmaceutically acceptable anion; R.sup.A, R.sup.B, and R.sup.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.sup.I, CN, NR.sup.JR.sup.K, NR.sup.LC(O)R.sup.M, S(O)R.sup.N, S(O).sub.2R.sup.N, SO.sub.2R.sup.OR.sup.P, SO.sub.2NR.sup.QR.sup.R, SO.sub.3R.sup.S, CO.sub.2R.sup.T; C(O)R.sup.U, and C(O)NR.sup.VR.sup.W; each of R.sup.I, R.sup.J, R.sup.K, R.sup.L, R.sup.M, R.sup.N, R.sup.O, R.sup.P, R.sup.Q, R.sup.R, R.sup.S, R.sup.T, R.sup.U, R.sup.V, and R.sup.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 and R.sup.K or R.sup.V and R.sup.W or R.sup.Q and R.sup.R can 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.sup.A, R.sup.B, and/or R.sup.C can be taken together with the phenyl ring to which they are attached can form a fused bicyclic or tricyclic ring system; X.sup.1 is selected from —CR.sup.XR.sup.Y—, —NR.sup.ZC(O)—, —NR.sup.ZC(O)CR.sup.XR.sup.Y—, —OC(O) —, —SC(O)—, —C(O)NR.sup.1A—, —C(O)O—, —(O)CS—, —NR.sup.1AS(O)—, — S(O)NR.sup.1A—, —NR.sup.1AC(O)NR.sup.1A—, —S(O)— and —S(O).sub.2—; each of R.sup.X, R.sup.Y, R.sup.Z, and R.sup.1A is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, and substituted or unsubstituted alkynyl; each of R.sup.D and R.sup.E is independently selected from H, D, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted cycloalkyl; or R.sup.D and R.sup.E together with the carbon to which they are attached form a substituted or unsubstituted C.sub.3-C.sub.6 cycloalkyl, substituted or unsubstituted heterocyclic; or R.sup.D and R.sup.Z together with the carbon and the —N—C(O) to which they are attached form an optionally substituted 5-8-membered lactam; R.sup.F and R.sup.G together with the N.sup.+ to which they are attached form an optionally substituted heterocyclic ring having zero, one or more nitrogen atoms in addition to the N+; or, each of R.sup.F and R.sup.G is independently selected from substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, and substituted or unsubstituted C.sub.3-C.sub.6 cycloalkyl; and R.sup.H is a substituted or unsubstituted aryl, a substituted or unsubstituted heteroaryl.
- **2**. The compound of claim 1, wherein Y.sup. is bromide, chloride, or iodide.
- **3**. The compound of claim 1, wherein X.sup.1 is —NHC(O)—.
- **4**. The compound of claim 1, wherein R.sup.H is selected from a C.sub.6-10 aryl or a C.sub.5-10 heteroaryl, each optionally substituted with C.sub.1-6 alkane, C.sub.3-C.sub.6 cycloalkyl, heterocyclyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, hydroxyl, amide, ester, sulfonamide, urea, nitrile, or halogen.
- **5**. The compound of claim 1, wherein R.sup.H is a C.sub.6-10 aryl or a 5- to 10-membered

