Use of *Tris*-Quaternary Ammonium Salts as Pain Modulating Agents

Joseph R. Holtman  
*University of Kentucky*, jrhol2@uky.edu

Peter Anthony Crooks  
*University of Kentucky*

Linda P. Dwoskin  
*University of Kentucky*, ldwoskin@email.uky.edu

J. Michael McIntosh  
*University of Kentucky*

Follow this and additional works at: [https://uknowledge.uky.edu/ps_patents](https://uknowledge.uky.edu/ps_patents)

Part of the [Pharmacy and Pharmaceutical Sciences Commons](https://uknowledge.uky.edu/ps_patents)

Recommended Citation

Holtman, Joseph R.; Crooks, Peter Anthony; Dwoskin, Linda P.; and McIntosh, J. Michael, "Use of *Tris*-Quaternary Ammonium Salts as Pain Modulating Agents" (2015). *Pharmaceutical Sciences Faculty Patents*. 40.  
[https://uknowledge.uky.edu/ps_patents/40](https://uknowledge.uky.edu/ps_patents/40)

This Patent is brought to you for free and open access by the Pharmaceutical Sciences at UKnowledge. It has been accepted for inclusion in Pharmaceutical Sciences Faculty Patents by an authorized administrator of UKnowledge. For more information, please contact UKnowledge@lsv.uky.edu.
USE OF TRIS-QUATERNARY AMMONIUM SALTS AS PAIN MODULATING AGENTS

Inventors: Joseph R. Holtman, Lexington, KY (US); Peter Anthony Crooks, Nicholasville, KY (US); Linda P. Dwoskin, Lexington, KY (US); J. Michael McIntosh, Salt Lake City, UT (US)

Assignees: University of Kentucky Research Foundation, Lexington, KY (US); University of Utah, Salt Lake City, UT (US)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 623 days.

Appl. No.: 12/576,300
Filed: Oct. 9, 2009

Prior Publication Data

Related U.S. Application Data
Provisional application No. 61/195,824, filed on Oct. 10, 2008.

Int. Cl. A01N 43/42 (2006.01)
A61K 31/47 (2006.01)
A61K 31/4709 (2006.01)

U.S. Cl.
CPC ................................. A61K 31/4709 (2013.01)

Field of Classification Search
None
See application file for complete search history.

REFERENCES CITED

U.S. PATENT DOCUMENTS
2013/0030018 A1 1/2013 Crooks et al.

FOREIGN PATENT DOCUMENTS

OTHER PUBLICATIONS
Finnerup et al. (Fundamental & Clinical Pharmacology, 2007, 21, 129-136).*

* cited by examiner

Primary Examiner — Dennis Heyer
Assistant Examiner — Daniel M Podgorski
Attorney, Agent, or Firm — Crowell & Moring LLP

ABSTRACT
Provided are tris-quaternary ammonium compounds which are modulators of nociception and pain.

7 Claims, 2 Drawing Sheets
Figure 1

GZ-556A

[Graph showing the effect of GZ-556A on flinches at different dose levels and time points.]
Figure 2
GZ-556A

Mean +/- SEM (n = 2-3 rats)
USE OF TRIS-QUATERNARY AMMONIUM SALTS AS PAIN MODULATING AGENTS

FIELD OF THE INVENTION

The invention relates to the use of tris-quaternary ammonium salts for pain modulation.

BACKGROUND OF THE INVENTION

The treatment of pain is a critical health issue. Acute (eg. postoperative pain) and chronic (eg. arthritis, low back, cancer) pain affects tens of millions of people annually in the US. Each year some 30 million people visit a physician with a complaint of a painful condition. Some 10% of these patients are seen with chronic pain as their main complaint. The financial loss due to pain has been estimated to exceed 100 billion dollars a year as a result of medical fees, decreased productivity, 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 postoperative pain) and chronic (eg. arthritis, low back, cancer) pain affects tens of millions of people annually in the US. Each year some 30 million people visit a physician with a complaint of a painful condition. Some 10% of these patients are seen with chronic pain as their main complaint. The financial loss due to pain has been estimated to exceed 100 billion dollars a year as a result of medical fees, decreased productivity, 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.

