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USE OF TRIS-QUATERNARY AMMONIUM SALTS AS PAIN MODULATING AGENTS

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References Cited
U.S. PATENT DOCUMENTS


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* cited by examiner

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FOREIGN PATENT DOCUMENTS
WO

OTHER PUBLICATIONS

7 Claims, 2 Drawing Sheets
Figure 1
GZ-556A

![Graph showing the effect of GZ-556A on flinches over time. The x-axis represents time in minutes, ranging from 0 to 70, and the y-axis represents flinches per 5-minute epoch, ranging from 0 to 100. The legend indicates different concentrations of GZ-556A and a control group (Saline).]
Figure 2
GZ-556A

Mean +/- SEM (n = 2-3 rats)
The treatment of moderate to severe nociceptive pain. Chronic and neuropathic pain. Nociceptive pain occurs as a result of noxious stimuli. Examples of nociceptive pain include postsurgical pain, litigation and the cost of drugs. New therapeutic agents with greater efficacy, in particular for chronic neuropathic pain syndromes (eg. complex regional pain syndrome), and with fewer side effects would result in significant societal benefit.

Pain can be broadly divided into two categories: nociceptive and neuropathic pain. Nociceptive pain occurs as a result of activation of peripheral nociceptors, actually free nerve endings by noxious stimuli (heat, pressure, inflammatory mediators). Examples of nociceptive pain include postsurgical pain, inflammatory pain (eg. arthritis) and low back pain. Such a pain is often described as “a constant, dull, aching pain”. Neuropathic pain occurs as a result of damage to the peripheral or central nervous system. Examples of neuropathic pain include radiculopathy (eg. disc impingement on a nerve), complex regional pain syndrome (CRPS I, II), diabetic peripheral neuropathy or central pain (stroke, spinal cord injury, multiple sclerosis). Patients typically describe neuropathic pain as “burning and tingling” in nature. It is characterized by hyperalgesia (increased painful response to a noxious stimulus) and allodynia (pain to a previously non-noxious stimulus).

The three side chains attached to the phenyl ring can be connected to the 1, 2, and 3 positions; or the 1, 2, and 4 positions; or the 1, 3 and 5 positions of the phenyl ring. The values for m1, m2 and m3 are each independently 0, 1, 2, 3, 4 or 5. The values for n1, n2, and n3 are each independently 1, 2, 3, 4 or 5. X1, X2 and X3 are each independently an organic or inorganic anion. L1, L2 and L3 are each independently chosen from the group consisting of – CH3, – CH2–, cis – CH = CH–, trans – CH – CH–, – C = C–, – CH2–S–, – S–CH2–, – Se–CH2–, – CH2–Se–, – CH2–O–, – O–CH2–, – CH2–NH–, – NH–CH2–, – CH3–NR– where R is a branched or straight chain alkyl group of one to four carbons, – NR–CH3–, and – N–N–.
A1 is carbon or nitrogen, provided that when A1 joins a ring atom with an unsaturated bond or is a nitrogen, R7 is absent, and when A1 joins a ring atom an unsaturated bond and is a nitrogen, both R8 and R9 are absent.

A2 is carbon or nitrogen, provided that when A2 joins a ring atom an unsaturated bond or is a nitrogen, R10 is absent, and when A2 joins a ring atom an unsaturated bond and is a nitrogen, both R11 and R12 are absent.

A3 is carbon or nitrogen, provided that when A3 joins a ring atom an unsaturated bond or is a nitrogen, R13 is absent, and when A3 joins a ring atom an unsaturated bond and is a nitrogen, both R14 and R15 are absent.

A4 is carbon or nitrogen, provided that when A4 joins a ring atom an unsaturated bond or is a nitrogen, R16 is absent, and when A4 joins a ring atom an unsaturated bond and is a nitrogen, both R17 and R18 are absent.

A5 is carbon or nitrogen, provided that when A5 joins a ring atom an unsaturated bond or is a nitrogen, R19 is absent, and when A5 joins a ring atom an unsaturated bond and is a nitrogen, both R20 and R21 are absent.

