TREATMENT OF DISEASES USING NALMEFENE AND ITS ANALOGS

BACKGROUND OF THE INVENTION

This application claims priority from U.S. Application Serial No 10/936,431 filed on September 8, 2004

The present invention relates to new medical uses of 6-methylene morphinans such as nalmefene.

In PCT publication WO 03/097608 we have described a number of new medical uses of opiod and opiood-like compounds, including naltrexone.

Nalmefene (6-methylene-6-desoxy-N-cyclopropylmethyl-14-ydroxydihydronormorphine) is a long-acting, orally available, potent narcotic antagonist with pure antagonist activity. It was first patented in U.S. Patents 3,814,768 and 3,896,226 (both in the name of Fishman).

It has been proposed for a variety of medical uses.

The use of nalmefene to treat arthritic disease or associated inflammation is described in U.S. 4,863,928 (Atkinson assigned to Baker Cummins). Among the conditions said to be treated are rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, psoriatic arthritis, acute gouty arthritis, Reiter's syndrome, bursitis and tendinitis.

In U.S. Pat. Nos. 4,877,791 and 4,923,875 it is disclosed that pure narcotic antagonists such as nalmefene and naltrexone may suppress histamine release from mast cells found in the bladder walls and the skin.

U.S. Patent 4994466 (Sherman assigned to Baker Cummins) describes a method of treatment for multiple sclerosis which may achieve symptomatic relief, prevent recurrence of the symptomatic phase and induce remission. In keeping with this object it discloses the daily administration to patients suffering from multiple sclerosis of from about 1 to about 100 milligrams of a pure narcotic antagonist, e.g., nalmefene or naltrexone. The oral route of administration is preferred for patient convenience, comfort and safety, but parenteral and other methods of administration may be utilized.

U.S. Patent 5013740 (Glover) suggests the use of nalmefene for treatment of "emotional numbness" associated wit post traumatic stress disorder and in treating comas.

U.S. Patents 5817665 and 5856332 (Dante) describe the use of an opioid antagonist, nalmefene being mentioned, in combination with one or more serotonin (5-hydroxytryptamine or 5-HT) or norepinephrine reuptake inhibitor(s) and/or lithium to treat mental or emotional disorders characterized by depression, obsessiveness, depression with anxiety, mania, manic depression, depression with manic episodes, and depression concomitant with an illness causing seizures which are inhibited by carbamazepine, or a combination of any of these mental or emotional illnesses, or mental or emotional illnesses with seizures

U.S. Patent 4873076 (Fishman) describes methods of inducing anesthesia or conscious sedation by administration of benzodiazepines in combination with opiate analgesics including nalmefene.

U.S. Patent 4880814 (Frost, assigned to Baker Cummins) describes the topical administration of nalmefene to the nasal passages of a patient suffering from allergic rhinitis in a pharmaceutically acceptable liquid vehicle

U.S. Patent 4946848 (Tuttle, assigned to Baker Cummins) describes a method of treating pruritus, whether antigen-induced or disease-induced, by orally administering to the subject from about 1 to about 25 mg of nalmefene

Apart from its utility in antagonizing the sedation, respiratory depression and other actions of opioid agents, nalmefene has also been found useful in treating diverse conditions such as hyperkinesia in children (U.S. Pat. No. 4,454,142), senile dementia (U.S. Pat. No. 4,511,570), sudden infant death syndrome (U.S. Pat. No. 4,639,455), autoimmune diseases (U.S. Pat. No. 4,857,533), arthritic and inflammatory diseases (U.S. Pat. No. 4,863,928), interstitial cystitis (U.S. Pat. No. 4,877,791 and European Publication 367533), allergic rhinitis (U.S. Pat. No. 4,880,813). In U.S. Pat. No. 4,923,875, there is disclosed the utility of topical nalmefene in treating urticaria, various eczemas, and other mast cell-mediated dermatological disorders, but not the use of oral nalmefene in systemic mast cell disease. In PCT Application No. US86/02268, it was disclosed that nalmefene is

useful for the treatment of antigen-induced allergic responses, including those where degranulation of mast cells may be a causative factor.