Nociceptive pain occurs as a result of a noxious or inflammatory origin (eg. arthritis). However, the NSAID's have limited efficacy when compared to the opioids. In addition, NSAID's have significant side effects (renal, gastrointestinal, cardiovascular). The discovery of the Cox-2 selective agents (eg. rofecoxib-Vioxx®, celecoxib-Celebrex®; valdecoxib-Bextra®) which have far less gastrointestinal toxicity, was thought to be an advance in NSAID pharmacology. Nonetheless, these agents still have low efficacy and evidence is now available linking them to significant cardiovascular events including stroke and myocardial infarction following chronic use. This has resulted in the removal of both rofecoxib and valdecoxib from the market. No suitable agent exists for the treatment of neuropathic pain. GABA- pastin (Neurontin®), an anticonvulsant, has found use for some neuropathic pain syndromes (eg. diabetic peripheral neuropathy, postherpetic neuralgia), but it still has limited efficacy. Duloxetine (Cymbalta®), an antidepressant, has recently been approved for the treatment of diabetic peripheral neuropathy. However, it has limited efficacy and usefulness for other neuropathic pain states. The N-methyl-D-aspartate (NMDA) receptor antagonists (eg. ketamine) have been proposed for the treatment of neuropathic pain. Their general use is impractical given the marked side effects including sedation, psychosis and motor impairment. The limitations of the currently available therapies clearly demonstrate the need for a broad spectrum new class of efficacious and safe analgesic drugs for the treatment of nociceptive and neuropathic pain.

Given the need for more effective, less toxic, analgesic drugs, a great deal of emphasis has been placed on identifying novel molecular targets that could form the basis for new analogues.

SUMMARY OF INVENTION

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

\[
X^1\Theta\Theta R^2 \rightarrow (CH_2)_m \rightarrow L^2 \rightarrow (CH_2)_n \rightarrow R^3 \Theta \Theta X^1
\]

In many patients, in particular those with chronic pain conditions of malignant (cancer-related pain) and non-malignant (arthritis, low back pain, CRPS) origin, pain is inadequately managed with currently available drugs. Available drugs are simple modifications (eg. extended release) of drugs from classes which have been available for decades including the opioids, nonsteroidal anti-inflammatory agents (NSAID's) or various adjuvants (antidepressants, anticonvulsants) initially approved for other uses besides pain. Opioids (eg. morphine, oxycodone) are often successfully used for the treatment of moderate to severe nociceptive pain. Chronic neuropathic pain is much less responsive to opioids. Use of opioid analgesics is associated with a broad range of significant side effects including cognitive impairment, respiratory depression and constipation. In addition, long-term opioid dosing results in the development of tolerance to the analgesic effect, drug abuse and dependence. The NSAID's (eg. ibuprofen) act by inhibition of the cyclo-oxygenase (Cox-1,2) enzyme. They are especially useful in nociceptive pain of inflammatory origin (eg. arthritis). However, the NSAID's have limited efficacy when compared to the opioids. In addition, NSAID's have significant side effects (renal, gastrointestinal, cardiovascular). The discovery of the Cox-2 selective agents (eg. rofecoxib-Vioxx®, celecoxib-Celebrex®, valdecoxib-Bextra®) which have far less gastrointestinal toxicity, was thought to be an advance in NSAID pharmacology. Nonetheless, these agents still have low efficacy and evidence is now available linking them to significant cardiovascular events including stroke and myocardial infarction following chronic use. This has resulted in the removal of both rofecoxib and valdecoxib from the market. No suitable agent exists for the treatment of neuropathic pain. GABA-pastin (Neurontin®), an anticonvulsant, has found use for some neuropathic pain syndromes (eg. diabetic peripheral neuropathy, postherpetic neuralgia), but it still has limited efficacy. Duloxetine (Cymbalta®), an antidepressant, has recently been approved for the treatment of diabetic peripheral neuropathy. However, it has limited efficacy and usefulness for other neuropathic pain states. The N-methyl-D-aspartate (NMDA) receptor antagonists (eg. ketamine) have been proposed for the treatment of neuropathic pain. Their general use is impractical given the marked side effects including sedation, psychosis and motor impairment. The limitations of the currently available therapies clearly demonstrate the need for a broad spectrum new class of efficacious and safe analgesic drugs for the treatment of nociceptive and neuropathic pain. Given the need for more effective, less toxic, analgesic drugs, a great deal of emphasis has been placed on identifying novel molecular targets that could form the basis for new analogues.
A1 is carbon or nitrogen, provided that when A1 joins a ring atom with an unsaturated bond or is a nitrogen, R1 is absent and when A1 joins a ring atom with an unsaturated bond and is a nitrogen, both R2 and R3 are absent.