A6 is carbon or nitrogen, provided that when A6 joins a ring atom an unsaturated bond or is a nitrogen, R22 is absent, and when A6 joins a ring atom an unsaturated bond and is a nitrogen, both R23 and R24 are absent.

A7 is carbon or nitrogen, provided that when A7 joins a ring atom an unsaturated bond or is a nitrogen, R25 is absent, and when A7 joins a ring atom an unsaturated bond and is a nitrogen, both R26 and R27 are absent.

A8 is carbon or nitrogen, provided that when A8 joins a ring atom an unsaturated bond or is a nitrogen, R28 is absent, and when A8 joins a ring atom an unsaturated bond and is a nitrogen, both R29 and R30 are absent.

A9 is carbon or nitrogen, provided that when A9 joins a ring atom an unsaturated bond or is a nitrogen, R31 is absent, and when A9 joins a ring atom an unsaturated bond and is a nitrogen, both R32 and R33 are absent.

A10 is carbon or nitrogen, provided that when A10 joins a ring atom an unsaturated bond or is a nitrogen, R34 is absent, and when A10 joins a ring atom an unsaturated bond and is a nitrogen, both R35 and R36 are absent.

A11 is carbon or nitrogen, provided that when A11 joins a ring atom an unsaturated bond or is a nitrogen, R37 is absent, and when A11 joins a ring atom an unsaturated bond and is a nitrogen, both R38 and R39 are absent.

A12 is carbon or nitrogen, provided that when A12 joins a ring atom an unsaturated bond or is a nitrogen, R40 is absent, and when A12 joins a ring atom an unsaturated bond and is a nitrogen, both R41 and R42 are absent.

A13 is carbon or nitrogen, provided that when A13 joins a ring atom an unsaturated bond or is a nitrogen, R43 is absent, and when A13 joins a ring atom an unsaturated bond and is a nitrogen, both R44 and R45 are absent.

A14 is carbon or nitrogen, provided that when A14 joins a ring atom an unsaturated bond or is a nitrogen, R46 is absent, and when A14 joins a ring atom an unsaturated bond and is a nitrogen, both R47 and R48 are absent.

A15 is carbon or nitrogen, provided that when A15 joins a ring atom an unsaturated bond or is a nitrogen, R49 is absent, and when A15 joins a ring atom an unsaturated bond and is a nitrogen, both R50 and R51 are absent.

R1, R2, and R3 are each independently five or six membered nitrogen containing rings as shown in formulas (IIA) and (IIB).

In another embodiment, a method is provided for preventing and/or treating nociception and pain associated disorders comprising administering a therapeutically effective amount of a compound as described above to a mammalian subject in need thereof.

In another embodiment, a composition is provided comprising a pharmaceutically acceptable carrier and a compound as described above.
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the time curve of the effect of GZ-556A in the Rodent Formalin Tonic Pain model following intraperitoneal administration. Data are mean±SEM, n=3.

FIG. 2 shows the dose response of the effect of GZ-556A in Phase 1 and 2 of the Rodent Formalin Tonic Pain model following intraperitoneal administration. Data are mean±SEM, n=3.

Before the present compositions and methods are described, it is to be understood that the invention is not limited to the particular methodologies, protocols, assays, and reagents described, as these can vary. It is also to be understood that the terminology used herein is intended to describe particular embodiments of the present invention, and is in no way intended to limit the scope of the present invention as set forth in the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications cited herein are incorporated herein by reference in their entirety for the purpose 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 limited by the particular methodologies, protocols, assays, and reagents described, as these can vary. Before the present compositions and methods are described, it is to be understood that the invention is not limited to the particular methodologies, protocols, assays, and reagents described, as these can vary.

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

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

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

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

The term “heterocyclic” refers to cyclic ring-containing moieties containing one or more heteratoms as part of the ring structure and having 3 to 24 carbon atoms, and “substituted heterocyclic” refers to heterocyclic moieties further bearing one or more substituents as set forth above.

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

The term “halogen” refers to fluorine, chlorine, bromine or iodine groups.