- heteroaryl, each optionally substituted with a substituted or unsubstituted C.sub.1-C.sub.6 alkyl, halo, nitrile, hydroxyl, and alkoxy.
- **6**. The compound of claim 1, wherein each of R.sup.A and R.sup.B is independently selected from H, halogen, C.sub.1-4 alkyl, and NR.sup.JR.sup.K; each of R.sup.J and R.sup.K is independently selected from H or C.sub.1-4 alkyl; and wherein R.sup.C is H, halogen, C.sub.1-4 alkyl, or NR.sup.JR.sup.K.
- 7. The compound of claim 1, wherein R.sup.A, R.sup.B, and R.sup.C are each independently selected from H, D, halogen, OR.sup.I, substituted or unsubstituted C.sub.1-C.sub.4 alkyl, and NR.sup.JR.sup.K; wherein each of R.sup.I, R.sup.J and R.sup.K is independently selected from H and substituted or unsubstituted C.sub.1-C.sub.4 alkyl.
- **8**. The compound of claim 1, wherein each of R.sup.A and R.sup.B is CH.sub.3, and R.sup.C is selected from the group consisting of H, CH.sub.3, halogen, nitrile, methoxy, and ethoxy.
- **9.** The compound of claim 1, wherein R.sup.D is C.sub.1-4 alkyl optionally substituted with halogen, oxygen, C.sub.3-8 cyclic alkyl, aryl, or heteroaryl, and wherein R.sup.E is H, D, or C.sub.1-4 alkyl.
- **10**. The compound of claim 1, wherein R.sup.D and R.sup.E are both hydrogen.
- **11**. The compound of claim 1, wherein R.sup.D is hydrogen and R.sup.E is an alkyl.
- **12**. The compound of claim 1, wherein R.sup.D and R.sup.E are taken together with the carbon to which they are attached to form a C.sub.3-C.sub.6 cycloalkyl.
- **13**. The compound of claim 1, wherein R.sup.F and R.sup.G together with the N.sup.+ to which they are attached form a substituted or unsubstituted five, six, seven-, or eight-membered heterocyclic ring.
- **14**. The compound of claim 1, wherein each of R.sup.F and R.sup.G is independently selected from unsubstituted C.sub.1-C.sub.4 alkyl.
- 15. The compound of claim 1, wherein the compound is selected from the Table below: TABLE-US-00022 Compound # Structure 1A Leembedded image 2A Leembedded image 3A Leembedded image 4A Leembedded image 5A Leembedded image 6A Leembedded image 7A Leembedded image 8A Leembedded image 9A Leembedded image 10A Leembedded image 11A Leembedded image 12A Leembedded image 13A Leembedded image 14A Leembedded image 15A Leembedded image 16A Leembedded image 17A Leembedded image 18A Leembedded image 19A Leembedded image 20A Leembedded image 21A Leembedded image 22A Leembedded image 23A Leembedded image 24A Leembedded image 25A Leembedded image 26A Leembedded image 27A Leembedded image 28 Leembedded image 29 Leembedded image 30A Leembedded image 31A Leembedded image 28 Leembedded image 29 Leembedded image 30A Leembedded image 31A Leembedded image 31A Leembedded image 30A
- 16. The compound of claim 1, wherein the compound is selected from the Table below: TABLE-US-00023 Compound # Structure 1B Lembedded image 2B Lembedded image 3B Lembedded image 4B Lembedded image 5B Lembedded image 6B Lembedded image 7B Lembedded image 8B Lembedded image 9B Lembedded image 10B Lembedded image 11B Lembedded image 12B Lembedded image 13B Lembedded image 14B Lembedded image 15B Lembedded image 16B Lembedded image 17B Lembedded image 18B Lembedded image 19B Lembedded image 20B Lembedded image 21B Lembedded image 22B Lembedded image 23B Lembedded image 24B Lembedded image 25B Lembedded image 26B Lembedded image 27B Lembedded image 30B Lembedded image 31B Lembedded image 31B Lembedded image 30B Lembedded image 31B Lembedded image 31B Lembedded image 30B Lembedded image 31B Lembedded image 31B Lembedded image 30B Lembedded image 31B Lembedded i
- **17**. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
- **18**. The composition of claim 17, wherein said composition is formulated for oral, intravenous, intramuscular, rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, inhalation, vaginal, intrathecal, epidural, or ocular administration.
- **19**. A method for treating pain, cough, itch, or a neurogenic inflammatory disorder in a patient, comprising administering to said patient an effective amount of the compound of claim 1.

- **20**. The method of claim 19, wherein said pain is selected from the group consisting of pain due to back and neck pain, lower back pain, cancer pain, gynecological and labor pain, fibromyalgia, arthritis, rheumatoid arthritis, osteoarthritis, rheumatological pains, orthopedic pains, acute and post herpetic neuralgia and other neuropathic pains (including peripheral neuropathy), sickle cell crises, vulvodynia, peri-anal pain, irritable bowel disease, irritable bowel syndrome, inflammatory bowel disease, oral mucositis, esophagitis, interstitial cystitis, urethritis and other urological pains, dental pain, headaches, trigeminal trophic syndrome, erythromelalgia, abdominal wall pain, chronic abdominal wall pain, allergic rhinitis, muscle pain, rectal pain, Levator ani syndrome, proctalgia fugax, hemorrhoid pain, stomach pain, skin ulcers, stomach ulcers, burn pain, ophthalmic irritation, conjunctivitis (e.g., allergic conjunctivitis), eve redness, dry eve, dry eve syndrome (chronic ocular pain), complex regional pain syndrome, post-surgical ocular pain, postoperative pain, acute postoperative 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).
- **21.** The method of claim 19, wherein said cough is selected from the group consisting of cough in patients with 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.
- 22. The method of claim 19, 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.

 23. The method of claim 19, wherein said neurogenic inflammatory disorder is selected from the group consisting of allergic inflammation, asthma, chronic cough, conjunctivitis, rhinitis, psoriasis, inflammatory bowel disease, interstitial cystitis, arthritis, colitis, contact dermatitis, diabetes, eczema, cystitis, gastritis, migraine headache, rosacea, sunburn, pancreatitis, chronic rhinosinusitis, traumatic brain injury, polymicrobial sepsis, tendinopathies, chronic urticaria, rheumatic disease, acute lung injury, exposure to irritants, inhalation of irritants, pollutants, chemical warfare agents, and atopic dermatitis.
- **24**. The method of claim 19, wherein a compound represented by Formula (I) is used in combination with one or more exogenous large pore receptor agonists.