U.S. Patent 5057322 and European Publication 471 525 (Frost, assigned to Baker Cummins) describes the use of a pure narcotic antagonist, e.g., nalmefene to treat patients suffering from mast cell disease.

U.S. Pat. No. 4,863,928 discloses a method of treating a human or animal patient suffering from an arthritic disease which comprises the daily administration of the narcotic antagonists nalmefene or naltrexone.

U.S. Pat. No. 5,086,058 discloses a method for treating alcoholism. The method involves having the patient drink alcoholic beverages while nalmefene, an opiate antagonist, blocks the positive reinforcement effects of ethanol in the brain.

Elevated insulin concentrations have been reduced, for a period of a few days, in a select patient population of four women with polycystic ovary syndrome with Acanthosis Nigerians, by administration of Nalmefene (J. R. Givens et al; J. Clin. Endocr. & Metab. 64/2, 1987, pp.377-382). It is reported that nalmefene has relative receptor binding characteristics similar to naltrexone, but of increased potency and without hepatic toxicity. This report covers concentrations of insulin and glucose, the insulin glucose ratio (I/G) as a measure of insulin resistance, as well as growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), dehydroepiandrosterone sulfate (DHEAS), cortisol, testosterone and prolactin (PRL) levels during the study. This report does, however, not report any values on blood lipids, i.e. free fatty acids (FFA), triglycerides (TG), and any of the cholesterol fractions.

U.S. Patents 5878750, 6262062 and 6528520 (Clemens) suggest the use of nalmefene to treat chronic heart disease risk factors.

U.S. Patent 6004970 (O"Malley) suggests the use of nalmefene in helping to quit smoking.

U.S. Patent 652225062 (Levine, assigned to the University of California) teaches treating pain in humans using a combination of the kappa-opioid nalbuphine, in a relatively low dosage, with a low dosage of an opioid antagonist selected from naloxone, naltrexone, and nalmefene.

U.S. Patent 6734188 (Rhodes) describes nalmefene as one of the less preferred opiod antagonists for treating irritable bowel syndrome and other discussion of its use for such a purpose is found in US Patent 6737400 (Crain, assigned to Albert Einstein College of Medicine).

Previous work in this area has generally focused upon the investigation of the use of these morphine derivatives as analgesics, morphine antagonists, or antitussives. However, recent literature has reported potential new uses for some morphine derivatives which may not be mediated through morphine receptors.

Recent advances in the research of neurodegenerative diseases of the central nervous system have revealed that the opioids may play a role in modulating the expression of inflammatory factors such as proinflammatory cytokines, free radicals and metabolites of arachidonic acid in microglia and in the mediation of immune-related neurodegeneration, *Adv. Exp. Med. Biol.* 402: 29-33 (1996); *Mov. Disord.* 12: 855-858 (1997). Naloxone, a morphine antagonist, is disclosed in *J. Pharmacol. Exp. Therap.* 293, 607-617 (2000) to protect rat dopaminergic neurons against inflammatory damage through inhibition of microglia activation and superoxide generation.

The potential for the development of tolerance and physical dependence with repeated opioid use is a characteristic feature of all the opioid drugs, and the possibility of developing psychological dependence (i.e., addiction) is one of the major concerns in the use of the treatment of pain with opioids. Another major concern associated with the use of opioids is the diversion of these drugs from the patient in pain to another (non-patient) for recreational purposes, e.g., to an addict. Thus, it is desirable to provide opioid and opioid-like compounds useful for the prevention or treatment of various disorders as described herein.