It is understood that in all substituted groups defined above, polymers arrived at by defining substituents with further substituents to themselves (e.g. substituted aryl having a substituted aryl group as a substituent which is itself substituted with a substituted aryl group, etc.) are not intended for inclusion herein. In such cases, the maximum number of such substituents is three. That is to say that each of the above definitions is constrained by a limitation that, for example, substituted aryl groups are limited to -substituted aryl-(substituted aryl)-(substituted aryl)-substituted aryl.

The three side chains attached to the phenyl ring can be connected to the 1, 2, or 3 positions; the 1, 2, or 4 positions; or the 1, 3, or 5 positions of the phenyl ring.

The values for m1, m2 and m3 are each independently 0, 1, 2, 3, 4 or 5.

The values for n1, n2, and n3 are each independently 1, 2, 3, 4 or 5.

X1, X2, and X3 are each independently an organic or inorganic anion.

L1, L2 and L3 are each independently chosen from the group consisting of -CH2-CH2-, cis-CH=CH-, trans-CH=CH-, C=CH-, CH2-S-, S-CH2-, Se-CH2-, CH2-Se-, CH2-O-, O-CH2-, CH2-NH-, NH-CH2-, CH2-NR- where R is a branched or straight chain alkyl group of one to four carbons, -NR-CH2-, where R is a branched or straight chain alkyl group of one to four carbons, -CH-N-, -N-CH-, and -N-N-.

R1, R2, and R3 are each independently five or six membered nitrogen containing rings as shown in formulas (IIA) and (IIIB).
A² is carbon or nitrogen, provided that when A² joins a ring atom with an unsaturated bond or is a nitrogen, R⁴ is absent, and when A² joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R⁸ are absent.

A³ is carbon or nitrogen, provided that when A³ joins a ring atom with an unsaturated bond or is a nitrogen, R¹⁰ is absent, and when A³ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹⁰ are absent.

A⁴ is carbon or nitrogen, provided that when A⁴ joins a ring atom with an unsaturated bond or is a nitrogen, R¹¹ is absent, and when A⁴ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹¹ are absent.

A⁵ is carbon or nitrogen, provided that when A⁵ joins a ring atom with an unsaturated bond or is a nitrogen, R¹² is absent, and when A⁵ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹² are absent.

A⁶ is carbon or nitrogen, provided that when A⁶ joins a ring atom with an unsaturated bond or is a nitrogen, R¹³ is absent, and when A⁶ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹³ are absent.

A⁷ is carbon or nitrogen, provided that when A⁷ joins a ring atom with an unsaturated bond or is a nitrogen, R¹⁴ is absent, and when A⁷ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹⁴ are absent.

A⁸ is carbon or nitrogen, provided that when A⁸ joins a ring atom with an unsaturated bond or is a nitrogen, R¹⁵ is absent, and when A⁸ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹⁵ are absent.

A⁹ is carbon or nitrogen, provided that when A⁹ joins a ring atom with an unsaturated bond or is a nitrogen, R¹⁶ is absent, and when A⁹ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹⁶ are absent.

A¹⁰ is carbon or nitrogen, provided that when A¹⁰ joins a ring atom with an unsaturated bond or is a nitrogen, R¹⁷ is absent, and when A¹⁰ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹⁷ are absent.

A¹¹ is carbon or nitrogen, provided that when A¹¹ joins a ring atom with an unsaturated bond or is a nitrogen, R¹⁸ is absent, and when A¹¹ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹⁸ are absent.

A¹² is carbon or nitrogen, provided that when A¹² joins a ring atom with an unsaturated bond or is a nitrogen, R¹⁹ is absent, and when A¹² joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R¹⁹ are absent.

A¹³ is carbon or nitrogen, provided that when A¹³ joins a ring atom with an unsaturated bond or is a nitrogen, R²⁰ is absent, and when A¹³ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R²⁰ are absent.

A¹⁴ is carbon or nitrogen, provided that when A¹⁴ joins a ring atom with an unsaturated bond or is a nitrogen, R²¹ is absent, and when A¹⁴ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R²¹ are absent.

