Bis-Quaternary Ammonium Salts and Methods for Modulating Neuronal Nicotinic Acetylcholine Receptors

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Provided are bis-quaternary ammonium compounds which are modulators of nicotinic acetylcholine receptors. Also provided are methods of using the compounds for modulating the function of a nicotinic acetylcholine receptor, and for the prevention and/or treatment of central nervous system disorders, substance use and/or abuse, and gastrointestinal tract disorders.
Total $[^3]$HJDA overflow (% control) vs. log [GZ 527B] (M)

$IC_{50}=0.05 \mu M (0.005-0.49)$

$n=5$; $I_{max}=100%$

Fractional release (% initial) vs. Time (min)

- Nicotine
- 10-5M
- 10-6M
- 10-7M
- 10-7.5
- 10-8M
BIS-QUATERNARY AMMONIUM SALTS AND METHODS FOR MODULATING NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS

FIELD OF THE INVENTION

The invention relates to bis-quaternary ammonium salts and their use in modulating nicotinic acetylcholine receptors.

BACKGROUND OF THE INVENTION

\(-\)-nicotine (NIC) activates presynaptic and postsynaptic neuronal nicotinic receptors that evoke the release of neurotransmitters from presynaptic terminals and that modulate the depolarization state of the postsynaptic neuronal membrane, respectively. Thus, nicotine produces its effect by binding to a family of ligand-gated ion channels, stimulated by acetylcholine (ACh) or nicotine which causes the ion channel to open and cations to flux with a resulting rapid (millisecond) depolarization of the target cell.

Neuronal nicotinic receptors are composed of two types of subunits, \(\alpha\) and \(\beta\), and assembles as heteromeric receptors with the general stoichiometry of 2\(\alpha\) and 3\(\beta\) or as homomeric receptors with 5\(\alpha\) subunits. Nine subtypes of the \(\alpha\) subunit (\(\alpha_2\) to \(\alpha_{10}\)) and three subtypes of the \(\beta\) unit (\(\beta_2\) to \(\beta_4\)) are found in the central nervous system. The most common nicotinic receptor subtype in the brain is composed of two \(\alpha_4\) and three \(\beta_2\) subunits, i.e., \(\alpha_4\beta_2\). These subunits display different, but overlapping, patterns of expression in the brain. Examples of heteromeric receptor subtypes include \(\alpha_4\beta_2\), \(\alpha_3\beta_2\), \(\alpha_3\beta_4\), \(\alpha_4\beta_3\), \(\alpha_4\beta_5\), \(\alpha_4\beta_6\), \(\alpha_4\beta_4\), \(\alpha_3\beta_2\), and others. The predominant homomeric subtype includes \(\alpha_7\), but other combinations have also been proposed.

For the most part, the actual subunit compositions and stoichiometries of nicotinic receptors in the brain remain to be elucidated. Thus, neuronal nicotinic receptor subtype diversity originates from differences in the amino acid sequence at the subunit level and from the multiple combinations of assemblies of subunits into functional receptor proteins, which affords a wide diversity of pharmacological specificity.

In spite of the extensive diversity in neuronal nicotinic receptor messenger RNA expression, only a limited number of tools are available to study the pharmacology of native receptors. Radioligands are used in many studies. \([\text{H}]\)NIC appears to label the same sites in the brain as \([\text{H}]\)ACh. It has been estimated that over 90% of \([\text{H}]\)NIC binding in the brain is due to association with the heteromeric receptor that is composed of \(\alpha_4\) and \(\beta_2\) subunits. Also abundant in the central nervous system are the homomeric receptors labeled by \([\text{H}]\)methyllycaconitine (MLA), which has high affinity for the \(\alpha_7\) nicotinic receptor subtype. Nicotinic receptor subtypes can be studied using functional assays, such as NIC-evoked neurotransmitter release (e.g., \([\text{H}]\)dopamine (DA) release, \([\text{H}]\)norepinephrine (NE) release, \([\text{H}]\)serotonin (5-HT) release, \([\text{H}]\)gamma-aminobutyric acid (GABA) release and \([\text{H}]\)glutamate release) from superfused rat brain slices. Nicotinic receptors are located in the cell body and terminal areas of these neurotransmitter systems. NIC facilitates neurotransmitter release from nerve terminals.

The structural and functional diversity of central nervous system nicotinic receptors has stimulated a great deal of interest in developing novel, subtype-selective agonists and/or antagonists. Some of these agonists are currently being evaluated in clinical trials for cognitive enhancement and neuroprotective effects, potentially beneficial for disease states such as Alzheimer’s and Parkinson’s disease.

SUMMARY OF INVENTION

In one embodiment, compounds corresponding to the following structure are provided.

\[X_1 \otimes R_2 - R_3 - R_4 \otimes X_2\]

\(X_1\) and \(X_2\) are each independently an organic or inorganic anion.

\(R\) is chosen from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, heterocyclic, substituted heterocyclic, alkoxy, alkylamine and thioalkyl.

\(R_1\) and \(R_2\) are each independently five or six membered rings as shown in formulas (IIA) and (IIB), wherein each ring of \(R_1\) and \(R_2\) has one, two or three nitrogen atoms, each ring of \(R_1\) and \(R_2\) has one quaternized nitrogen, and the ring atoms from \(R_1\) and \(R_2\) which are attached to \(R\) cannot both be nitrogen atoms.

\[A_1\] is carbon or nitrogen, provided that when \(A_1\) joins a ring atom with an unsaturated bond or is a nitrogen, \(R_5\) is absent, and when \(A_1\) joins a ring atom with an unsaturated bond and is a nitrogen, both \(R_5\) and \(R_6\) are absent.

\(A_2\) is carbon or nitrogen, provided that when \(A_2\) joins a ring atom with an unsaturated bond or is a nitrogen, \(R_4\) is absent, and when \(A_2\) joins a ring atom with an unsaturated bond and is a nitrogen, both \(R_4\) and \(R_5\) are absent.

\(A_3\) is carbon or nitrogen, provided when \(A_3\) joins a ring atom with an unsaturated bond or is a nitrogen, \(R_6\) is absent, and when \(A_3\) joins a ring atom with an unsaturated bond and is a nitrogen, both \(R_6\) and \(R_7\) are absent.

\(A_4\) is carbon or nitrogen, provided that when \(A_4\) joins a ring atom with an unsaturated bond or is a nitrogen, \(R_8\) is absent, and when \(A_4\) joins a ring atom with an unsaturated bond and is a nitrogen, both \(R_8\) and \(R_9\) are absent.

