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MERIDAMYCIN ANALOGUES FOR THE TREATMENT OF NEURODEGENERATIVE DISORDERS

BACKGROUND OF THE INVENTION

This invention relates to meridamycin compounds, methods of preparation, and methods of use thereof.

Meridamycin has been identified for uses such as an antidote for an overdose of macrophilin-binding-immunosuppressants such as FK506 or rapamycin, a steroid potentiator, and/or an anti-infective agent for infections or infectious diseases caused by organisms producing MIP (macrophage infectivity potentiator) or Mip-like factors. See, International Patent Publication No. WO 94/18207. In addition, meridamycin may be useful in the treatment of inflammatory/hyperproliferative skin diseases.

Meridamycin has been isolated from a strain of *Streptomyces hydroscopicus* as described in Salituro et al., Tet. Lett, 36(7): 997-1000 (1995).

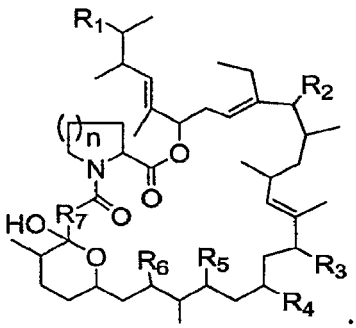
Meridamycin and derivatives thereof have been prepared as described in US Published Patent Application No. US 2005/0272133A1 (Dec 8, 2005; US Patent Appln No. 11/143,980) and US Patent Application Publication No. US 2005-0197379-A1. Compounds derived from meridamycin (described in International Patent Publication No. WO 2005/084673) have been shown to demonstrate neuroprotective effects (see also, International Patent Publication No. WO 2005/085257 and US Patent Application Publication No. US 2005-0197379 A1.

What are needed in the art are alternate meridamycin derivatives.

SUMMARY OF THE INVENTION

In one aspect, the invention provides a compound of the structure:

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In another aspect, the invention provides methods of preparing the compounds of the invention.

In still another aspect, the invention provides compositions containing the compounds of the invention.

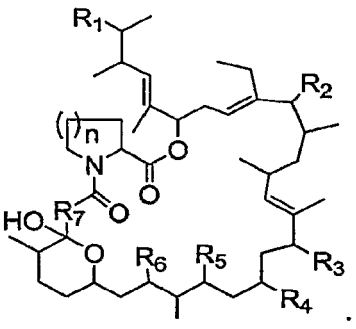
In a further aspect, the invention provides for the use of the compounds of the invention in preparing medicaments.

In still a further aspect, the invention provides a method of treating a neurological disorder comprising administering a compound of the invention to a mammalian subject.

Other aspects and advantages of the invention will be readily apparent from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

As described herein, the invention provides a compound of the structure:

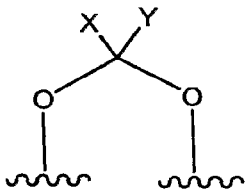


wherein:

R_1 and R_2 are, independently selected from the group consisting of, OH, oxo, O(C_1 to C_6 alkyl), O(substituted C_1 to C_6 alkyl), O(acyl), O(aryl), O(substituted aryl), or O(heterocyclyl), O(substituted heterocyclyl);

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of OH, oxo, O(C_1 to C_6 alkyl), O(substituted C_1 to C_6 alkyl), O(acyl), O(aryl), O(substituted aryl), O(heterocyclyl), and O(substituted heterocyclyl); or

R_3 and R_4 and/or R_4 and R_5, or R_5 and R_6. are joined (taken together) to form a structure: –



wherein X and Y are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl;

R_7 is CH_2, CHOH, or C=O; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment, R_1 and R_2 are independently selected from among oxo, OH or O(acyl). One suitable O(acyl) is $OC(O)CH_3$. Other suitable O(acyl)s can be selected.

In another embodiment, R_3 and R_4 or R_4 and R_5 are joined, wherein X and Y are CH_3.

In yet another embodiment, R_7 is C(O).

In still another embodiment, R_1 and R_2 are OH; R_3 and R_4 are joined; R_5 and R_6 are joined; R_7 is C(O); and n is 2

In yet another embodiment, R_1, R_2, R_3, R_4, R_5, and R_6 are $OC(O)CH_3$; R_7 is C(O); and n is 2.

In another embodiment, R_1, R_2, R_3, and R_4 are $OC(O)CH_3$; R_4 and R_5 are OH; R_7 is C(O); and n is 2.

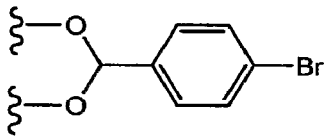
In still another embodiment, R_1, R_2, R_5, and R_6 are OH; R_3 and R_4 are joined; R_7 is C(O); and n is 2.

In a further embodiment, R_1, R_2, R_3, R_4, and R_5 are $OC(O)CH_3$; R_6 is OH; R_7 is C(O); and n is 2.

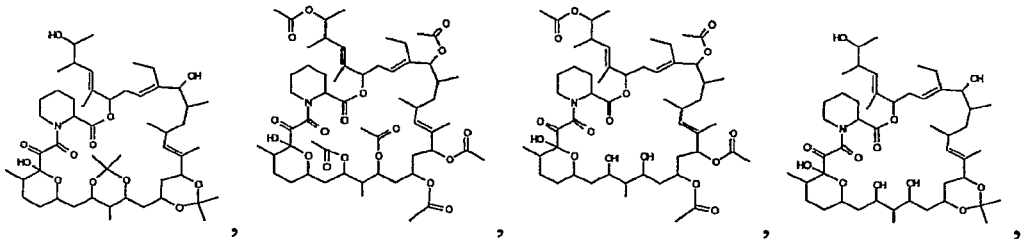
In another embodiment, R_1 and R_2 are oxo; R_3 and R_4 and R_5 and R_6 are joined; R_7 is C(O); and n is 2.

In yet another embodiment, R_1 and R_2 are oxo; R_3, R_4, R_5, and R_6 are OH; R_7 is C(O); and n is 2.

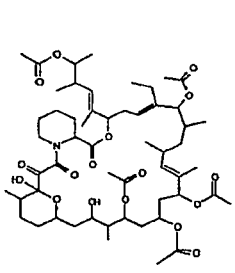
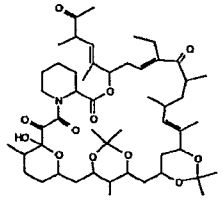
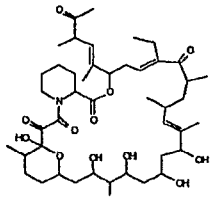
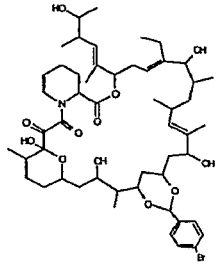
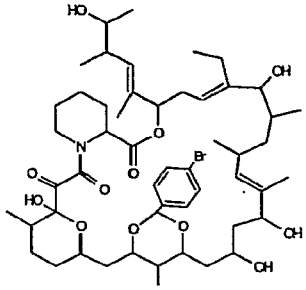
In a further embodiment, R_4 and R_5 are taken together to form a ring of the structure



Examples of suitable compounds of the invention include:



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The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having one to ten carbon atoms, desirably one to eight carbon atoms and, most desirably, one to six carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with at least one carbon-carbon double bond and two to eight carbon atoms, desirably two to six carbon atoms; "alkynyl" group is intended to cover both straight- and branched-chain alkyl groups with at least one carbon-carbon triple bond and two to eight carbon atoms, desirably two to six carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl and n-butyl. Examples of alkenyl include ethenyl, prop-1-yl and prop-2-yl. Examples of alkynyl include ethynyl.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl groups defined above having from one to three substituents selected from halogen, CN, OH, NO_2, amino, aryl, heterocyclyl, substituted aryl, substituted heterocyclyl, alkoxy, substituted alkoxy, aryloxy, substituted aryloxy, alkylcarbonyl, alkylcarboxy, alkylamino, and arylthio. Where there is more than one substituent they may be the same or different. These substituents may be attached to any carbon of an alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refer to a carbocyclic aromatic system, which may be a single ring, or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl, and indane. The aryl is suitably a 6 to 13 carbon aryl or a 6 to 10 carbon aryl.