A¹⁵ is carbon or nitrogen, provided that when A¹⁵ joins a ring atom with an unsaturated bond or is a nitrogen, R²² is absent, and when A¹⁵ joins a ring atom with an unsaturated bond and is a nitrogen, both R⁷ and R²² are absent.

R¹⁴ or R²³ is absent when any of the bonds to the amnonium nitrogen is unsaturated, and R¹⁴ or R²³ is a straight chain or branched alkyl group of four carbons or fewer when all of the bonds to the ammonium nitrogen are saturated.

where Y¹ is selected from hydrogen, lower alkyl, alkenyl, alkynyl or aryl, and where Y¹ is not hydrogen in SOY² and if Y² is alkyl or alkynyl, the site of unsaturation is not conjugated with a heteroatom; COY², where Y² is selected from hydrogen, alky1, substituted alkyl, cyanoalkyl, substituted cyanoalkyl, alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, aralky1, substituted aralkyl, aralkynyl, substituted aralkynyl, heterocyclic, or substituted heterocyclic, and where if Y² comprises alkyl or alkynyl, the site of unsaturation is not conjugated with the carbonyl group; OY², where Y² is selected from hydrogen, alky1, substituted alkyl, cyanoalkyl, substituted cyanoalkyl, alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, aralky1, substituted aralkyl, aralkynyl, substituted aralkynyl, heterocyclic, or substituted heterocyclic, where if Y² comprises alkyl or alkynyl, the site of unsaturation is not conjugated with the nitrogen; SY², where Y² is selected from hydrogen, alkyl, substituted alkyl, cyanoalkyl, substituted cyanoalkyl, alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, aralky1, substituted aralkyl, aralkynyl, substituted aralkynyl, heterocyclic, or substituted heterocyclic, where if Y² comprises alkyl or alkynyl, the site of unsaturation is not conjugated with the sulfur; or R⁴ and R⁷ together with A¹ and A², or R⁵ and R⁸ together with A³ and A⁴, or R⁶ and R⁹ together with A⁵ and A⁶, or R¹⁰ and R¹¹ together with A⁷ and A⁸, or R¹² and R¹³ together with A⁹ and A¹⁰, or R¹⁴ and R¹⁵ together with A¹¹ and A¹² independently form a three to eight member cyclic, substituted cycloalkane, cycloalkene, substituted cycloalkene, aryl, substituted aryl, heterocycle with one to three hetero atoms in the ring, or substituted heterocycle with one to three hetero atoms in the ring.

For example, R¹, R², and R² include pyrrole, pyrrolidine, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, piperidine, quinoline, tetrahydroquinoline, isoquinoline, tetrahydropyrrolidine, thiazole, pyrazine, piperazine, pyridazine, and triazine.

As another example, R⁴R⁶, R⁸, R⁴, R⁶, R⁸, R¹⁰R¹¹, R¹², and R¹³ or R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, and R²², include hydrogen, methyl, ethyl, propyl, butyl, trifluoromethyl, pyrrolidine, N-alkyl pyrrolidine (for example where the alkyl chain is methyl, ethyl or propyl), unsaturated pyrrolidine, unsubstituted pyrrolidine, unsubstituted N-alkyl pyrrolidine (for example where the alkyl chain is methyl, ethyl or propyl), aziridine, N-methyl aziridine, azetidine, N-methyl azetidine, unsubstituted azetidine, unsubstituted N-methyl azetidine, piperidine, N-methyl piperidine, unsaturated piperidine, unsubstituted N-methyl piperidine, unsubstituted N-methyl piperidine, azepane, N-methyl azepane, unsubstituted N-methyl azepane, azocane, N-methyl azocane, unsubstituted azocane, unsubstituted N-methyl azocane, 1-aza­ bicyclo[3.2.1]octane, 1-aza­bicyclo[2.2.1]heptane, 8-methyl­8-aza­bicyclo[3.2.1]octane, 1-aza­tricyclo[3.3.1.1³⁷]decane, methyl cycloalkyl, methyl substituted cycloalkyl, methylpyrrolidine, methyl N-alkyl pyrrolidine (for example...
where the alkyl chain is methyl, ethyl or propyl, methyl unsaturated pyrrolidine, methyl unsaturated N-alkyl pyrrolidine (for example where the alkyl chain is methyl, ethyl or propyl), methyl azidine, methyl N-methyl azidine, methyl azetidine, methyl N-methyl azetidine, methyl unsaturated azetidine, methyl unsaturated N-alkyl azetidine, methyl piperidine, methyl N-methyl piperidine, methyl unsaturated piperidine, methyl unsaturated N-alkyl piperidine, methyl azepane, methyl N-methyl azepane, methyl unsaturated azepane, methyl unsaturated N-alkyl azepane, methyl azocane, methyl N-methyl azocane, methyl unsaturated azocane, methyl unsaturated N-alkyl azocane, methyl-1-aza-bicyclo[3.2.1]octane, methyl-1-aza-bicyclo[3.2.1]octane, methyI-1-aza-bicyclo[3.2.1]octane, methyl-1-aza-bicyclo[3.2.1]octane, and methyl-1-aza-tricyclo [3.3.1.1^{10}]
decane.