\(A_5\) is carbon or nitrogen, provided that when \(A_5\) joins a ring atom with an unsaturated bond or is a nitrogen, \(R_9\) is absent, and when \(A_5\) joins a ring atom with an unsaturated bond and is a nitrogen, both \(R_9\) and \(R_{10}\) are absent.
A' is carbon or nitrogen, provided that when A' joins a ring atom with an unsaturated bond or is a nitrogen, R' is absent, and when A' joins a ring atom with an unsaturated bond and is a nitrogen, both R' is absent. A' is carbon or nitrogen, provided that when A' joins a ring atom with an unsaturated bond or is a nitrogen, R' is absent, and when A' joins a ring atom with an unsaturated bond and is a nitrogen, both R' is absent. A' is carbon or nitrogen, provided that when A' joins a ring atom with an unsaturated bond or is a nitrogen, R' is absent, and when A' joins a ring atom with an unsaturated bond and is a nitrogen, both R' is absent. A' is carbon or nitrogen, provided that when A' joins a ring atom with an unsaturated bond or is a nitrogen, R' is absent, and when A' joins a ring atom with an unsaturated bond and is a nitrogen, both R' is absent. 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of describing and disclosing the methodologies, reagents, and tools reported in the publications that might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

The term “nicotinic acetylcholine receptor” refers to the endogenous acetylcholine receptor having binding sites for acetylcholine which also bind to nicotine. The term “nicotinic acetylcholine receptor” includes the term “neuronal nicotinic acetylcholine receptor.”

The terms “subtype of nicotinic acetylcholine receptor,” and “nicotinic acetylcholine receptor subtype” refer to various subunit combinations of the nicotinic acetylcholine receptor, and may refer to a particular homomeric or heteromeric complex, or multiple homomeric or heteromeric complexes.

The term “agonist” refers to a substance which interacts with a receptor and increases or prolongs a physiological response (i.e. activates the receptor).

The term “partial agonist” refers to a substance which interacts with and activates a receptor to a lesser degree than an agonist.

The term “antagonist” refers to a substance which interacts with and decreases the extent or duration of a physiological response of that receptor.

The terms “disorder,” “disease,” and “condition” are used inclusively and refer to any status deviating from normal.

The term “central nervous system associated disorders” includes any cognitive, neurological, and mental disorders causing aberrant or pathological neural signal transmission, such as disorders associated with the alteration of normal neurotransmitter release in the brain.

The term “lower alkyl” refers to straight or branched chain alkyl radicals having in the range of 1 to 4 carbon atoms.

The term “alkyl” refers to straight or branched chain alkyl radicals having 1 to 19 carbon atoms, and “substituted alkyl” refers to alkyl radicals further bearing one or more substituents including, but not limited to, hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), aryl, heterocyclic, halogen, trifluoromethyl, cyano, nitro, amino, carboxyl, carbamate, sulfonyl, and sulfonamide.

The term “cycloalkyl” refers to cyclic ring-containing moieties containing 3 to 8 carbon atoms, and “substituted cycloalkyl” refers to cycloalkyl moieties further bearing one or more substituents as set forth above.

The term “alkenyl” refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond and having 2 to 19 carbon atoms, and “substituted alkenyl” refers to alkenyl groups further bearing one or more substituents as set forth above.

The term “alkynyl” refers to straight or branched chain hydrocarbyl moieties having at least one carbon-carbon triple bond and having 2 to 19 carbon atoms, and “substituted alkynyl” refers to alkynyl moieties further bearing one or more substituents as set forth above.

The term “aryl” refers to aromatic groups having 6 to 24 carbon atoms, and “substituted aryl” refers to aryl groups further bearing one or more substituents as set forth above.

The term “arylnaphthyl” refers to aryl-substituted naphthyl groups, and “substituted arylnaphthyl” refers to arylnaphthyl groups further bearing one or more substituents as set forth above.

The term “aryllactyl” refers to aryl-substituted lactyl groups, and “substituted aryllactyl” refers to aryllactyl groups further bearing one or more substituents as set forth above.

The term “arylalkyl” refers to aryl-substituted alkyl groups, and “substituted aryalkyl” refers to aryalkyl groups further bearing one or more substituents as set forth above.

The term “arylsulfonyl” refers to aryl-substituted sulfonyl groups, and “substituted arylsulfonyl” refers to arylsulfonyl groups further bearing one or more substituents as set forth above.

The term “arylsulfinyl” refers to aryl-substituted sulfinyl groups, and “substituted arylsulfinyl” refers to arylsulfinyl groups further bearing one or more substituents as set forth above.

The term “arylsulfonyl” refers to aryl-substituted sulfonyl groups, and “substituted arylsulfonyl” refers to arylsulfonyl groups further bearing one or more substituents as set forth above.

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The term “arylsulfonyl” refers to aryl-substituted sulfonyl groups, and “substituted arylsulfonyl” refers to arylsulfonyl groups further bearing one or more substituents as set forth above.
absent, and when $A_1$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_3$ and $R_4$ are absent.

$A_3$ is carbon or nitrogen, provided that when $A_3$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_10$ is absent, and when $A_3$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_4$ is carbon or nitrogen, provided that when $A_4$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_11$ is absent, and when $A_4$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_5$ is carbon or nitrogen, provided that when $A_5$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_12$ is absent, and when $A_5$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_6$ is carbon or nitrogen, provided that when $A_6$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_13$ is absent, and when $A_6$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_7$ is carbon or nitrogen, provided that when $A_7$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_14$ is absent, and when $A_7$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_8$ is carbon or nitrogen, provided that when $A_8$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_15$ is absent, and when $A_8$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_9$ is carbon or nitrogen, provided that when $A_9$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_16$ is absent, and when $A_9$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_{10}$ is carbon or nitrogen, provided that when $A_{10}$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_{17}$ is absent, and when $A_{10}$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_{11}$ is carbon or nitrogen, provided that when $A_{11}$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_{18}$ is absent, and when $A_{11}$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_{12}$ is carbon or nitrogen, provided that when $A_{12}$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_{19}$ is absent, and when $A_{12}$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_{13}$ is carbon or nitrogen, provided that when $A_{13}$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_{20}$ is absent, and when $A_{13}$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_{14}$ is carbon or nitrogen, provided that when $A_{14}$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_{21}$ is absent, and when $A_{14}$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.

$A_{20}$ is carbon or nitrogen, provided that when $A_{20}$ joins a ring atom with an unsaturated bond or is a nitrogen, $R_{25}$ is absent, and when $A_{20}$ joins a ring atom with an unsaturated bond and is a nitrogen, both $R_15$ and $R_16$ are absent.
cane, methyl N-methyl azocane, methyl unsaturated azo-
cane, methyl unsaturated N-methyl azocane, methyl-1-aza-
bicycle [3.2.1] octane, methyl-1-aza-bicycle [2.2.1] heptane, 8-methyl-8-aza-bicycle [3.2.1] octane, and methyl-
1-aza-tricyclo [3.3.1.1[3,13]] decane.