The term "substituted aryl" refers to aryl as defined above having one to four substituents selected from halogen, CN, OH, NO_2, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, and arylthio. Where there is more than one substituent they may be the same or different.

The term "heterocyclyl" is used herein to describe a 4- to 7-membered monocyclic or a stable multicyclic heterocyclyl ring which is saturated, partially unsaturated, or unsaturated, and which includes carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized. The heterocyclyl ring also includes any multicyclic ring in which any of above defined heterocyclyl rings is fused to an aryl ring. The heterocyclyl ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclyl groups include, for example, tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, isoquinolinyl, and tetrahydrothiopyran.

The term "substituted heterocyclyl" is used herein to describe the heterocyclyl defined above having one to four substituents selected from halogen, CN, OH, NO_2, amino, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, aryloxy, substituted aryloxy, alkyloxy, substituted alkyloxy, alkylcarbonyl, substituted alkylcarbonyl, alkylcarboxy, substituted alkylcarboxy, alkylamino, substituted alkylamino,

arylthioand substituted arylthio. Where there is more than one substituent they may be the same or different.

The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl as defined above and the point of attachment is on the oxygen atom.

The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl as defined above and the point of attachment is on the oxygen atom.

The term "arylthio" is used herein to refer to the SR group, where R is aryl or substituted aryl as defined above and the point of attachment is on the sulfur atom.

The term "alkylcarbonyl" or "acyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl as defined above and the point of attachment is on the carbon atom.

The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl as defined above and the point of attachment is on the carbon atom.

The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups, as defined above e.g.containing one to eight carbon atoms, which may be either the same or different and the point of attachment is on the nitrogen atom.

The term "halogen" refers to Cl, Br, F, or I.

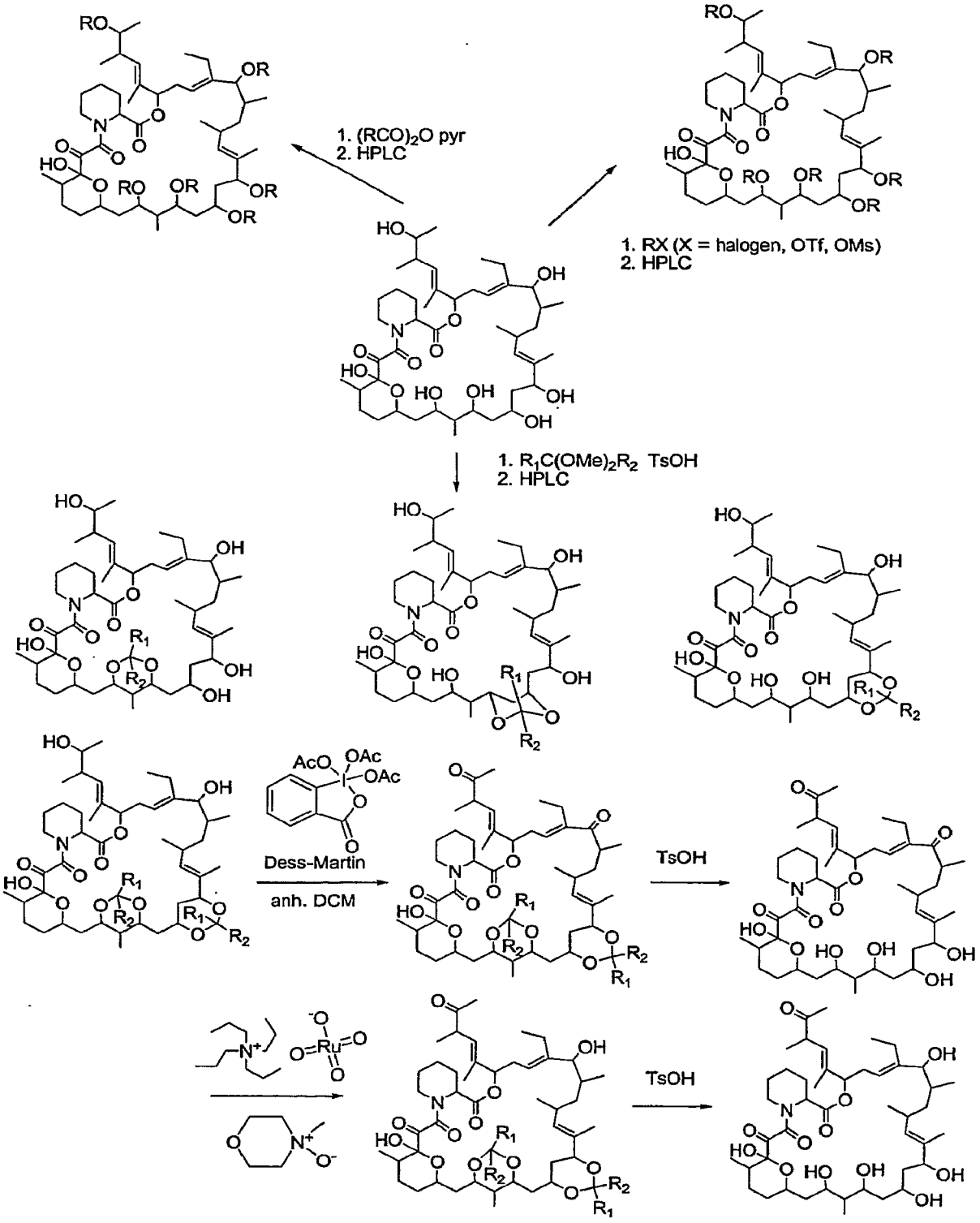
The compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include, but are not limited to, the following salts with organic and inorganic acids such as acetic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, mallic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, toluenesulfonic and similarly known acceptable acids, and mixtures thereof.

These salts, as well as other compounds of the invention may be in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo*. In one embodiment, the prodrugs are esters. See, e.g., B. Testa and J. Caldwell, "Prodrugs Revisited: The

"Ad Hoc" Approach as a Complement to Ligand Design", Medicinal Research Reviews, 16(3):233-241, ed., John Wiley & Sons (1996).

The compounds of the present invention can be prepared as described generally in the following schemes. These methods and variations thereof will be readily understood to one skilled in the art of organic synthesis. The compounds of the present invention can be prepared using the methods described below, together with synthetic methods known in the synthetic organic arts or variations of these methods by one skilled in the art. [See, generally, *Comprehensive Organic Synthesis*, "Selectivity, Strategy & Efficiency in Modern Organic Chemistry", ed., I. Fleming, Pergamon Press, New York (1991); *Comprehensive Organic Chemistry*, "The Synthesis and Reactions of Organic Compounds", ed. J.F. Stoddard, Pergamon Press, New York (1979)]. Suitable methods include, but are not limited to, those outlined below.