As a further example, when R^4 and R^5 together with A^1 and A^2 or R^6 and R^7 together with A^3, or R^15 and R^16 together with A^6 and A^7, or R^15 and R^16 together with A^6 and A^7 independently form a three to eight-membered ring, that ring can be a heterocycle containing up to three hetero atoms (for example nitrogen, oxygen or sulfur) in the ring, and further can be substituted with one or more substituents. For example, possible rings include benzene, pyridine, pyran, indene, isoindene, benzoindene, isoindeno, isoindole, cyclopentala[b]pyridine, pyrano[3,4-b]pyrrole, indazole, indazole, and X_1, X_2, and X_3 are Br.

In a compound of Formula (I), preferably R^6 is hydrogen, alkyl, or forms an aryl ring with A^2, A^3 and R^2. More preferably, R^6 is hydrogen, methyl or forms a phenyl group with A^2, A^3 and R^2.

In a compound of Formula (I), preferably R^7 is hydrogen or alkyl. More preferably, R^7 is hydrogen or methyl.

In a compound of Formula (I), preferably R^8 is hydrogen. In a compound of Formula (I), preferably m=0.

In a compound of Formula (I), preferably n=3.

In a compound of Formula (I), preferably L^1, L^2 and L^3 are --CH_2--CH_2-- or --C=C--.

In a compound of Formula (I), preferably X^{18}, X^{28}, and X^{38} are halogens. More preferably, X^{18}, X^{28}, and X^{38} are bromide.

In one embodiment, the compound of Formula (I) is defined wherein the phenyl ring is 1,3,5 substituted; wherein m=0; wherein n=3; wherein L is --CH_2--CH_2--; wherein R^2, R^2, and R^3 are pyridinium rings; wherein R^4 is hydrogen, methyl or forms a phenyl group with A^1, A^2 and R^2; wherein R^5 is hydrogen, methyl, phenyl, butyl, 1-methyl-2-pyrrolidinyl, forms a phenyl group with A^1, A^2 and R^2; or forms a phenyl group with A^1, A^2 and R^3; wherein R^5 is hydrogen, methyl or forms a phenyl group with A^2, A^3 and R^5; and wherein X^1, X^2, and X^3 are Br.

In another embodiment, the compound of Formula (I) is defined wherein the phenyl ring is 1,3,5 substituted; wherein m=0; wherein n=3; wherein L is --CH_2--CH_2--; wherein R^1, R^2, and R^3 are pyridinium rings; wherein R^4 is hydrogen, methyl or forms a phenyl group with A^1, A^2 and R^2; wherein R^5 is hydrogen, methyl, phenyl, butyl, 1-methyl-2-pyrrolidinyl, forms a phenyl group with A^1, A^2 and R^2, or forms a phenyl group with A^1, A^2 and R^3; or forms a phenyl group with A^2, A^3 and R^5; wherein R^5 is hydrogen, methyl or forms a phenyl group with A^2, A^3 and R^5; and wherein X^1, X^2, and X^3 are Br.