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 R5 and R6 are absent.

A3 is carbon or nitrogen, provided that when A3 joins a ring atom with an unsaturated bond or is a nitrogen, R7 is absent and when A3 joins a ring atom with an unsaturated bond and is a nitrogen, both R8 and R9 are absent.

A4 is carbon or nitrogen, provided that when A4 joins a ring atom with an unsaturated bond or is a nitrogen, R10 is absent and when A4 joins a ring atom with an unsaturated bond and is a nitrogen, both R11 and R12 are absent.

A5 is carbon or nitrogen, provided that when A5 joins a ring atom with an unsaturated bond or is a nitrogen, R13 is absent and when A5 joins a ring atom with an unsaturated bond and is a nitrogen, both R14 and R15 are absent.

A6 is carbon or nitrogen, provided that when A6 joins a ring atom with an unsaturated bond or is a nitrogen, R16 is absent and when A6 joins a ring atom with an unsaturated bond and is a nitrogen, both R17 and R18 are absent.

A7 is carbon or nitrogen, provided that when A7 joins a ring atom with an unsaturated bond or is a nitrogen, R19 is absent and when A7 joins a ring atom with an unsaturated bond and is a nitrogen, both R20 and R21 are absent.

A8 is carbon or nitrogen, provided that when A8 joins a ring atom with an unsaturated bond or is a nitrogen, R22 is absent and when A8 joins a ring atom with an unsaturated bond and is a nitrogen, both R23 and R24 are absent.

A9 is carbon or nitrogen, provided that when A9 joins a ring atom with an unsaturated bond or is a nitrogen, R25 is absent and when A9 joins a ring atom with an unsaturated bond and is a nitrogen, both R26 and R27 are absent.

A10 is carbon or nitrogen, provided that when A10 joins a ring atom with an unsaturated bond or is a nitrogen, R28 is absent and when A10 joins a ring atom with an unsaturated bond and is a nitrogen, both R29 and R30 are absent.

A11 is carbon or nitrogen, provided that when A11 joins a ring atom with an unsaturated bond or is a nitrogen, R31 is absent and when A11 joins a ring atom with an unsaturated bond and is a nitrogen, both R32 and R33 are absent.

A12 is carbon or nitrogen, provided that when A12 joins a ring atom with an unsaturated bond or is a nitrogen, R34 is absent and when A12 joins a ring atom with an unsaturated bond and is a nitrogen, both R35 and R36 are absent.

A13 is carbon or nitrogen, provided that when A13 joins a ring atom with an unsaturated bond or is a nitrogen, R37 is absent and when A13 joins a ring atom with an unsaturated bond and is a nitrogen, both R38 and R39 are absent.

A14 is carbon or nitrogen, provided that when A14 joins a ring atom with an unsaturated bond or is a nitrogen, R40 is absent and when A14 joins a ring atom with an unsaturated bond and is a nitrogen, both R41 and R42 are absent.