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1. (RCO)2O pyr
2. HPLC
1. RX (X = halogen, OTf, OMs)
2. HPLC
1. R1C(OMe)2R2 TsOH
2. HPLC
Dess-Martin
anh. DCM
TsOH
TsOH

In one aspect, the invention provides a method of preparing a compound having the structure I, wherein:

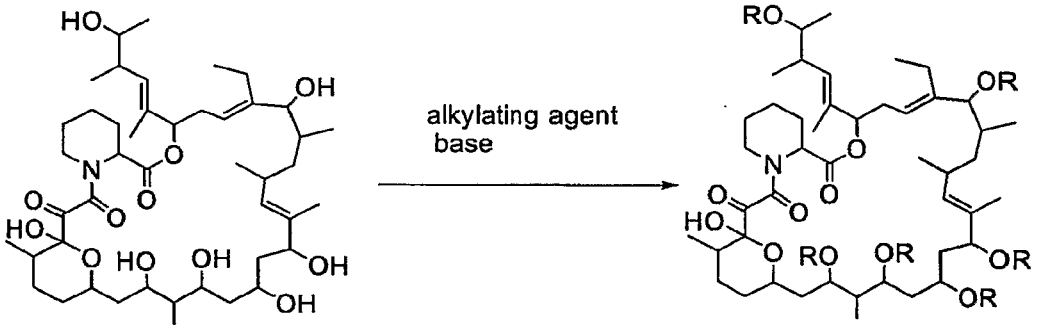
R_1, R_2, R_3, R_4, R_5, and R_6 are, independently, O(C_1 to C_6 alkyl) or O(substituted C_1 to C_6 alkyl);

R_7 is CH_2, CHOH, or C=O; and

n is 1 or 2;

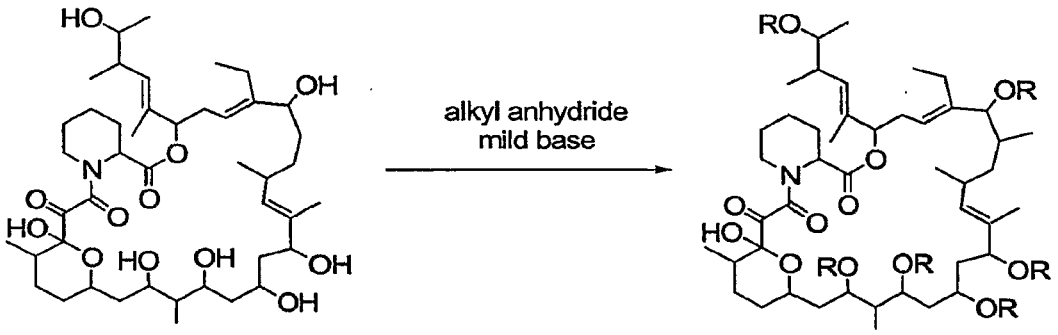
or a pharmaceutically acceptable salt thereof. This method involves reacting meridamycin with an alkylating agent or alkyl anhydride.

Meridamycin and derivatives thereof have been prepared as described in US Published Patent Application US 2005-0272133 A1 and US Patent Application Publication No. US 2005-0197379-A1, which are hereby incorporated by reference. However, the present invention is not limited by the source of meridamycin



Suitable alkylating agents may be readily selected from among an alkyl halide, alkyl triflate, or alkyl mesylate. However, other suitable reagents may be substituted. For compounds of the invention, when R^1 and R^2 are other than Oalkyl groups, an acid halide or aryl anhydride are typically utilized to obtain the compound of the invention. Typically, a mild base (e.g. pyridine) is utilized when the akylating agent is an anhydride. Alternatively, the reaction may be performed utilizing a suitable anhydride (e.g., acetic anhydride).

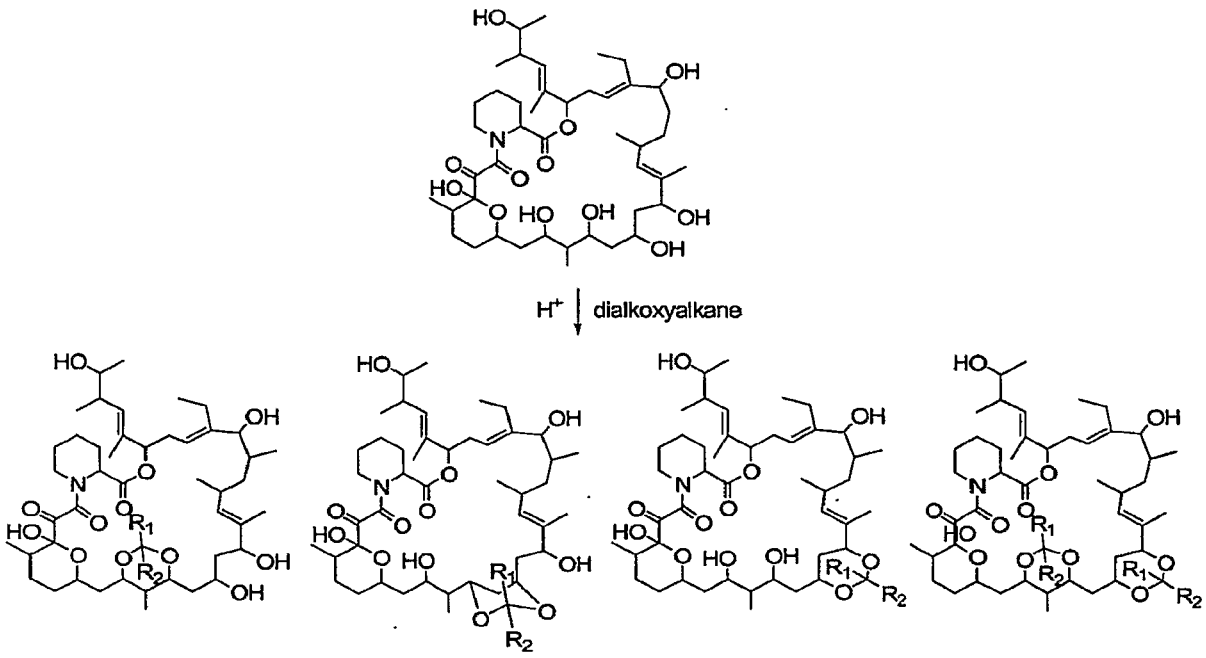
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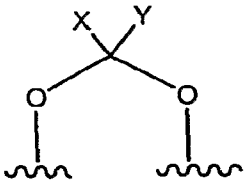
In another embodiment, the invention provides a method of preparing a compound of formula I, wherein R_1 and R_2 are OH; R_3 and R_4; R_4 and R_5; R_5 and R_6; or a combination thereof are joined, and Y are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyle; R_7 is CH_2, CHOH, or C=O; and n is 1 or 2;

or a pharmaceutically acceptable salt thereof. This method involves reacting meridamycin with a dialkoxyalkane in the presence of an acid catalyst, e.g., TsOH, paratoluenesulfonic acid, or another mild acid. In one embodiment, the dialkoxyalkane is 2,2-dimethoxypropane.