An exemplary compound for this application is presented below:

The compounds of the present invention can contain one or more stereocenters. The invention includes all possible diastereomers and all enantiomeric forms as well as racemic mixtures. The compounds can be separated into substantially optically pure compounds.
Central nervous system disorders which can be treated according to the method of the present invention include disorders of nociception, and pain.

In yet another embodiment, the present invention is directed to a method for preventing pain, 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) can reduce a pain 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 can be delivered in 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 appropriate formulation. Various formulations and drug delivery systems are available in the art. See, e.g., Remington’s Pharmaceutical Sciences (1995) Remington’s Pharmaceutical Sciences.

Suitable routes of administration can, 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, intraarticular, intranasal, or intraocular injections. In addition, the agent or composition thereof can be administered sublingually or via a spray. The agent or composition thereof can 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 can 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 can 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 compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurry, suspensions and the like, for oral ingestion by a subject. The compounds can 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 carboxymethyl-cellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof as sodium alginate. Also, wetting agents such as sodium dodecyl sulfate can be included.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, tragacanth, agar, or tragacanth gum. Also suitable are lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can 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-fit 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 can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can 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 micro-needle 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 effectors, 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 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. 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 can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can 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 can 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 injection suspensions can contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain surfactants or surfactant combinations that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can 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 can also be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the present compounds can 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 can be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% 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:5 W) 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 can be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components can be varied. For example, other low-toxicity nonpolar surfactants can be used instead of polysorbate 80, the fraction size of polyethylene glycol can be varied, other biocompatible polymers can replace polyethylene glycol, e.g., polyvinyl pyrrolidone, and other sugars or polysaccharides can substitute for dextrose.

Alternatively, other delivery systems for hydrophobic molecules can be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Liposomal delivery systems are discussed above in the context of gene-delivery systems. Certain organic solvents such as dimethylsulfoxide also can be employed, although usually at the cost of greater toxicity. Additionally, the compounds can be delivered using sustained-release systems, such as semi-permeable matrices of solid hydrophobic polymers containing the effective amount of the composition to be administered. Various sustained-release materials are established and available to those of skill in the art. Sustained-release capsules can, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for stabilization can be employed.

For any composition used in the present methods of treatment, a therapeutically effective dose can be estimated initially using a variety of techniques well known in the art. Dosage ranges appropriate for human subjects can be determined, for example, using data obtained from animal studies.

A therapeutically effective dose of an agent refers to that amount of the agent that results in amelioration of symptoms.

Toxicity and therapeutic efficacy of such molecules can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the ratio LD_{50} / ED_{50}. Agents that exhibit high therapeutic indices are preferred.

Dosages preferably fall within a range of circulating concentrations that includes the LD_{50} with little or no toxicity. Dosages can vary within this range depending upon the dosage form employed and the route of administration 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 can, 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 can, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device can be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier can 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 example, which is intended to be purely exemplary of the invention. The present invention is not limited in scope by the exemplified embodiment, which is intended as an illustration of a single aspect 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 1,3,5-tris-(5-hydroxypent-1-ynyl)-benzene
1,3,5-Tribromobenzene (10 g, 31.76 mmol), 4-pentyln-1-ol (10.69 g, 127.06 mmol) and bis(triphenylphosphine)palladium(II) dichloride were stirred in triethylamine under nitrogen for 5 minutes. Copper(I) iodide (92 mg, 0.48 mmol) was added and the mixture was stirred for 6 hours at 80°C. The mixture was cooled to room temperature, filtered through a celite pad and rinsed with ethyl acetate. The combined filtrate was evaporated to dryness under reduced pressure. The resulting residue was purified by column chromatography (CHCl₃:MeOH 10:1) to afford 7.61 g of 1,3,5-tris-(5-hydroxy-1-pentynyl)benzene. Yield 74%. 1H NMR (300 MHz, CDCl₃) δ 7.31 (s, 3H), 3.81 (t, J=6.0 Hz, 6H), 2.52 (t, J=6.9 Hz, 6H), 1.85 (m, 6H); 13C NMR (75 MHz, CDCl₃) δ 133.8, 124.2, 90.5, 80.0, 61.9, 31.5, 16.2 ppm.