A15 is carbon or nitrogen, provided that when A15 joins a ring atom with an unsaturated bond or is a nitrogen, R43 is absent and when A15 joins a ring atom with an unsaturated bond and is a nitrogen, both R44 and R45 are absent.

A16 is carbon or nitrogen, provided that when A16 joins a ring atom with an unsaturated bond or is a nitrogen, R46 is absent and when A16 joins a ring atom with an unsaturated bond and is a nitrogen, both R47 and R48 are absent.

A17 is carbon or nitrogen, provided that when A17 joins a ring atom with an unsaturated bond or is a nitrogen, R49 is absent and when A17 joins a ring atom with an unsaturated bond and is a nitrogen, both R50 and R51 are absent.

A18 is carbon or nitrogen, provided that when A18 joins a ring atom with an unsaturated bond or is a nitrogen, R52 is absent and when A18 joins a ring atom with an unsaturated bond and is a nitrogen, both R53 and R54 are absent.

A19 is carbon or nitrogen, provided that when A19 joins a ring atom with an unsaturated bond or is a nitrogen, R55 is absent and when A19 joins a ring atom with an unsaturated bond and is a nitrogen, both R56 and R57 are absent.

A20 is carbon or nitrogen, provided that when A20 joins a ring atom with an unsaturated bond or is a nitrogen, R58 is absent and when A20 joins a ring atom with an unsaturated bond and is a nitrogen, both R59 and R60 are absent.

A21 is carbon or nitrogen, provided that when A21 joins a ring atom with an unsaturated bond or is a nitrogen, R61 is absent and when A21 joins a ring atom with an unsaturated bond and is a nitrogen, both R62 and R63 are absent.

A22 is carbon or nitrogen, provided that when A22 joins a ring atom with an unsaturated bond or is a nitrogen, R64 is absent and when A22 joins a ring atom with an unsaturated bond and is a nitrogen, both R65 and R66 are absent.

A23 is carbon or nitrogen, provided that when A23 joins a ring atom with an unsaturated bond or is a nitrogen, R67 is absent and when A23 joins a ring atom with an unsaturated bond and is a nitrogen, both R68 and R69 are absent.

A24 is carbon or nitrogen, provided that when A24 joins a ring atom with an unsaturated bond or is a nitrogen, R70 is absent and when A24 joins a ring atom with an unsaturated bond and is a nitrogen, both R71 and R72 are absent.

A25 is carbon or nitrogen, provided that when A25 joins a ring atom with an unsaturated bond or is a nitrogen, R73 is absent and when A25 joins a ring atom with an unsaturated bond and is a nitrogen, both R74 and R75 are absent.

A26 is carbon or nitrogen, provided that when A26 joins a ring atom with an unsaturated bond or is a nitrogen, R76 is absent and when A26 joins a ring atom with an unsaturated bond and is a nitrogen, both R77 and R78 are absent.

A27 is carbon or nitrogen, provided that when A27 joins a ring atom with an unsaturated bond or is a nitrogen, R79 is absent and when A27 joins a ring atom with an unsaturated bond and is a nitrogen, both R80 and R81 are absent.

A28 is carbon or nitrogen, provided that when A28 joins a ring atom with an unsaturated bond or is a nitrogen, R82 is absent and when A28 joins a ring atom with an unsaturated bond and is a nitrogen, both R83 and R84 are absent.

A29 is carbon or nitrogen, provided that when A29 joins a ring atom with an unsaturated bond or is a nitrogen, R85 is absent and when A29 joins a ring atom with an unsaturated bond and is a nitrogen, both R86 and R87 are absent.

A30 is carbon or nitrogen, provided that when A30 joins a ring atom with an unsaturated bond or is a nitrogen, R88 is absent and when A30 joins a ring atom with an unsaturated bond and is a nitrogen, both R89 and R90 are absent.