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In a further embodiment, the invention provides a method of preparing a compound of the structure I: wherein R_1 and R_2 are oxo; R_3 and R_4; R_4 and R_5; R_5 and R_6; or a combination thereof are joined; X and Y are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl; R_7 is CH_2, CHOH, or C=O; and n is 1 or 2; or a pharmaceutically acceptable salt thereof. This method involves reacting a compound of structure I, wherein: R_1 and R_2 are OH; R_3 and R_4; R_4 and R_5; R_5 and R_6; or a combination thereof are joined to form a structure: –



X and Y are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl;

R_7 is CH_2, CHOH, or C=O; and

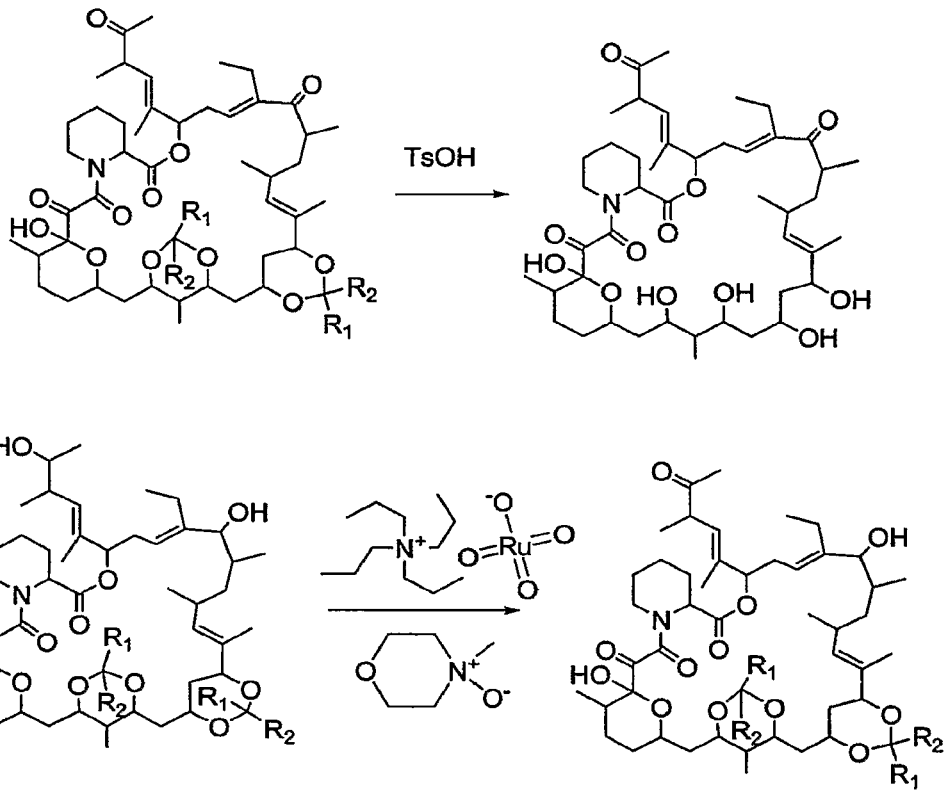
n is 1 or 2;

or a pharmaceutically acceptable salt thereof;

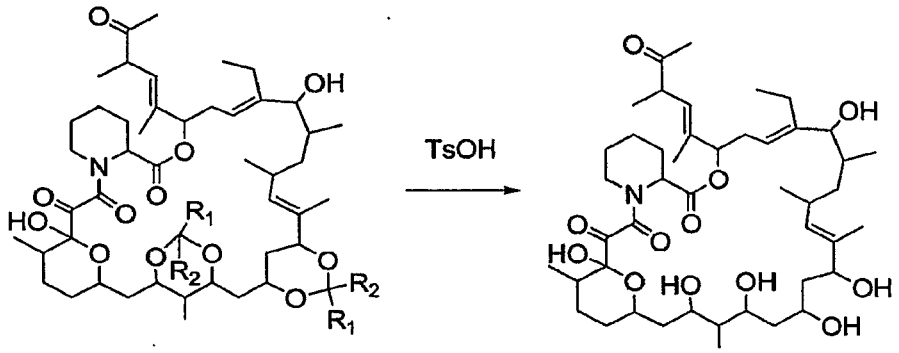
with the Dess-Martin periodinane reagent. Alternatively, the compound is reacted with tetrapropylammonium ruthenate and N-morpholine oxide

In still another aspect, the invention provides a method of preparing a compound of structure I, wherein: R_1 is oxo; R_2 is OH; R_3, R_4, R_5, and R_6 are OH; R_7 is CH_2, CHOH, or C=O; and n is 1 or 2; or a pharmaceutically acceptable salt thereof. This method involves reacting the product of the reaction with the Dess-Martin periodinane reagent (or the tetrapropylammonium ruthenate and N-morpholine oxide)

with a weak acid, e.g., paratoluenesulfonic acid.



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In one aspect, the invention provides the use of the meridamycin compounds produced by the routes described herein and the compounds of the invention in pharmaceutical compositions and methods for a variety of neurological disorders.

The term "preventing neurodegeneration" refers to preventing neuronal cell death by apoptosis, autophagy, or any other mechanism, resulting from a pathological condition including but not limited to a neurodegenerative disease, ischemia, trauma, and any condition resulting from an excess of an excitatory amino acid such as glutamate.

The term "promoting neuroregeneration" refers to inducing in neuronal cell events which include but are not limited to neurite outgrowth or long term potentiation. Neuroprotective agents are useful for the treatment of *e.g.*, neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, neuronal damage following ischemia or trauma, and any other pathological condition in which neuronal damage is implicated.

Although not intending to be limited in its therapeutic applications, it is desirable to use the meridamycin compounds described herein for treatment of conditions of the central nervous system, neurological disorders, and disorders of the peripheral nervous system. Conditions affecting the central nervous system include, but are not limited to, epilepsy, stroke, cerebral ischemia, cerebral palsy, multiple sclerosis, Alper's disease, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), dementia with Lewy bodies, Rhett syndrome, neuropathic pain, spinal cord trauma, or traumatic brain injury.

Neurological disorders according to the invention include, but are not limited to, various peripheral neuropathic and neurological disorders related to neurodegeneration including, but not limited to trigeminal neuralgia, glossopharyngeal neuralgia, Bell's palsy, myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar inherited muscular atrophy, herniated, ruptured or prolapsed vertebral disk syndromes, cervical spondylosis, plexus disorders, thoracic outlet destruction syndromes, peripheral neuropathies such as those caused by lead, acrylamides, gamma-diketones (glue-sniffer's neuropathy), carbon disulfide, dapsone, ticks, porphyria, Gullain-Barre syndrome, dementia, Alzheimer's disease, Parkinson's disease, and Huntington's chorea.

Specific situations in which neurotrophic therapy is indicated to be warranted include, but are not limited to, central nervous system disorders, Alzheimer's disease, aging, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, spinal cord injury, epilepsy, inflammatory disorders, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, psoriasis, adult respiratory distress syndrome, central nervous system trauma, and stroke.

The meridamycin compounds of this invention are also useful in preventing, treating or inhibiting senile dementias, dementia with Lewy bodies, mild cognitive impairment, Alzheimer's disease, cognitive decline, associated neurodegenerative disorders, as well as providing neuroprotection or cognition enhancement.

The term "subject" or "patient," as used herein, refers to a mammal, which may be a human or a non-human animal.

The terms "administer," "administering," or "administration," as used herein, refer to either directly administering a compound or composition to a patient, or administering a prodrug derivative or analog of the compound to the patient, which will form an equivalent amount of the active compound or substance within the patient's body.

The terms "effective amount" and "therapeutically effective amount," as used herein, refer to the amount of a compound that, when administered to a patient, is

effective to at least partially ameliorate a condition from which the patient is suspected to suffer.