As a further example, when R¹ and R² together with A³ and A⁴, or R¹ and R² together with A³ and A⁴, or R¹ and R² together with A³ and A⁴, or R¹ and R² together with A³ and A⁴, or R¹ and R² together with A³ and A⁴, independently form a three to eight-membered ring, that ring may be a heterocycle containing up to three hetero atoms (for example nitrogen, oxygen or sulfur) in the ring, and further may be substituted with one or more substituents. For example, possible rings include benzene, pyridine, pyran, indene, isoindene, benzofuran, isobenzofuran, benzo[b]thiophene, benzofuran, indole, indolenine, isoindole, cyclopenta[b]pyridine, pyrano[3,4-b]pyridine, indazole, indoxazine, benzoxazole, anthranil, naphthalene, tetrazen, decalin, chromen, coumarin, chroman-4-one, iso-
coumarin, isochromen-3-one, quinoline, isoquinoline, cin-
trifluromethane sulfate, p-toluenesulfonate, benzenesul-
nervous system tissue. In this regard, the compound of

Moreover, the compounds of the invention may act either
at presynaptic sites or postsynaptic sites, for example, at a
postsynaptic acetylcholine receptor containing an α7 sub-
unit. When acting at a postsynaptic site, neurotransmitter
release per se is not altered. Rather, the compounds of the
invention may act by interacting with a postsynaptic ace-

X¹⁸ and X²⁸, for example, include F, Cl, Br, I, NO₂⁻, HSO₄⁻, SO₃²⁻, PO₄³⁻, methanesulfonate, trifluoromethane sulfate, p-toluenesulfonate, benzenesul-
fonic acid, salicylic, propionate, ascorbate, aspartate, fumar-
ate, galacturate, maleate, citrate, glutamate, glycocolate, lact-
te, malate, maleate, tartrate, oxalate, succinate, or similar
pharmaceutically acceptable organic acid addition salts,
including the pharmaceutically acceptable salts listed in the
Journal of Pharmaceutical Sciences volume 66, page 2,
1977, which are hereby incorporated by reference. The
above salt forms may be in some cases hydrates or solvates
with alcohols and other solvents.

In a compound of Formula (I), preferably R¹ and R² are
substituted, six-membered, aromatic rings. More preferably,
R¹ and R² are substituted pyridinium rings, wherein A³, A⁴,
A⁶ or A⁷ is nitrogen.

In a compound of Formula (I), preferably R¹ is absent.

In a compound of Formula (I), preferably R¹ and R² are
substituted pyridinium rings, wherein A³, A⁴, A⁶ or A⁷ is
nitrogen.

In a compound of Formula (I), preferably R¹ and R² are
substituted pyridinium rings, wherein A³, A⁴, A⁶ or A⁷ is
nitrogen.

In any compound of Formula (I), preferably R¹ and R² are
allogens. More preferably, X¹⁸ and X²⁸ are bromide or iodide.

In one embodiment, the compound of Formula (I) is
defined wherein R is (CH₃)₂CH₊, R¹ and R² are pyridinium
rings, A³ is nitrogen, R¹ is methyl, and X¹ and X² are
bromide or iodide.

In another embodiment, the compound of Formula (I) is
defined wherein R is (CH₃)₂CH₊, R¹ and R² are pyridinium
rings, A³ is nitrogen, R¹ is methyl, R¹ is hydrogen or methyl, and X¹ and X² are bromide or iodide.

In a compound of Formula (I), preferably X¹⁸ and X²⁸ are
halogens. More preferably, X¹⁸ and X²⁸ are bromide or iodide.

In one embodiment, the compound of Formula (I) is
defined wherein R is —(CH₃)₂CH₊, R¹ and R² are pyridinium
rings, A³ is nitrogen, R¹ is methyl, X¹ and X² are bromide or iodide.

In another embodiment, the compound of Formula (I) is
defined wherein R is (CH₃)₂CH₊, R¹ and R² are pyridinium
rings, A³ is nitrogen, R¹ is methyl, and X¹ and X² are bromide or iodide.
rotransmitter release. The neurotransmitter affected may include dopamine, norepinephrine, serotonin, gamma-aminobutyric acid, or glutamate. Alternatively, the compound of Formula (I) may act by interacting with a postsynaptic acetylcholine receptor to change the membrane potential of the cell thereby increasing or decreasing the likelihood of firing an action potential, or to alter one or more second messenger systems within the cell so as to decrease or increase the nicotinic cholinergic response.

In another embodiment, the present invention is directed to a method for preventing and/or treating a central nervous system associated disorder comprising administering to a mammalian subject in need thereof a therapeutically effective amount of a compound of Formula (I). In such a method, the compound of Formula (I) may selectively bind to one or more subtypes of nicotinic acetylcholine receptor. The compound of Formula (I) may act as an agonist or partial agonist of nicotinic acetylcholine receptor function. Hence the compound of Formula (I) may increase or prolong the release of a neurotransmitter from a central nervous system tissue. The neurotransmitter affected may include dopamine, norepinephrine, serotonin, gamma-aminobutyric acid, or glutamate. Alternatively, the compound of Formula (I) may act as an antagonist of nicotinic acetylcholine receptor function. Hence the compound of Formula (I) may decrease the extent or duration of the release of a neurotransmitter from a central nervous system tissue. In this regard, the compound of Formula (I) may act by decreasing stimulant-evoked neurotransmitter release. The neurotransmitter affected may include dopamine, norepinephrine, serotonin, gamma-aminobutyric acid, or glutamate. Alternatively, the compound of Formula (I) may act by interacting with a postsynaptic acetylcholine receptor to change the membrane potential of the cell thereby increasing or decreasing the likelihood of firing an action potential, or to alter one or more second messenger systems within the cell so as to decrease or increase the nicotinic cholinergic response.

Central nervous system disorders which may be treated according to the method of the present invention include Alzheimer’s disease, dementia, cognitive dysfunctions (including disorders of attention, focus and concentration), attention deficit disorders, affective disorders, extrapyramidal motor function disorders, Parkinson’s disease, progressive supranuclear palsy, Huntington’s disease, Gilles de la Tourette syndrome, tardive dyskinesia, neuroendocrine disorders, dysregulation of food intake, disorders of nociception, pain, mood and emotional disorders, depression, panic anxiety, psychosis, schizophrenia, or epilepsy.