A31 is carbon or nitrogen, provided that when A31 joins a ring atom with an unsaturated bond or is a nitrogen, R91 is absent and when A31 joins a ring atom with an unsaturated bond and is a nitrogen, both R92 and R93 are absent.

A32 is carbon or nitrogen, provided that when A32 joins a ring atom with an unsaturated bond or is a nitrogen, R94 is absent and when A32 joins a ring atom with an unsaturated bond and is a nitrogen, both R95 and R96 are absent.

A33 is carbon or nitrogen, provided that when A33 joins a ring atom with an unsaturated bond or is a nitrogen, R97 is absent and when A33 joins a ring atom with an unsaturated bond and is a nitrogen, both R98 and R99 are absent.

A34 is carbon or nitrogen, provided that when A34 joins a ring atom with an unsaturated bond or is a nitrogen, R100 is absent and when A34 joins a ring atom with an unsaturated bond and is a nitrogen, both R101 and R102 are absent.

A35 is carbon or nitrogen, provided that when A35 joins a ring atom with an unsaturated bond or is a nitrogen, R103 is absent and when A35 joins a ring atom with an unsaturated bond and is a nitrogen, both R104 and R105 are absent.

A36 is carbon or nitrogen, provided that when A36 joins a ring atom with an unsaturated bond or is a nitrogen, R106 is absent and when A36 joins a ring atom with an unsaturated bond and is a nitrogen, both R107 and R108 are absent.

A37 is carbon or nitrogen, provided that when A37 joins a ring atom with an unsaturated bond or is a nitrogen, R109 is absent and when A37 joins a ring atom with an unsaturated bond and is a nitrogen, both R110 and R111 are absent.

A38 is carbon or nitrogen, provided that when A38 joins a ring atom with an unsaturated bond or is a nitrogen, R112 is absent and when A38 joins a ring atom with an unsaturated bond and is a nitrogen, both R113 and R114 are absent.
FIG. 1 shows the time course 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 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 those 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 entitled to antedate such disclosure by virtue of prior invention.

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 “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, 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 radicals having in the range of 1 to 4 carbon atoms.

The term “alkenyI” refers to straight or branched chain hydrocarbyl radicals 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 radicals having 2 to 19 carbon atoms, and “substituted alkynyl” refers to alky...
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 a nitrogen and is a nitrogen, both R and R 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 and R 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 and R are absent.

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

A is carbon or nitrogen, provided that when A joins a ring atom with an unsaturated bond or a nitrogen, R is absent, and when A joins a ring atom with an unsaturated bond and is a nitrogen, both R and R 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 and R 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 and R 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 and R 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 and R are absent.
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 aziridine, methyl N-methyl aziridine, 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-methyl azepane, methyl azocane, methyl N-methyl azocane, methyl unsaturated azocane, methyl unsaturated N-methyl azocane, methyl-1-aza-bicyclo[3.2.1]octane, methyl-1-aza-bicyclo[2.2.1]heptane, 8-methyl-1-aza-bicyclo[3.2.1]octane, and methyl-1-aza-tricyclo[3.3.1.1^3.7]decane.

As a further example, when R^4 and R^5 together with A^1 and A^2 and R^6 and R^7 together with A^3 and A^4, or R^15 and R^16 together with A^6 and A^7, or R^1 and R^2 together with A^6 and A^7, and A^3 and R^6 independently form a three to eight-membered ring, that ring can be a heterocyclic 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, isodioene, benzo furan, isobenzofuran, benzol[b] thiophene, benzol[b]thiophene, indole, indolenine, isoindole, cyclopentab[b]pyridine, pyrano[3,4-b]pyrrole, indazol, indoxazol, benzoxazole, anthranil naphthalene, tetralin, decalin, chromene, coumarin, chroman-4-one, isocoumarin, isochromen-3-one, quinoline, isoquinoline, cinnoline, quinoxalin, naphthylidine, pyridil[3,4-b]-pyridine, pyrilo[3,2-b]pyridine, pyrido[4,3-b]pyridazine, benzoxazine, anthracene, phenanthrene, phenalen, fluorene, carbazole, xanthene, acenine, octahydro-[1]pyridine, 1-methylloctahydro-[1]pyridine, octahydroindol, 1-methyloctahydro-indole, octahydro-cyclopentab[b]pyrrole, 1-methyloctahydro-cyclopetab[b]pyrrole, decacyclonouline, and 1-methyldecahydroquinoline.