When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that the effective dosage may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual subject being treated. Effective administration of the meridamycin compounds of this invention may be given at monthly, weekly, or daily, or other suitable intervals. For example, a parenteral dose may be delivered on a weekly basis at a dose of about 10 mg to about 1000 mg, about 50 mg to about 500 mg, or about 100 mg to about 250 mg per week. A suitable oral dose may be greater than about 0.1 mg/day. Preferably, administration will be greater than about 10 mg/day, more specifically greater than about 50 mg/day in a single dose or in two or more divided doses. The oral dose generally will not exceed about 1,000 mg/day and more specifically will not exceed about 600 mg/day. The projected daily dosages are expected to vary with route of administration.

Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, intranasally, vaginally, and transdermally.

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (*e.g.*, corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc,

sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The meridamycin compounds can also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

The invention further provides products, including packaging, containing the compounds formulated for delivery. In another aspect, the invention provides kits including, *e.g.*, needles, syringes, and other packaging, for delivery of the compound of the invention. Optionally, such a kit may include directions for administration of the drug, diluent, and or a carrier for mixing of a solid form of a compound of the invention.

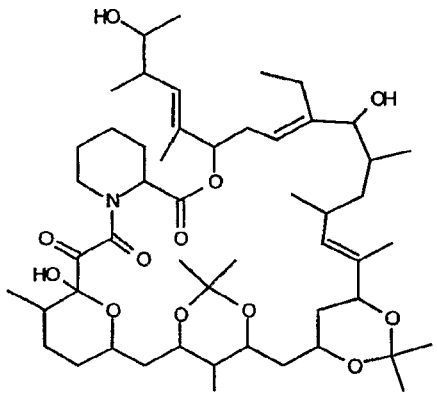
The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature.

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The following examples are illustrative only and are not intended to be a limitation on the present invention.

EXAMPLES

Example 1



Meridamycin (0.069 g, 0.084 mmol) was dissolved in 5 mL dimethylformamide (DMF). Excess 2,2-dimethoxypropane (0.5 mL, 4 mmol) and a catalytic amount of paratoluenesulfonic acid was added to this DMF solution. The reaction mixture was stirred at 25 °C for 20 hours with magnetic stirring. Chloroform (5 mL) was added to this mixture and the resulting solution was filtered over a small column of basic alumina. The products were then chromatographed via reversed-phase HPLC (column: 250 x 20 mm YMC ODS-A with 50 x 20 guard, mobile phase: 50 to 80 % acetonitrile:water in 30 minutes, then to 90% acetonitrile in 15 minutes, hold at 90% for an additional 15 minutes) to yield the product (0.028 g, 37% yield, t_R = 10.6 min, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid)/acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

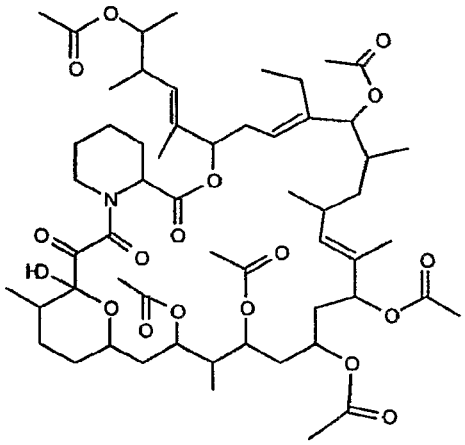
Theoretical Neutral Mass: 901.59153
Theoretical Elemental: $C_{51}H_{83}NO_{12}$

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Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+Na]^{1+}$	924.57895	924.58075	-1.80	-1.94	60.9

Example 2



Meridamycin (0.05 g, 0.06 mmol) was dissolved in pyridine (1.0 mL), acetic anhydride (1.0 mL) was added to this solution, and the reaction was stirred for 3 hours. The solvents were removed *in vacuo* and the products then chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 50 to 95 % acetonitrile:water in 20 minutes, hold at 95% for an additional 30 minutes) to yield a fraction that was further chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 80 % acetonitrile:water for 30 minutes, then to 90% acetonitrile in 5 minutes, hold at 95% for an additional 10 minutes) to yield the product (0.006 g, 9% yield, t_R = 8.07 minutes, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid) /acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

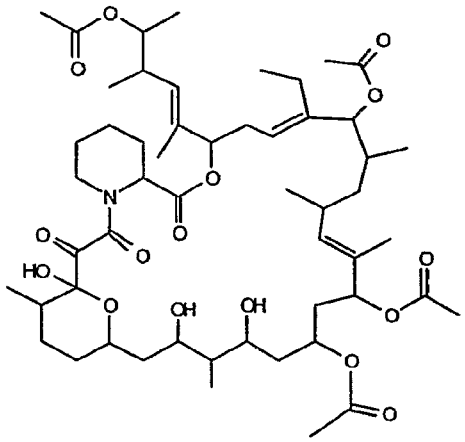
Theoretical Neutral Mass: 1073.59231
Theoretical Elemental: $C_{57}H_{87}NO_{18}$

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Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+Na]^{1+}$	1096.58138	1096.58153	-0.15	-0.13	100.0
$[M+NH_4]^{1+}$	1091.62488	1091.62613	-1.25	-1.15	3.9
$[M+K]^{1+}$	1112.55633	1112.55547	0.86	0.77	1.6
$[M+H+Na]^{2+}$	548.79139	548.79440	-3.01	-5.49	1.8

Example 3



Meridamycin (0.05 g, 0.06 mmol) was dissolved in pyridine (1.0 mL), acetic anhydride (1.0 mL) was added to this pyridine solution, and the reaction was allowed to stir for 3 hours. Solvents were removed *in vacuo* and the products were then chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 50 to 95 % acetonitrile:water in 20 minutes, hold at 95% for an additional 30 minutes) to yield the product (0.008 g, 14 % yield, t_R = 7.40 minutes, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid)/acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

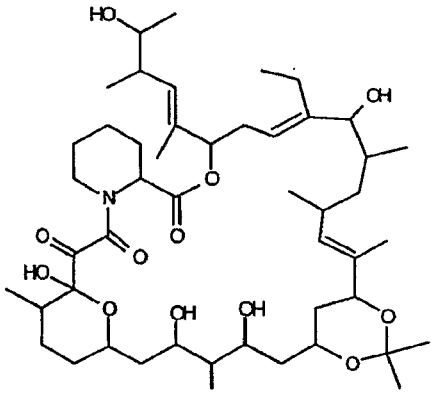
Theoretical Neutral Mass: 989.57119
Theoretical Elemental: $C_{53}H_{83}NO_{16}$

Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+H]^{1+}$	990.57913	990.57847	0.66	0.67	2.6
$[M+Na]^{1+}$	1012.56339	1012.56041	2.98	2.95	37.0

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Example 4



Meridamycin (0.1 g, 0.12 mmol) was dissolved in 2,2-dimethoxypropane (1.50 mL) and a catalytic amount of paratoluenesulfonic acid was added. The reaction mixture was stirred at 25 °C for 16 hours with magnetic stirring. Chloroform (5 mL) was added to the solution and the resulting solution was filtered over a small column of sodium bicarbonate. The products were then chromatographed via reversed-phase HPLC (column: 250 x 20 mm YMC ODS-A with 50 x 20 guard, mobile phase: 50 to 80 % acetonitrile:water in 30 minutes, then to 90% acetonitrile in 15 minutes, hold at 90% for an additional 15 minutes) to yield the product (0.008 g, 8 % yield) t_R = 10.0 minutes, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid)/acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