In yet another embodiment, the present invention is directed to a method for preventing and/or treating substance use and/or abuse comprising administering to a mammalian subject in need thereof a therapeutically effective amount of a compound of Formula (I). In such a method, the compound of Formula (I) may selectively bind to one or more subtypes of nicotinic acetylcholine receptor. The compound of Formula (I) may act as an agonist or partial agonist of nicotinic acetylcholine receptor function. Hence the compound of Formula (I) may increase or prolong the release of a neurotransmitter from a central nervous system tissue. The neurotransmitter affected may include dopamine, norepinephrine, serotonin, gamma-aminobutyric acid, or glutamate. Alternatively, the compound of Formula (I) may act as an antagonist of nicotinic acetylcholine receptor function. Hence the compound of Formula (I) may decrease the extent or duration of the release of a neurotransmitter from a central nervous system tissue. In this regard, the compound of Formula (I) may act by decreasing stimulant-evoked neurotransmitter release. The neurotransmitter affected may include dopamine, norepinephrine, serotonin, gamma-aminobutyric acid, or glutamate. Alternatively, the compound of Formula (I) may act by interacting with a postsynaptic acetylcholine receptor to change the membrane potential of the cell thereby increasing or decreasing the likelihood of firing an action potential, or to alter one or more second messenger systems within the cell so as to decrease or increase the nicotinic cholinergic response.

The compounds of the present invention can be delivered directly or in pharmaceutical compositions along with suitable carriers or excipients, as is well known in the art. For example, a pharmaceutical composition of the invention may include a conventional additive, such as a stabilizer, buffer, salt, preservative, filler, flavor enhancer and the like, as known to those skilled in the art. Exemplary buffers include phosphates, carbonates, citrates and the like. Exemplary preservatives include EDTA, EGTA, BHA, BHT and the like.

An effective amount of such agents can readily be determined by routine experimentation, as can the most effective and convenient route of administration and the most appro-
methyl cellulose, hydroxypropylmethyl-cellulose, sodium tablets or dragee coatings for identification or to characterize formulation. Various formulations and drug delivery systems are available in the art. See, e.g., Gennaro, A. R., ed. (1995) Remington’s Pharmaceutical Sciences.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, nasal, or intestinal administration and parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intracochlear injections. In addition, the agent or composition thereof may be administered sublingually or via a spray, including a sublingual tablet or a sublingual spray. The agent or composition thereof may be administered in a local rather than a systemic manner. For example, a suitable agent can be delivered via injection or in a targeted drug delivery system, such as a depot or sustained release formulation.

The pharmaceutical compositions of the present invention may be manufactured by any of the methods well-known in the art, such as by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. As noted above, the compositions of the present invention can include one or more physiologically acceptable carriers such as excipients and auxiliaries that facilitate processing of active molecules into preparations for pharmaceutical use.

Proper formulation is dependent upon the route of administration chosen. For injection, for example, the composition may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks’ solution, Ringer’s solution, or physiological saline buffer. For transmucosal or nasal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. In a preferred embodiment of the present invention, the present compounds are prepared in a formulation intended for oral administration. For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compositions of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

Pharmaceutical preparations for oral use can be obtained as solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or algicin acid or a salt thereof such as sodium alginate. Also, wetting agents such as sodium dodecyl sulfate may be included.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, t alc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations for oral administration include push-f1t capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

In one embodiment, the compounds of the present invention can be administered transdermally, such as through a skin patch, or topically. In one aspect, the transdermal or topical formulations of the present invention can additionally comprise one or multiple penetration enhancers or other collectors, including agents that enhance migration of the delivered compound. Transdermal or topical administration could be preferred, for example, in situations in which location specific delivery is desired.

For administration by inhalation, the compounds for use according to the present invention are 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 any other suitable gas. In the case of a pressurized aerosol, the appropriate dosage unit may 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 may be formulated. These typically contain a powder mix of the compound and a suitable powder base such as lactose or starch.

Compositions formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilizing and/or dispersing agents. Formulations for parenteral administration include aqueous solutions or other compositions in water-soluble form.

Suspensions of the active compounds may also be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil and synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

As mentioned above, the compositions of the present invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the present compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.
Suitable carriers for the hydrophobic molecules of the invention are well known in the art and include co-solvent systems comprising, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 88% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system is effective in dissolving hydrophobic compounds and produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied. For example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80, the fraction size of polyethylene glycol may be varied, other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone, and other sugars or carbohydrates may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic molecules may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for therapeutic efficacy of such molecules can be determined by a solution utilized. The exact formulation, route of administration, and dosage should be chosen, according to methods known in the art, in view of the specifics of a subject’s condition.

The amount of agent or composition administered will, of course, be dependent on a variety of factors, including the sex, age, and weight of the subject being treated, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician.

The present compositions may, if desired, be presented in a pack or dispenser device containing one or more unit dosage forms containing the active ingredient. Such a pack or device may be, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

These and other embodiments of the present invention will readily occur to those of ordinary skill in the art in view of the disclosure herein, and are specifically contemplated.

EXAMPLES

The invention is further understood by reference to the following examples, which are intended to be purely exemplary of the invention. The present invention is not limited in scope by the exemplified embodiments, which are intended as illustrations of single aspects of the invention only. Any methods that are functionally equivalent are within the scope of the invention. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications fall within the scope of the appended claims.

Example 1

Preparation of 2,2’-(1,12-dodecanediyl)bispyridine

LDA (2M) (20 mL, 40.00 mmol) was added dropwise to a solution of 2-picoline (3.73 g, 40.00 mmol) in THF (60 mL) at -78°C. The mixture was stirred for 30 min and then 1,10-diiododecane (6.31 g, 16.00 mmol) in THF (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 4 hrs. 50% saturated NH4Cl was added to the reaction mixture. The aqueous phase was extracted with ethylacetate (40 mLx3), and the combined organic liquids were washed with 50% saturated brine (40 mLx3) and saturated brine (40 mLx3), dried over anhydrous Na2SO4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes:ethylacetate:2:1 to 1:1) to afford 3.75 g of the title compound. Yield: 72%. 1H NMR (300 MHz, CDCl3) δ 1.13-1.42 (m, 16H), 1.60-1.81 (m, 4H), 2.78 (t, J=7.8 Hz, 4H), 7.08 (ddd, J=7.5, 5.1, 0.6 Hz, 2H), 7.13 (d, J=7.5 Hz, 2H), 7.57 (dt, J=7.5, 1.8 Hz, 2H), 8.52 (dd, J=3–5.1, 0.6 Hz, 2H) ppm; 13C NMR (75 MHz, CDCl3) δ 29.7, 29.75, 29.8, 29.9, 30.2, 38.7, 120.9, 122.8, 136.3, 149.2, 162.5 ppm.
Example 2

Preparation of N,N'-dimethyl-2,2'-((1,12-dodecanediyl)bispyridinium diiodide

2,2'-(1,12-Dodecanediyl)bispyridine (370 mg, 1.14 mmol) was dissolved in acetone (15 mL). Methyl iodide (1.62 g, 11.40 mmol) was added and the mixture was stirred for 48 hrs at room temperature. The precipitate was filtered and washed with diethyl ether. The obtained pale yellow solid was dried under vacuum to give 643 mg of the title compound. Yield: 93%. 1H NMR (300 MHz, CDCl3): δ 7.59 (s, 2H), 7.49 (s, 2H), 4.00 (q, J = 7.8 Hz, 2H), 4.52 (s, 6H), 2.89 (t, J = 7.8 Hz, 2H), 8.91 (d, J = 5.7 Hz, 2H) ppm; 13C NMR (75 MHz, CDCl3): δ 26.5, 28.6, 28.7, 28.9, 31.8, 45.2, 124.9, 127.6, 144.9, 146.2, 158.3 ppm.