Example 3
Preparation of 1,3,5-tris-(5-bromopentyl)benzene

1,3,5-tris-(5-hydroxy-1-pentynyl)benzene (2.84 g, 8.6 mmol) was dissolved in methanol (30 mL) and 10% Pd/C (5% w/w) was added. The resulting mixture was hydrogenated on a Parr hydrogenation apparatus (45 psi) for 4 hours. The catalyst was removed by filtration through a celite pad. The filter cake was rinsed with methanol, and the combined organic liquids were concentrated under reduced pressure. The crude product was purified by column chromatography (CHCl₃:MeOH 6:1) to afford 2.84 g of 1,3,5-tris-(5-hydroxy-1-pentynyl)benzene. Yield 96%. 1H NMR (300 MHz, CDCl₃) δ 6.81 (s, 3H), 3.62 (t, J=6.3 Hz, 6H), 2.57 (t, J=7.5 Hz, 6H), 1.53-1.70 (m, 12H), 1.38 (m, 6H) ppm; 13C NMR (75 MHz, CDCl₃) δ 142.5, 126.1, 63.1, 36.1, 32.9, 31.5, 25.7 ppm.

Example 2
Preparation of 1,3,5-tris-(5-hydroxypentyl)benzene

1,3,5-Trihydroxypentylbenzene (2.83 g, 8.41 mmol) and carbon tetrabromide (10.99 g, 32.80 mmol) were dissolved in dry methylene chloride (50 mL) and cooled to 0°C. Triphenylphosphine (9.03 g, 34.33 mmol) was added dropwise and the mixture was stirred for 30 minutes at 0°C. The mixture was poured into hexanes (250 mL), filtered through a short silica gel column and washed with ethyl acetate/hexanes (1:4). The combined organic solvents were evaporated to dryness under reduced pressure. The resulting residue was purified by column chromatography (hexanes:ethyl acetate 8:1) to afford 4.08 g of 1,3,5-tris-(5-bromopentyl)-benzene. Yield 92%. 1H NMR (300 MHz, CDCl₃) δ 6.81 (s, 3 h), 3.41 (t, J=6.9 Hz, 6H), 2.60 (t, J=7.5 Hz, 6H), 1.88 (m, H), 1.45 (m, 6H) ppm; 13C NMR (75 MHz, CDCl₃) δ 142.4, 126.1, 35.9, 34.2, 32.9, 30.9, 28.2 ppm.
Example 4
Preparation of 1,3,5-tris-[5-(1-quinolinium)pentyl]benzene tribromide

A mixture of 1,3,5-tris-(5-bromopentyl)benzene (251 mg, 0.48 mmol) and quinoline (930 mg, 7.20 mmol) was heated at 60-70°C for 12 hours. The resultant mixture was washed with diethyl ether and then dissolved in water (15 mL), the aqueous solution was washed with diethyl ether (30 mL x 5), then lyophilized to afford 390 mg of 1,3,5-tris-[5-(1-quinolinium)pentyl]-benzene tribromide. Yield 89%. 1H NMR (300 MHz, CD3OD) δ 9.46 (dd, J=6.0, 1.5 Hz, 3H), 9.22 (d, J=8.4 Hz, 3H), 8.57 (d, J=9.0 Hz, 3H), 8.45 (dd, J=8.4, 1.5 Hz, 3H), 8.30 (m, 3H), 8.02-8.14 (m, 6H), 6.8 (s, 3H), 5.11 (t, 7.5 Hz, 6H), 2.56 (t, J=7.5 Hz, 6H), 2.14 (m, 6H), 1.69 (m, 6H), 1.52 (m, 6H) ppm; 13C NMR (75 MHz, CD3OD) δ 150.3, 148.9, 143.4, 139.4, 137.3, 132.2, 131.8, 131.4, 127.2, 123.1, 119.9, 59.4, 36.7, 32.3, 31.1, 27.3 ppm.