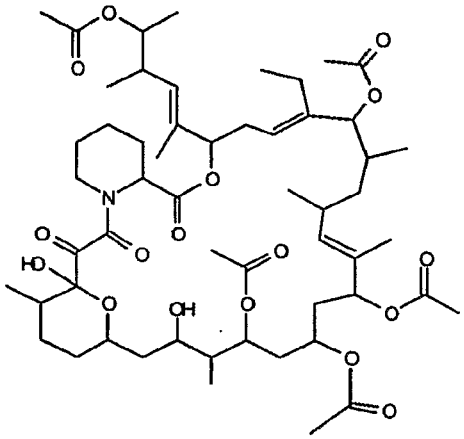
Theoretical Neutral Mass: 861.56023
Theoretical Elemental: $C_{48}H_{79}NO_{12}$

Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+H]^{1+}$	862.57146	862.56751	3.95	4.58	2.8
$[M+Na]^{1+}$	884.55113	884.54945	1.68	1.90	29.1
$[M+K]^{1+}$	900.52258	900.52339	-0.81	-0.90	1.9

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Example 5



Meridamycin (0.05 g, 0.06 mmol) was dissolved in pyridine (1.0 mL), acetic anhydride (1.0 mL) was added to this pyridine solution, and the reaction was allowed to stir for 3 hours. Solvents were removed *in vacuo* and the products were then chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 50 to 95 % acetonitrile:water in 20 minutes, hold at 95% for an additional 30 minutes) to yield a fraction that was further chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 80 % acetonitrile:water for 30 minutes, then to 90 % acetonitrile in 5 minutes, hold at 95% for an additional 10 minutes) to yield the product (0.003 g, 5 % yield, $t_R = 7.72$ minutes, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid)/acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

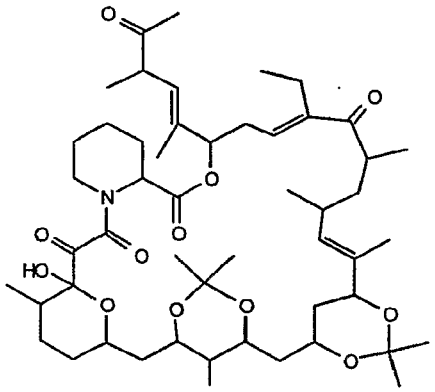
Theoretical Neutral Mass: 1031.58175
Theoretical Elemental: $C_{55}H_{85}NO_{17}$

Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+H]^{1+}$	1032.58632	1032.58903	-2.71	-2.62	5.6
$[M+Na]^{1+}$	1054.57069	1054.57097	-0.28	-0.26	78.8
$[M+H+Na]^{2+}$	527.78532	527.78912	-3.80	-7.20	1.6

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Example 6



Anhydrous dichloromethane (1.0 mL) was added to a solution of the compound of Example 1 (0.011g, 0.012 mmol) in a 0.3 M solution of Dess-Martin periodinane in dichloromethane (50 μL). The reaction was stirred under argon for 4 hours, dichloromethane (DCM, 10 mL) was added and the organic layer was washed with saturated sodium carbonate. The organic layer was dried, reduced *in vacuo*, and chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 50% to 95% acetonitrile:water in 20 minutes, hold at 95% for an additional 30 minutes) to yield the product (0.008 g, 74 % yield, t_R = 10.13 minutes, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid)/acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

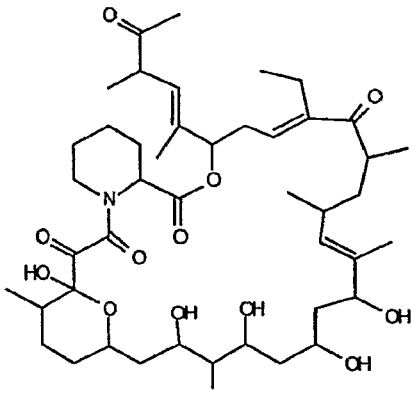
Theoretical Neutral Mass: 897.56023
Theoretical Elemental: $C_{51}H_{79}NO_{12}$

Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+Na]^{1+}$	920.54952	920.54945	0.07	0.08	53.8
$[M+NH_4]^{1+}$	915.59351	915.59405	-0.54	-0.59	9.2
$[M+H+K]^{2+}$	468.76132	468.76533	-4.01	-8.56	2.4

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Example 7



A catalytic amount of paratoluenesulfonic acid was added to a solution of the product of Example 6 (0.005 g, 0.006 mmol) in 2:1 methanol:water (3 mL). The reaction was stirred for 24 hours, the solvents were removed *in vacuo*, and the products were chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 50% to 80% acetonitrile:water in 10 minutes, hold at 80% for an additional 20 minutes) to yield the product (0.002 g, 41 % yield, $t_R = 6.21$ minutes, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid)/acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

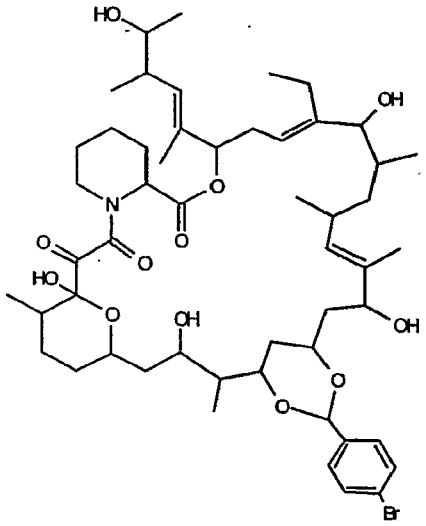
Theoretical Neutral Mass: 817.49763
Theoretical Elemental: $C_{45}H_{71}NO_{12}$

Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+H]^{1+}$	818.50303	818.50491	-1.88	-2.29	41.3
$[M+Na]^{1+}$	840.48364	840.48685	-3.21	-3.82	4.3
$[M+K]^{1+}$	856.45711	856.46079	-3.68	-4.29	0.2
$[M+CH_3OH+H]^{1+}$	850.52978	850.53112	-1.34	-1.57	2.8

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Example 8



Meridamycin (0.05 g, 0.061 mmol) was dissolved in DMF (2 mL). Excess p-bromobenzaldehyde dimethyl acetal (0.022 mL, 0.128 mmol, 2.1 eq) and a catalytic amount of paratoluenesulfonic acid was added to this DMF solution. The reaction mixture was stirred at 25 °C for 16 hours with magnetic stirring. Chloroform (5 mL) was added to this solution and the resulting solution was filtered over a small column of sodium bicarbonate. The products were then chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 50% to 80% acetonitrile:water in 15 minutes, then to 95% in 35 minutes) to yield the product (0.008 g, 13 % yield, t_R = 7.33 minutes, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid)/acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

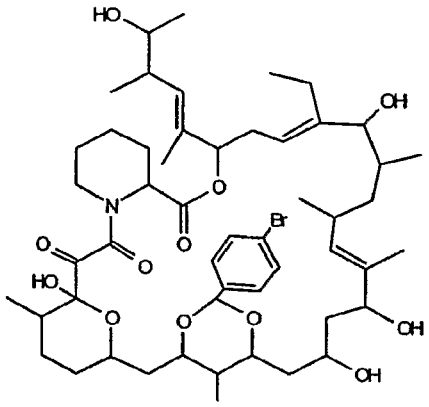
Theoretical Neutral Mass: 987.47074
Theoretical Elemental: $C_{52}H_{78}BrNO_{12}$

Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+H]^{1+}$	988.47663	988.47802	-1.39	-1.40	1.1

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Example 9



Meridamycin (0.05 g, 0.061 mmol) was dissolved in DMF (2 mL). Excess p-bromobenzaldehyde dimethyl acetal (0.022 mL, 0.128 mmol, 2.1 eq) and a catalytic amount of paratoluenesulfonic acid was added to this DMF solution. The reaction mixture was stirred at 25 °C for 16 hours with magnetic stirring. Chloroform (5 mL) was added to the solution and the resulting solution was filtered over a small column of sodium bicarbonate. The products were then chromatographed via reversed-phase HPLC (column: 250 x 10 mm YMC ODS-A, mobile phase: 50% to 80% acetonitrile:water in 15 minutes, then to 95% in 35 minutes) to yield the product (0.002 g, 3% yield, t_R = 6.94 minutes, analytical HPLC conditions: column = YMC ODS-A S-3 120 Å, mobile phase/gradient: 95% water (+ 0.025% formic acid)/acetonitrile (+ 0.025% formic acid) to 5% water in 6 minutes, hold at 5% for 9 minutes).