Example 3

Preparation of 3,3'-(1,12-dodecanediyl)bispyridine

LDA (2M) (20.40 mL, 40.80 mmol) was added dropwise to a solution of 3-picoline (3.80 g, 40.80 mmol) in THF (60 mL) at -78°C. The mixture was stirred for 30 min and then 1,10-diiododecane (6.31 g, 16.32 mmol) in THF (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 4 hrs. 50% saturated NH4Cl was added to the reaction mixture. The aqueous phase was extracted with ethylacetate (40 mL×2), and the combined organic liquors were washed with 50% saturated brine (40 mL×3) and saturated brine (40 mL), dried over anhydrous Na2SO4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes:ethylacetate 2:1 to 1:1) to afford 3.98 g of the title compound. Yield: 75%. 1H NMR (300 MHz, CDCl3): δ 1.17-1.50 (m, 16H), 1.53-1.70 (m, 4H), 2.59 (t, J = 7.8 Hz, 2H), 8.43 (d, J = 5.1 Hz, 2H), 8.44 (s, 2H) ppm; 13C NMR (75 MHz, CDCl3): δ 29.4, 29.7, 29.8, 29.9, 31.4, 33.3, 123.3, 135.8, 138.4, 147.2, 150.0 ppm.

Example 4

Preparation of N,N'-dimethyl-3,3'-(1,12-dodecanediyl)bispyridinium diiodide

3,3'-(1,12-Dodecanediyl)bispyridine (300 mg, 0.92 mmol) was dissolved in acetone (10 mL). Methyl iodide (1.42 g, 10 mmol) was added and the mixture was stirred for 12 hrs at room temperature. The precipitate was filtered and washed with diethyl ether. The obtained pale yellow solid was dried under vacuum to give 505 mg of the title compound. Yield: 90%. 1H NMR (300 MHz, CD3OD): δ 1.10-1.45 (m, 16H), 1.64-1.82 (m, 4H), 2.89 (t, J = 7.8 Hz, 4H), 4.52 (s, 6H), 8.02 (dd, J = 8.1, 6.0 Hz, 2H), 8.31 (d, J = 8.1 Hz, 2H), 8.84 (d, J = 6.0 Hz, 2H), 9.00 (s, 2H) ppm; 13C NMR (75 MHz, CD3OD): δ 29.0, 29.1, 29.2, 29.3, 30.3, 32.7, 127.7, 142.6, 144.5, 144.6, 144.9 ppm.

Example 5

Preparation of 4,4'-(1,12-dodecanediyl)bispyridine

LDA (2M) (20 mL, 40.00 mmol) was added dropwise to a solution of 4-picoline (3.73 g, 40.00 mmol) in THF (60 mL) at -78°C. The mixture was stirred for 30 min and then 1,10-diiododecane (6.31 g, 16.00 mmol) in THF (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 4 hrs. 50% saturated NH4Cl was added to the reaction mixture. The aqueous phase was extracted with ethylacetate (40 mL×2), and the combined organic liquors were washed with 50% saturated brine (40 mL×3) and saturated brine (40 mL), dried over anhydrous Na2SO4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes:ethylacetate 1:1 to 1:2) to afford 4.16 g of the title compound. Yield: 80%. 1H NMR (300 MHz, CDCl3): δ 1.18-1.40 (m, 16H), 1.53-1.70 (m, 4H), 2.59 (t, J = 7.5 Hz, 4H), 7.10 (d, J = 6.0 Hz, 4H), 8.48 (d, J = 6.0 Hz, 4H) ppm; 13C NMR (75 MHz, CDCl3): δ 29.4, 29.7, 29.8, 29.9, 30.3, 35.5, 124.0, 149.6, 151.8 ppm.
Example 6

Preparation of N,N'-dimethyl-4,4'-(1,12-dodecanediyl)bispyridinium diiodide

4,4'-(1,12-Dodecanediyl)bispyridine (340 mg, 1.05 mmol) was dissolved in acetone (15 mL). Methyl iodide (1.50 g, 10.6 mmol) was added and the mixture was stirred for 12 hrs at room temperature. The precipitate was filtered and washed with diethyl ether. The obtained pale yellow solid was dried under vacuum to give 599 mg of the title compound. Yield: 94%. 1H NMR (300 MHz, DMSO-d6) δ 1.17-1.36 (m, 16H), 1.55-1.71 (m, 4H), 2.86 (t, J=7.8 Hz, 4H), 4.28 (s, 6H), 7.98 (d, J=6.9 Hz, 4H), 8.84 (d, J=6.6 Hz, 2H) ppm; 13C NMR (75 MHz, DMSO-d6) δ 28.5, 28.7, 28.9, 29.0, 29.1, 34.5, 47.1, 127.0, 144.5, 161.8 ppm.

Example 7

Preparation of 3,3'-(1,12-dodecanediyl)bis-5-methylpyridine

LDA (2M) (15 mL, 30.00 mmol) was added dropwise to a solution of 3,5-lutidine (3.38 g, 31.50 mmol) in THF (50 mL) at -78° C. The mixture was stirred for 30 min and then 1,10-diiododecane (4.73 g, 12.00 mmol) in THF (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 4 hrs. 50% saturated NH4Cl was added to the reaction mixture. The aqueous phase was extracted with ethylacetate (40 mL×2), and the combined organic liquors were washed with 50% saturated brine (40 mL×3) and saturated brine (40 mL), dried over anhydrous Na2SO4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes:ethylacetate 2:1 to 1:1) to afford 2.82 g of the title compound. Yield: 67%. 1H NMR (300 MHz, CDC13) δ 1.17-1.40 (m, 16H), 1.47-1.68 (m, 4H), 2.30 (s, 6H), 2.56 (t, J=7.5 Hz, 4H), 7.29 (s, 2H), 8.24 (s, 2H), ppm; 13C NMR (75 MHz, CDC13) δ 18.6, 29.5, 29.7, 29.8, 29.9, 31.5, 33.1, 132.7, 136.5, 137.5, 147.1, 147.7 ppm.