Aerobic organisms, which derive their energy from the reduction of oxygen, are susceptible to the damaging actions of the small amounts of O_2^-, OH and H_2O_2 that inevitably form during the metabolism of oxygen, especially in the reduction of oxygen by the electron transfer system of mitochondria. These three species, together with unstable intermediates in the peroxidation of lipids, are referred to as Reactive Oxygen Species (ROS). Many diseases such as, but not limited to, Alzheimer's Disease, Parkinson's disease, aging, cancer, myocardial infarction, atherosclerosis, autoimmune diseases, radiation injury, emphysema, sunburn, and joint

disease (a. *Everything cytokine & beyond*, Cytokines Mini-Reviews, Chapter:Reactive Oxygen Species (ROS), Copyright 2003 ©R&D Systems; b. Channon KM, Guzik TJ, Mechanisms of superoxide production in human blood vessels: relationship to endothelial dysfunction, clinical and genetic risk factors. *J. Physiol. Pharmacol.* **2002**, *53*(4), 515-524; c. Henrotin, YE et al. The role of reactive oxygen species in homeostasis and degradation of cartilage. *OsteoArthritis and Cartilage* **2003**, *11*, 747–755; d. Arzimanoglou A et al. Epilepsy and neuroprotection: An illustrated review article. *Epileptic Disord* **2002**,*3*, 173-82; e. Seidman MD et al., Biologic activity of mitochondrial metabolites on aging and age-related hearing loss. *Am J Otol* **2000**, 21(2):161-7.) are linked to damage from ROS as a result of an imbalance between radical-generating and radical-scavenging systems - a condition called *oxidative stress*. The discovery by McCord and Fridovich (McCord, J.M. & I. Fridovich *J. Biol. Chem.* **1969**, 244:6049) of the superoxide dismutase (SOD) activity of erythrocuprein, together with the finding that almost all mammalian cells contain SOD, suggests a physiological role of at least the central ROS, superoxide.

TNF-α (tissue necrosis factor), a cytokine that plays a critical role in eliciting the body's inflammatory response and is present in abnormally high levels in the joints of individuals suffering from rheumatoid arthritis, has been implicated as an immune modulator in the immune system. Inhibitors of TNF-α have been shown to halt the progression of cartilage destruction and relieve the symptoms of severe arthritis. Approximately 30% of moderate to severe arthritic patients are not responsive to these treatments (Feldman M, Maini RN, Discovery of TNF-α as a therapeutic target in rheumatoid arthritis: preclinical and clinical studies. *Joint Bone Spine* **2002**, 69, 12-18; Lipsky PE, *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N. Engl. J. Med.* **2000**, 343 1954-1602). Animal studies in association with studies conducted in humans indicate a potential role for TNF modulation in Crohn's disease, ulcerative colitis, insulin resistance, multiple sclerosis, multiple organ failure, pulmonary fibrosis, and atherosclerosis (Newton RC, Decicco CP, Therapeutic potential and strategies for inhibiting tumor necrosis factor-a. *J. Med. Chem.* **1999**, 42, 2295-2314). Biswas P, *et al.* reported that TNF-α drives HIV-1 replication in U937 cell clones (Biswas P, *et al.* Tumor necrosis factor-alpha drives HIV-1 replication in U937 cell clones and upregulates CXCR4. *Cytokine.* 2001,13, 55-59). Liver damages are associated with TNF-α release have been reported recently (McClain CJ, *et al.* Advances in Alcoholic Liver Disease, *Current*