Theoretical Neutral Mass: 987.47074
Theoretical Elemental: $C_{52}H_{78}BrNO_{12}$

Exact Mass High Resolution Results

Adduct	Exptl.	Exact	mmu	ppm	RI %
$[M+H]^{1+}$	988.47973	988.47802	1.71	1.73	2.2
$[M+Na]^{1+}$	1010.45847	1010.45996	-1.49	-1.47	44.4
$[M+NH_4]^{1+}$	1005.50368	1005.50456	-0.88	-0.88	72.7

Example 10

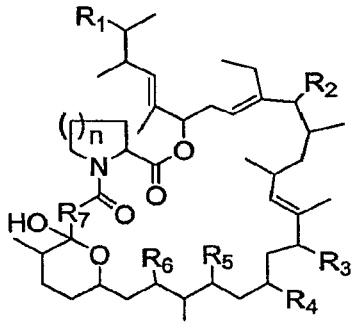
Dissociated cortical neuron cultures were prepared as previously described (Pong et al., 2001). Briefly, embryonic day 15 rat fetuses were collected and dissected in ice-cold PBS. Dissected cortices were pooled together and transferred to an enzymatic dissociation medium containing papain. After 30 minutes, the tissue was mechanically triturated with a fire-polished glass Pasteur pipette. Single-cell suspensions in complete media were seeded on poly-L-ornithine and laminin coated 96-well plates. 24 hours later, cultures were treated with various concentrations of compound for 72 hours. The cultures were then fixed and stained with an anti-tubulin primary antibody (TUJ-1) and a fluorescent-tagged secondary antibody. Neurite outgrowth was determined by using the Enhanced Neurite Outgrowth (ENO) algorithm with the Cellomics ArrayScan and expressed as average neurite length or total neurite length per cell.

The compounds of examples 1-6 were all active in cortical neuron assays with an EC_{50} less than 1 μM.

All publications cited in this specification are incorporated herein by reference. While the invention has been described with reference to particular embodiments, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of the structure:

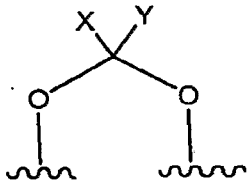


wherein:

R_1 and R_2 are, independently selected from the group consisting of, OH, oxo, O(C_1 to C_6 alkyl), O(substituted C_1 to C_6 alkyl), O(acyl), O(aryl), O(substituted aryl), or O(heterocyclyl), O(substituted heterocyclyl);

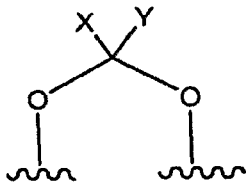
R_3, R_4, R_5, and R_6 are independently selected from the group consisting of OH, oxo, O(C_1 to C_6 alkyl), O(substituted C_1 to C_6 alkyl), O(acyl), O(aryl), O(substituted aryl), O(heterocyclyl), and O(substituted heterocyclyl); or

R_3 and R_4 and/or R_5 and R_6 are joined together to form a structure:,



or R_4 and R_5 are joined to form a structure: –

: –



wherein X and Y are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl;

R_7 is CH_2, CHOH, or C=O; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

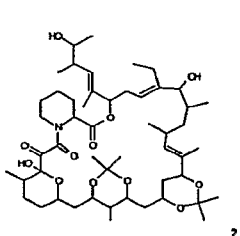
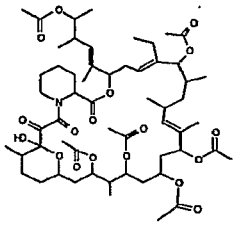
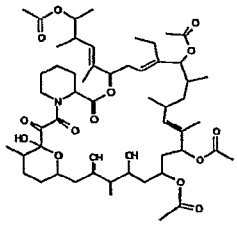
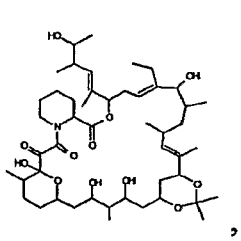
2. The compound according to claim 1, wherein R_1 and R_2 are independently oxo, OH or O(acyl).

3. The compound according to claim 2, wherein said O(acyl) is $OC(O)CH_3$.

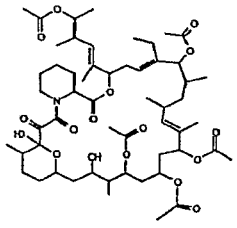
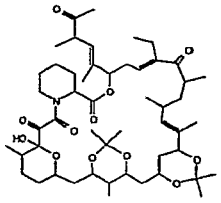
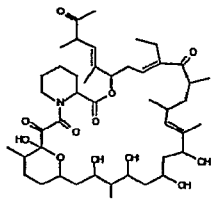
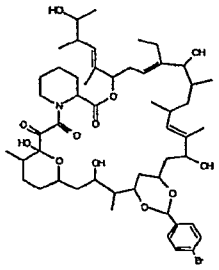
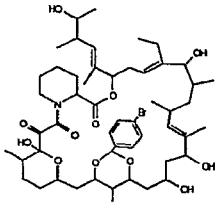
4. The compound according to any one of claims 1 to 3, wherein R_3 and R_4 or R_4 and R_5 are joined, wherein X and Y are CH_3.

5. The compound according to any one of claims 1 to 4, wherein R_7 is C(O).

6. The compound according to claim 1 which is selected from the group consisting of:

, , , ,

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,

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, and

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7. The compound according to claim 1, wherein R_1 and R_2 are OH; R_3 and R_4 are joined; R_5 and R_6 are joined; R_7 is C(O); and n is 2

8. The compound according to claim 1, wherein R_1, R_2, R_3, R_4, R_5, and R_6 are $OC(O)CH_3$; R_7 is C(O); and n is 2.

9. The compound according to claim 1, wherein R_1, R_2, R_3, and R_4 are $OC(O)CH_3$; R_4 and R_5 are OH; R_7 is C(O); and n is 2.

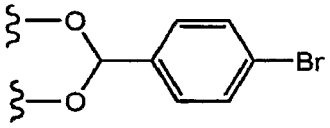
10. The compound according to claim 1, wherein R_1, R_2, R_5, and R_6 are OH; R_3 and R_4 are joined; R_7 is C(O); and n is 2.

11. The compound according to claim 1, wherein R_1, R_2, R_3, R_4, and R_5 are $OC(O)CH_3$; R_6 is OH; R_7 is C(O); and n is 2.

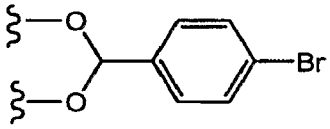
12. The compound according to claim 1, wherein R_1 and R_2 are oxo; R_3 and R_4 and R_5 and R_6 are joined; R_7 is C(O); and n is 2.