Example 8

Preparation of N,N'-dimethyl-3,3'-(1,12-dodecanediyl)bis-5-methylpyridinium diiodide
Example 9
Preparation of N-methyl-3-(12-bromododecyl)-pyridinium iodide

LDA (2M) (10.5 mL, 21.22 mmol) was added dropwise to a solution of 3-picoline (2.17 g, 23.34 mmol) in THF (60 mL) at -78 °C. The mixture was stirred for 30 min and then 1,11-dibromoundecane (10 g, 31.83 mmol) was added in one portion. The resulting mixture was warmed to 0 °C and stirred for 4 hrs. 50% saturated NH₄Cl was added to the reaction mixture. The aqueous phase was extracted with ethylacetate (40 mL×2), and the combined organic liquors were washed with 50% saturated brine (40 mL×3) and saturated brine (40 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes:ethylacetate 4:1) to afford 4.47 g 3-(12-bromododecyl)-pyridine. Yield: 59%.

The above product (960 mg, 2.95 mmol) was dissolved in acetone (15 mL). Methyl iodide (2 g, 10.41 mmol) was added and the mixture was stirred for 12 hrs at room temperature. The solvent was removed. The residue was suspended in diethyl ether, filtered, and washed with diethyl ether. The obtained pale yellow solid was dried under vacuum to give 1.28 g of the title compound. Yield: 93%. 1 H NMR (300 MHz, CDCl₃) δ 1.13-1.47 (m, 16H), 1.63-1.90 (m, 4H), 2.89 (t, J=7.8 Hz, 2H), 3.19 (t, J=6.9 Hz, 2H), 4.70 (s, 3H), 8.04 (dd, J=7.8, 6.0 Hz, 2H), 8.25 (d, J=7.8 Hz, 2H), 9.15 (s, 1H), 9.20 (s, J=6.0 Hz, 1H) ppm; 13 C NMR (75 MHz, CDCl₃) δ 18.8, 27.3, 30.2, 30.3, 36.55, 30.6, 30.7, 30.8, 31.7, 32.6, 33.7, 63.0, 128.6, 128.7, 141.2, 143.0, 144.1, 145.3, 145.5, 146.2, 146.3, 147.2 ppm.

Example 10
Preparation of 1-methyl-3-(12-(3-methylpyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide

A mixture of N-methyl-3-(12-bromododecyl)-pyridinium iodide (315 mg, 0.67 mmol), 3-picoline (1 mL) and butanone (5 mL) was heated at 80 °C for 24 hrs. Solvent was removed under reduced pressure. The resulted mixture was washed with diethyl ether and then dissolved in water (10 mL), the aqueous solution was extracted with chloroform (15 mL×3). Water was removed by lyophilization to afford 325 mg of the title compound. Yield: 86%. 1 H NMR (300 MHz, CDCl₃) δ 1.23-1.50 (m, 16H), 1.66-1.81 (m, 2H), 1.94-2.12 (m, 2H), 2.60 (s, 3H), 4.43 (s, 3H), 4.63 (t, J=7.5 Hz, 2H), 7.97-8.05 (m, 2H), 8.45 (t, J=6.9 Hz, 2H), 8.77 (d, J=6.0 Hz, 1H), 8.87 (d, J=7.8 Hz, 1H), 8.89 (s, 1H), 9.00 (s, 1H) ppm; 13 C NMR (75 MHz, CDCl₃) δ 18.8, 27.3, 30.2, 30.3, 30.8, 30.8, 31.7, 32.6, 33.7, 63.0, 128.6, 128.7, 141.2, 143.0, 144.1, 145.3, 145.5, 146.2, 146.3, 147.2 ppm.

Example 11
Preparation of 3,5-dimethyl-1-(12-(1-methylpyridin-1-ium-3-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide

A mixture of N-methyl-3-(12-bromododecyl)-pyridinium iodide (285 mg, 0.61 mmol), 3,5-lutidine (1 mL) and butanone (5 mL) was heated at 80 °C for 24 hrs. Solvent was removed under reduced pressure. The resulted mixture was washed with diethyl ether and then dissolved in water (10 mL), the aqueous solution was extracted with chloro-
Example 12
Preparation of (S)-1-methyl-3-(12-(1-methylpyrroloidin-2-yl)pyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide

A mixture of N-methyl-3-(12-bromododecyl)-pyridinium iodide (250 mg, 0.53 mmol), pyridine (1 mL) and butanone (5 mL) was heated at 80°C for 24 hrs. Solvent was removed under reduced pressure. The resulting mixture was washed with diethyl ether and then dissolved in water (10 mL), the aqueous solution was extracted with chloroform (15 mLx3). Water was removed by lyophilization to afford 278 mg of the title compound. Yield: 95%. 1H NMR (300 MHz, CD3OD) δ 1.20-1.50 (m, 16H), 1.62-1.77 (m, 16H), 1.80-2.10 (m, 5H), 2.23 (s, 3H), 2.35-2.56 (m, 2H), 2.87 (t, J=7.8 Hz, 2H), 3.32 (m, 1H), 3.58 (t, J=8.4 Hz, 1H), 4.37 (s, 3H), 4.64 (t, J=7.5 Hz, 2H), 7.95 (dd, J=8.1, 6.3 Hz, 1H), 8.09 (dd, J=8.1, 6.3 Hz, 1H), 8.40 (d, J=7.8 Hz, 1H), 8.53 (d, J=8.1 Hz, 1H), 8.61 (d, J=6.0 Hz, 1H), 8.68 (s, 1H), 8.82 (d, J=6.9 Hz, 1H), 8.83 (s, 1H) ppm. 13C NMR (75 MHz, CD3OD) δ 27.3, 30.2, 30.3, 30.6, 30.63, 30.7, 30.8, 31.7, 32.7, 33.7, 62.8, 128.7, 144.1, 145.4, 146.3, 146.8 ppm.

Example 13
Preparation of 1-methyl-3-(12-(pyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide

Example 14
Inhibition of [3H]NIC and [3H]Methyllycaconitine Binding Assays

Whole brain, excluding cortex and cerebellum, was homogenized in 20 vol of ice-cold buffer, containing (in mM): 2 HEPES, 11.8 NaCl, 0.48 KCl, 0.25 CaCl2 and 0.12 MgSO4, pH 7.5. Homogenate was centrifuged (25,000 g, 15 min, 4°C.). Pellets were resuspended in 20 vol of ice-cold buffer and incubated at 37°C, for 10 min, cooled to 4°C and centrifuged (25,000 g, 15 min, 4°C). Pellets were resuspended and centrifuged using the same conditions. Final pellets were stored in assay buffer, containing (in mM): 2 HEPES, 4.8 KCl, 2.5 CaCl2, and 1.2 MgSO4, pH 7.5 at -70°C. Upon use, final pellets were resuspended in ~20 vol assay buffer. Samples (250 µl) contained 100-140 µg of membrane protein, 3 nM [3H]nicotine or 3 nM [3H]methyllycaconitine, and analog (100 nM) in assay buffer containing 50 mM Tris. Control was in the absence of analog. In [3H]nicotine and [3H]methyllycaconitine binding assays, nonspecific binding was determined in the presence of 10 µM cytisine and 10 µM nicotine, respectively. Incubations proceeded for 60 min at room temperature using 96-well plates and were terminated by harvesting on Unifilter-96 GF/B filter plates presoaked in 0.5% polyethyleneimine, using a Packard FilterMate harvester. After washing 5 times with 350 µl ice-cold assay buffer, filter plates were dried (60 min, 4°C.), bottom-sealed, and filled with Packard’s MicroScint 20 cocktail (40 µl/well). After 20 min, filter plates were top-sealed, and radioactivity determined using a Packard TopCount. Protein concentrations were determined using the Bradford dye-binding procedure bovine serum albumin as the standard. The results are summarized in Table 1.