X^18, X^28, and X^38 for example, include F-, Cl-, Br-, I-, NO_2, HSO_4, SO_4, HPO_4, PO_4, methanesulfonate, trifluormethane sulfate, p-toluenesulfonate, benzensusulfonate, salicylate, proprionate, ascorbate, aspartate, fumarate, galactarate, maleate, citrate, glutamate, glycolate, lactate, maleate, malate, 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 can be in some cases hydrates or solvates with alcohols and other solvents.

In a compound of Formula (I), preferably the phenyl ring is substituted at the 1, 3 and 5 positions.

In a compound of Formula (I), preferably A^1, A^2, A^3, A^4, A^5 and A^6 are carbon.

In a compound of Formula (I), preferably R^1, R^2, R^3 and R^4 are substituted, six-membered, aromatic rings. More preferably, R^1, R^2, R^3, and R^4 are substituted pyridinium rings.

In a compound of Formula (I), preferably R^5 is hydrogen, alkyl, or forms an aryl ring with A^1, A^2 and R^6. More preferably, R^5 is hydrogen, alkyl, or forms a phenyl group with A^1, A^2 and R^6.

In a compound of Formula (I), preferably R^5 is hydrogen, alkyl, phenyl, 1-methyl-2-pyrrolidinyl, forms a six-membered ring with A^1, A^2 and R^6. More preferably, R^5 is hydrogen, alkyl, or forms an aryl ring with A^1, A^2 and R^6. More preferably, R^5 is hydrogen, methyl, butyl, phenyl, 1-methyl-2-pyrrolidinyl, forms a phenyl group with A^1, A^2 and R^6, or forms a phenyl group with A^1, A^2 and R^6.
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 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 appropriate 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 can, for example, include oral, rectal, transmucosal, nasal, or intestinal administration and parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrahepatic, direct intraarticular, intravenous, intraperitoneal, 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’s 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, slurries, 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 carboxymethylcellulose, 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 such 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, cellulose gum, acacia, tragacanth, gelatin, alginate, casein, or the like. Moreover, lubricants 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 total 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 formulational 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 suitable stabilizers or agents 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, for example, 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 dimethyl sulfoxide 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 LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (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 LD₅₀/ED₅₀. Agents that exhibit high therapeutic indices are preferred.

Dosages preferably fall within a range of circulating concentrations that includes the ED₅₀ 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, depend upon 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 will fall within the scope of the appended claims.

Example 1

Preparation of 1,3,5-tris-(5-hydroxy-pent-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 2
Preparation of 1,3,5-tris-(5-hydroxypentyl)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-pentyl)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 3
Preparation of 1,3,5-tris-(5-bromopentyl)benzene

1,3,5-tris-(5-hydroxypentyl)benzene (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, 3H), 3.41 (t, J=6.9 Hz, 6H), 2.60 (t, J=7.5 Hz, 6H), 1.88 (m, 6H); 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, 4H), 8.30 (m, 3H), 8.02-8.14 (m, 6H), 6.8 (s, 3H), 5.11 (t, J=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):

\[
\text{Formula (I)}
\]

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-CH2-; R1, R2, and R3 are each quinolinium or isoquinolinium and attached to (CH2)n1, (CH2)n2, or (CH2)n3 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 pain.

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

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):

\[
\text{Formula (I)}
\]

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-CH2-; R1, R2, and R3 are each quinolinium or isoquinolinium and attached to (CH2)n1, (CH2)n2, or (CH2)n3 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.