13. The compound according to claim 1, wherein R_1 and R_2 are oxo; R_3, R_4, R_5, and R_6 are OH; R_7 is C(O); and n is 2.

14. The compound according to claim 1, wherein R_1, R_2, R_3, and R_6 are OH; R_7 is C(O); n is 2; and R_4 and R_5 are taken together to form a ring of the structure:



15. The compound according to claim 1, wherein R_1, R_2, R_3 and R_4 are OH; R_7 is C(O); n is 2; and R_5 and R_6 are taken together to form a ring of the structure:

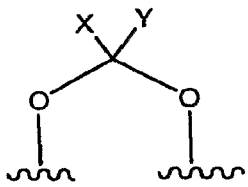


16. A compound as claimed in claim 1, wherein

R_1 and R_2 are, independently, OH, oxo, or O(acyl);

R_3, R_4, R_5, and R_6 are independently selected from the group consisting of OH and O(acyl); or

R_3 and R_4; R_4 and R_5; R_5 and R_6; or a combination thereof are joined to form a structure: –



wherein X and Y are independently selected from the group consisting of H and C_1 to C_6 alkyl;

R_7 is C=O; and

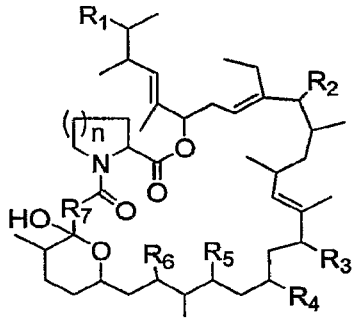
n is 2;

or a pharmaceutically acceptable salt thereof.

17. Use of a compound according to any of claims 1 to 16 in the preparation of a medicament for treating a neurological disorder in a mammal.

18. Use according to claim 17, wherein said neurological disorder is selected from the group consisting of epilepsy, stroke, cerebral ischemia, cerebral palsy, Alper's disease, Parkinson's disease, Alzheimer's disease, multiple sclerosis, Huntington's disease, amyotrophic lateral sclerosis, dementia with Lewy bodies, Rhett syndrome, neuropathic pain, spinal cord trauma, traumatic brain injury, senile dementias, mild cognitive impairment, or cognitive decline.

19. A method of preparing a compound of the structure:



wherein:

R_1, R_2, R_3, R_4, R_5, and R_6 are, independently, O(C_1 to C_6 alkyl) or O(substituted C_1 to C_6 alkyl);

R_7 is CH_2, CHOH, or C=O; and

n is 1 or 2;

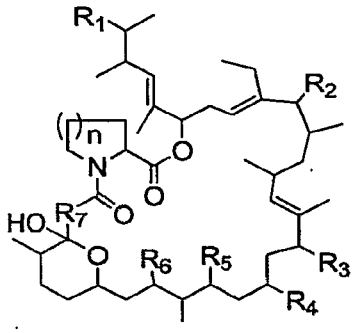
or a pharmaceutically acceptable salt thereof;

wherein said method comprises reacting meridamycin with an alkylating agent or alkyl anhydride

20. The method according to claim 19, wherein said alkylating agent is an alkyl halide, alkyl triflate, or alkyl mesylate.

21. The method according to claim 19, wherein said alkyl anhydride is acetic anhydride.

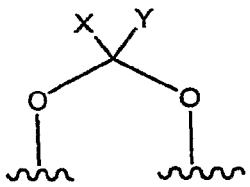
22. A method of preparing a compound of the structure:



wherein:

R_1 and R_2 are OH;

R_3 and R_4 and/or R_4 and R_5, or R_5 and R_6, are joined to form a structure:



X and Y are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl;

R_7 is CH_2, CHOH, or C=O; and

n is 1 or 2;

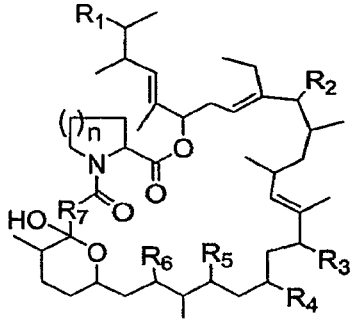
or a pharmaceutically acceptable salt thereof;

wherein, said method comprises reacting meridamycin with a dialkoxyalkane in the presence of an acid catalyst.

23. The method according to claim 22, wherein said dialkoxyalkane is 2,2-dimethoxypropane.

24. The method according to claim 22, wherein said acid catalyst is paratoluenesulfonic acid.

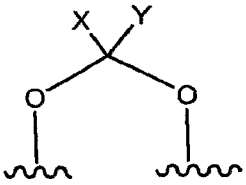
25. A method of preparing a compound of the structure:



wherein:

R_1 and R_2 are oxo;

R_3 and R_4 and/or R_4 and R_5, or R_5 and R_6, are joined to form a structure:



wherein X and Y are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl;

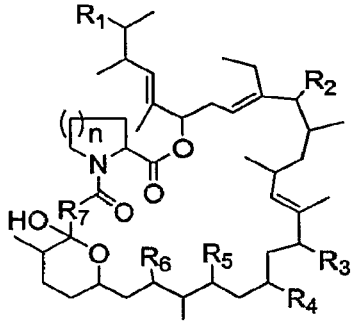
R_7 is CH_2, CHOH, or C=O; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof;

wherein said method comprises reacting the compound of claim 22 with the Dess-Martin periodinane reagent.

26. A method of preparing a compound of the structure:

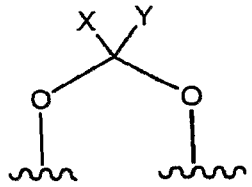


wherein:

R_1 is oxo;

R_2 is OH;

R_3 and R_4 and/or R_4 and R_5, or R_5 and R_6, are joined to form a structure:



X and Y are independently selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl;

R_7 is CH_2, CHOH, or C=O; and

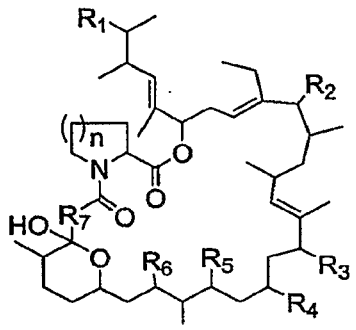
n is 1 or 2;

or a pharmaceutically acceptable salt thereof;

wherein said method comprises treating the compound of claim 22 with tetrapropylammonium ruthenate and N-morpholine oxide.

27. A method for preparing a compound of the structure:

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wherein:

R_1 is oxo;

R_2 is OH;

R_3, R_4, R_5, and R_6 are OH;

R_7 is CH_2, CHOH, or C=O; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof;

wherein said method comprises reacting the product of claim 26 with a weak acid.

28. The method according to claim 27, wherein said weak acid is paratoluenesulfonic acid.

29. A method of treating a mammal comprising administering to said mammal a compound of any one of claims 1 to 16.

30. A method for treating a neurological disorder comprising administering a compound of any one of claims 1 to 16 to a mammal.

31. The method according to any one of claims 1 to 6, wherein said compound is combined with one or more pharmaceutically acceptable carriers, excipients, or diluents.

32. The method according to any one of claims 1 to 6, wherein said neurological disorder is epilepsy, stroke, cerebral ischemia, cerebral palsy, Alper's disease, Parkinson's disease, Alzheimer's disease, multiple sclerosis, Huntington's disease, amyotrophic lateral sclerosis, dementia with Lewy bodies, Rhett syndrome, neuropathic pain, spinal cord trauma, traumatic brain injury, senile dementias, mild cognitive impairment, or cognitive decline.