Example 15
Inhibition of Nicotine-Evoked [3H]Neurotransmitter Release Assay

The [3H]dopamine overflow assay using superfused rat striatal slices preloaded with [3H]dopamine was used to...
determine the ability of a probe concentration (100 nM) of each bis-quaternary ammonium analog to inhibited nicotine-evoked [3H]dopamine overflow. Briefly, coronal slices of rat striata (500 µm, 6-8 mg) were obtained using a McIlwain tissue chopper. Slices were incubated for 30 min in Krebs’ buffer (in mM: 118 NaCl, 4.7 KCl, 1.2 MgCl2, 1.0 NaH2PO4, 1.3 CaCl2, 11.1 α-D-glucose, 25 NaHCO3, 0.11 L-ascorbic acid and 0.004 ethylenediaminetetraacetic acid (EDTA), pH 7.4, saturated with 95% O2/5% CO2) at 34°C in a metabolic shaker. Slices were then incubated for an additional 30 min in fresh buffer containing 0.1 µM [3H]dopamine. After rinsing, each slice was transferred to the superfusion chambers, maintained at 34°C and superfused for 30 min in the absence or presence of analog, followed by superfusion with 0.1 µM [3H]dopamine and an additional 12 consecutive five minute samples were collected to determine basal outflow of [3H]DA. The bis-quaternary analogs were added to the superfusion buffer after the collection of the third sample and remained in the buffer until 12 consecutive five minute samples were collected. Subsequently, S(-)-nicotine (10 µM) was added to the buffer and an additional 12 consecutive five minute samples were collected. At the end of the experiment, each slice was solubilized and the [3H] content of the tissue determined. Radioactivity in the superfusate and tissue samples was determined by liquid scintillation spectrometry. Fractional release for tritium collected in each sample was divided by the total tritium present in the tissue at the time of sample collection and was expressed as a percentage of total tritium. Basal [3H]outflow was calculated from the average of the tritium collected in the two five minute samples just before addition of the quaternary analog. The sum of the increase in collected tritium resulting from either exposure to the test compound or exposure to S(-)-nicotine in the absence and presence of the test compound equaled total [3H]overflow. [3H]Overflow was calculated by subtracting the [3H]outflow during an equivalent period of prestimulation from the values in samples collected during and after drug exposure. Inasmuch as the radiolabelled compounds were not separated and identified, the tritium collected in superfusate is referred to as either [3H]outflow or [3H]overflow, rather than as [3H]dopamine. [3H]Overflow primarily represents [3H]dopamine in the presence of nomifensine and pargyline in the superfusion buffer.

All of the bis-quaternary analogs were evaluated for their ability to evoke [3H]dopamine release from rat striatal slices using the probe 100 nM concentration (Table 1). None of the compounds examined had any significant [3H]dopamine releasing properties in this assay in the concentration range tested. One analog GZ527B was evaluated for full concentration dependent inhibition of the effect of nicotine to evoke [3H]dopamine release (FIG. 1). In both studies, the antagonist activity was evaluated by comparing the NIC-evoked [3H]overflow in the absence and presence of the analogs.

**TABLE 1**

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>Inhibition of [3H]Nicotine Binding (Kᵢ (µM) ± SEM)</th>
<th>Inhibition of [3H]MLA Binding (Kᵢ (µM) ± SEM)</th>
<th>% inhibition at 100 nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>GZ527B</td>
<td>8.20 ± 1.78</td>
<td>&gt;100</td>
<td>32%</td>
</tr>
</tbody>
</table>

Rat Striatal Nicotinic Receptors and Nicotine-evoked [3H]Dopamine Release from Superfused Rat Striatal Slices
<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>Inhibition of $[^3H]$Nicotine binding $K_i$ (μM ± SEM)</th>
<th>Inhibition of $[^3H]$MLA binding $K_i$ (μM ± SEM)</th>
<th>Inhibition nicotine-evoked $[^3H]$DA release (% inhibition at 100 nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GZ-527A</td>
<td>7.88 ± 1.68</td>
<td>&gt;100</td>
<td>67%</td>
</tr>
<tr>
<td>GZ-527B</td>
<td>8.17 ± 0.17</td>
<td>&gt;100</td>
<td>49%</td>
</tr>
<tr>
<td>GZ-528A</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>30%</td>
</tr>
<tr>
<td>GZ-528B</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>43%</td>
</tr>
<tr>
<td>GZ-529A</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>25%</td>
</tr>
<tr>
<td>GZ-529B</td>
<td>6.62 ± 1.14</td>
<td>&gt;100</td>
<td>43%</td>
</tr>
<tr>
<td>GZ-530A</td>
<td>23.4 ± 3.94</td>
<td>&gt;100</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Table 1-continued**

bis-Quaternary Ammonium Salts: Inhibition of $[^3H]$Nicotine and $[^3H]$MLA Binding to Rat Striatal Nicotinic Receptors and Nicotine-evoked $[^3H]$Dopamine Release from Superfused Rat Striatal Slices.
modifications and variations are intended to be included herein within the scope of this disclosure and the present invention and protected by the following claims.