Example 5

A rat model of tonic inflammatory pain (the formalin test) was used in this study (Wheeler-Aceto and Cowan, 1991). Fifty µl of formalin (5%) was injected subcutaneously (SC) into the dorsal surface of the left hind paw. This procedure typically produces a biphasic behavioral response consisting of flinching, lifting and licking. The first phase (0-10 min) is thought to result from direct stimulation of nociceptors (nociceptive pain) whereas the second phase (20-60 min) is thought to involve central sensitization. Rats (4-8/dose/treatment) were pretreated 15 min prior to formalin (SC) injection with GZ-556A (90-180 mg/kg) administered by the IP route. Saline served as control. Incidences of formalin-induced flinching were counted continuously in 5 min intervals for 60 min. Each rat received only one treatment. The results are presented in FIGS. 1 and 2.

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications can be made without departing from the spirit and scope of the invention. All such 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.

What is claimed is:

1. A method for treating neuropathic pain resulting from damage to the peripheral nervous system, comprising administering to a mammalian subject in need thereof a therapeutically effective amount of a compound of Formula (I):

   \[
   \begin{align*}
   X^1 & \otimes R^1 = -(CH_2)_{n_1} = L^1 = -(CH_2)_{n_2} = R^2 \otimes X^1 \\
   X^2 & \otimes R^2 = -(CH_2)_{n_2} = L^2 = -(CH_2)_{n_3} = R^3 \otimes X^1 \\
   X^3 & \otimes R^3 = -(CH_2)_{n_3} = L^3 = -(CH_2)_{n_4} = R^4 \otimes X^1
   \end{align*}
   \]

   wherein

   - the three side chains attached to the phenyl ring are connected to the 1, 3 and 5 positions of the phenyl ring;
   - m1, m2 and m3 are each 0;
   - n1, n2, and n3 are each 3;
   - X1, X2, and X3 are each independently an organic or inorganic anion;
   - L1, L2 and L3 are each -(CH2)n;
   - R1, R2, and R3 are each quinolinium or isoquinolinium and attached to (CH2)n, (CH2)n', or (CH2)n at the quaternized nitrogen of the quinolinium or isoquinolinium.

2. The method of claim 1, wherein the compound of Formula (I) is 1,3,5-tris-[5-(1-quinolinium)-pentyl]-benzene tribromide.

3. The method of claim 1, wherein the pain is chronic.

4. The method of claim 1, wherein the pain is cancer-related.

5. The method of claim 1, wherein the pain is non-malignant.

6. A method for treating inflammatory pain resulting from activation of peripheral nociceptor, comprising administering to a mammalian subject in need thereof a therapeutically effective amount of a compound of Formula (I):

   \[
   \begin{align*}
   X^1 & \otimes R^1 = -(CH_2)_{n_1} = L^1 = -(CH_2)_{n_2} = R^2 \otimes X^1 \\
   X^2 & \otimes R^2 = -(CH_2)_{n_2} = L^2 = -(CH_2)_{n_3} = R^3 \otimes X^1 \\
   X^3 & \otimes R^3 = -(CH_2)_{n_3} = L^3 = -(CH_2)_{n_4} = R^4 \otimes X^1
   \end{align*}
   \]

   wherein

   - the three side chains attached to the phenyl ring are connected to the 1, 3 and 5 positions of the phenyl ring;
   - m1, m2 and m3 are each 0;
   - n1, n2, and n3 are each 3;
   - X1, X2, and X3 are each independently an organic or inorganic anion;
   - L1, L2 and L3 are each -(CH2)n;
   - R1, R2, and R3 are each quinolinium or isoquinolinium and attached to (CH2)n, (CH2)n', or (CH2)n at the quaternized nitrogen of the quinolinium or isoquinolinium.

7. The method of claim 6, wherein the compound of Formula (I) is 1,3,5-tris-[5-(1-quinolinium)-pentyl]-benzene tribromide.

* * * *