We claim:

1. A bis-quaternary ammonium compound of Formula (I)

\[
\text{X}^{1-\text{R}} \equiv \text{R}^{-1-\text{R}} \equiv \text{X'}^{1-\text{R}} \equiv \text{R'1-\text{R}}^{1-\text{R}}
\]  

(I)

wherein \(X^{1-}\) and \(X^{2-}\) are each independently an organic or inorganic anion;

wherein \(R\) is selected from the group consisting of 

\(-(\text{CH}_2)_{12}-;\)

wherein \(R^1\) and \(R^2\) are each six membered rings as shown in formula (IIA), wherein each ring of \(R^1\) and \(R^2\) has one quaternized nitrogen atom, and the ring atoms from \(R^1\) and \(R^2\) which are attached to \(R\) cannot both be nitrogen atoms:

![Formula image]

wherein one of \(A^1\), \(A^3\), and \(A^4\), is nitrogen and the remaining \(A^1\), \(A^2\), \(A^3\), \(A^4\), and \(A^5\) are carbon;

wherein \(R^1\), \(R^2\), \(R^3\), \(R^4\), and \(R^5\) are each independently selected from the hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, heteroaryalkyl, substituted heteroaryalkyl, halo, cyano, nitro, \(\text{SO}_{Y^1}\), \(\text{SO}_{Y^2}\), \(\text{SO}_{Y^3}\), \(\text{SO}_{Y^4}\), or \(\text{SO}_{Y^5}\), where \(Y^1\) is selected from hydrogen, lower alkyl, alkyl, alkenyl or aryl, and where \(Y^1\) is not hydrogen in \(\text{SO}_{Y^1}\) and if \(Y^1\) is alkyl or alkenyl, the site of unsaturation is not conjugated with a heteroatom; \(\text{CO}_{Y^2}\), where \(Y^2\) is selected from hydrogen, alkyl, cycloalkyl, alkoxy, alkenyl, alkyl, arylalkyl, arylalkyl, arylalkenyl, or heterocyclic, and where if \(Y^2\) comprises alkyl or alkenyl, the site of unsaturation is not conjugated with the carbonyl group; \(\text{OY}_{Y^3}\), where \(Y^3\) is selected from hydrogen, alkyl, cycloalkyl, alkenyl, alkyl, aryl, arylalkyl, arylalkyl, arylalkenyl, or heterocyclic, and where if \(Y^3\) comprises alkyl or alkenyl, the site of unsaturation is not conjugated with the oxygen; \(\text{NY}^4\), where \(Y^4\) and \(Y^5\) are each independently selected from hydrogen, alkyl, cycloalkyl, alkenyl, aryl, arylalkyl, arylalkyl, arylalkenyl, arylalkynyl, acyl, alkylsulfonyl, or heterocyclic, where if \(Y^4\) or \(Y^5\) comprises alkenyl or alkynyl, the site of unsaturation is not conjugated with alkene, alkene or alkynyl, the site of unsaturation is not conjugated with the sulfur; and any of \(R^1\), \(R^2\), \(R^3\), \(R^4\), or \(R^5\) attached to the nitrogen atom is independently a straight or branched alkyl group of four carbons or fewer.

2. The compound of claim 1, wherein:

\(R\) is \(-(\text{CH}_3)_{12};\)

\(R^1\) and \(R^2\) are pyridinium rings;

\(A^1\) is nitrogen;

\(A^2\) is methyl;

\(R^3\) is hydrogen or methyl; and

\(X^1\) and \(X^2\) are bromide or iodide.

3. The compound of claim 1, wherein:

\(R\) is \(-(\text{CH}_3)_{12};\)

\(R^1\) and \(R^2\) are pyridinium rings;

\(A^1\) is nitrogen;

\(R^3\) is methyl; and

\(X^1\) and \(X^2\) are bromide or iodide.

4. The compound of claim 1, wherein:

\(R\) is \(-(\text{CH}_3)_{12};\)

\(R^1\) and \(R^2\) are pyridinium rings;

wherein for \(R^1\), \(A^1\) is nitrogen, \(R^2\) is methyl, \(R^3\) is hydrogen or methyl, and \(X^1\) is bromide or iodide; and \(X^1\) and \(X^2\) is hydrogen, methyl or 1-methyl-2-pyridilinyl, and \(X^2\) is bromide or iodide.

5. The compound of claim 1 selected from the group consisting of:

\(\text{N,N'-dimethyl-3,3'-(1,12-dodecanediyl)bispyridinium diiodide;}\)

\(\text{N,N'-dimethyl-4,4'-(1,12-dodecanediyl)bispyridinium diiodide;}\)

\(\text{N,N'-dimethyl-3,3'-(1,12-dodecanediyl)bis-5-methylpyridinium diiodide;}\)

\(1\)-methyl-3-(3-methylpyridin-1-ium-1-yl)dodecylpyridin-1-ium mono-bromide mono-iodide;

\(3.5\)-dimethyl-1-(12-(1-methylpyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide; and

\(1\)-methyl-3-(12-(pyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide.

6. A bis-quaternary ammonium compound of Formula (I)

\[
\text{X}^{1-\text{R}} \equiv \text{R}^{-1-\text{R}} \equiv \text{X'}^{1-\text{R}} \equiv \text{R'1-\text{R}}^{1-\text{R}}
\]  

(I)

wherein \(X^{1-}\) and \(X^{2-}\) are each independently an organic or inorganic anion;

wherein \(R\) is selected from the group consisting of 

\(-(\text{CH}_2)_{12};\)

wherein \(R^1\) and \(R^2\) are each six membered rings as shown in formula (IIA), wherein each ring of \(R^1\) and \(R^2\) has one quaternized nitrogen atom, and the ring atoms from \(R^1\) and \(R^2\) which are attached to \(R\) cannot both be nitrogen atoms:
wherein one of $A^1$, $A^2$, and $A^4$ is nitrogen and the remaining $A^1$, $A^2$, $A^3$, $A^4$, and $A^6$ are carbon; wherein $R^9$, $R^{10}$, $R^{11}$, and $R^{13}$ are each independently selected from hydrogen, methyl, and 1-methyl-2-pyrrolidinyl; and any of $R^9$, $R^{10}$, or $R^{11}$, when attached to the quaternized nitrogen, is independently a straight or branched lower alkyl group.

7. (S)-1-methyl-3-(12-(3-(1-methylpyrrolidin-2-yl)pyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide.


10. A composition comprising a pharmaceutically acceptable carrier and a compound of claim 3.


14. A method for treating substance abuse comprising administering to a mammalian subject in need thereof a therapeutically effective amount of a bis-quaternary ammonium compound selected from the group consisting of:

- N,N'-dimethyl-2,2'-(1,12-dodecanediyl)bispyridinium diiodide;
- N,N'-dimethyl-3,3'-(1,12-dodecanediyl)bispyridinium diiodide;
- N,N'-dimethyl-4,4'-(1,12-dodecanediyl)bispyridinium diiodide;
- 1-methyl-3-(12-(3-methylpyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide;
- 3,5-dimethyl-1-(12-(1-methylpyridin-1-ium-3-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide;
- (S)-1-methyl-3-(12-(3-(1-methylpyrrolidin-2-yl)pyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide; and
- 1-methyl-3-(12-(pyridin-1-ium-1-yl)dodecyl)pyridin-1-ium mono-bromide mono-iodide.

15. The method for treating substance abuse according to claim 14, wherein the bis-quaternary ammonium compound is selected from the group consisting of nicotine abuse, cocaine abuse, and alcohol abuse.

16. The method for treating substance abuse according to claim 14, wherein the bis-quaternary ammonium compound is N,N'-dimethyl-4,4'-(1,12-dodecanediyl)bispyridinium diiodide.