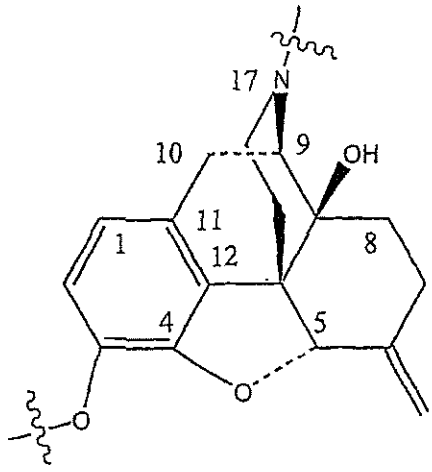
Gastroenterology Reports, 2004, 6, 71–76). During the course of sepsis, nitric oxide (NO) is produced. Its metabolites impair normal vascular reactivity, in conjunction with elevated endotoxin levels. Inhibitors of NO synthase restore blood pressure, lower the cardiac index and increase pulmonary and systemic vascular resistance. Selective NOS inhibitors targeted against iNOS may prove to be beneficial. A small study with an inhibitor of NOS action, namely methylene blue, which inhibits the associated guanylyl cyclase enzyme, has indicated beneficial effects versus the cardiovascular parameters described above in patients with septic shock [Preiser, JC, Lejeune P, Roman A, et al. Methylene blue administration in septic shock: a clinical trial. Crit. Care Med., 23: 259-64(1995); Gachot B, Bedos JP, Veber B, et al. Short term effects of methylene blue on hemodynamics and gas exchange in humans with septic shock, Intensive Care Med 21:1027-31; Vincent, JL, Sun Q, Dubois, M-J, Clinical Trials of Immunomodulatory Therapies in Severe Sepsis and Septic Shock, CID, 34: 1084-1093 (2002)].

Summary of the Invention

The present invention relates to use of a compound according to the formula R-A-X, R being attached to the oxygen atom and X to the nitrogen atom, in treatment of various diseases or conditions or for the production of medicaments, for treatment of such conditions wherein:

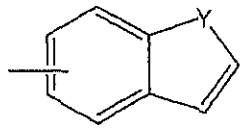
R is H, alkyl, allyl, phenyl, benzyl, or $(CH_2)_mR_4$, wherein m is from 0 to 6, and R_4 can be a ring structure.

A is

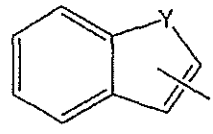


X can be hydrogen, allyl, cinnamoyl, crotonyl, $(CH_2)C_6H_5$-4F, $(CH_2)_nC=CR_1R_2$, $(CH_2)_nC\equiv CR_3$, $(CH_2)_nR_5$, and $(CH_2)_mCHR_6R_7$, wherein m is 0 to 6 and and n is from 0 to 6. R_3 can be H, alkyl, or the same as R_4, wherein R_4 is described above and R_5 can be alkyl, CN, COR_8, or structures selected from the group consisting of the following structures:

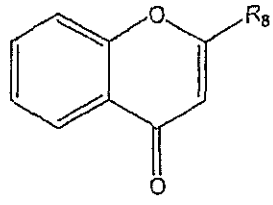
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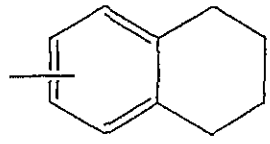
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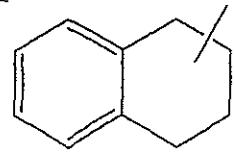
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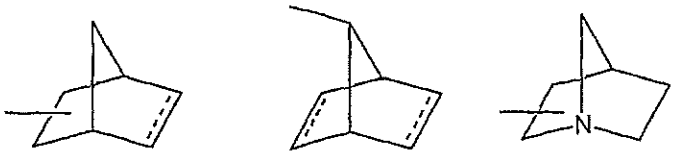
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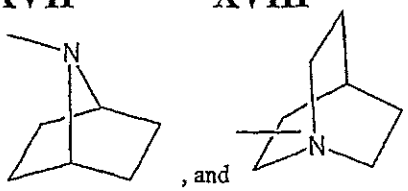
XIII



XIV XV XVI



XVII XVIII



, and ,

wherein Y can be O, S or N. R_6 and R_7 are each independently the same as R_4 as defined above; and R_8 is alkyl, the same as R_4 as defined above, or the same as R_5 when R_5 can be the structures described above (IX – XVIII). The novel compounds according to the formula R-A-X can be enantiomers, diastereoisomers, and pharmaceutically acceptable salts thereof.

Ring structures that can constitute R_4 can be, for example, phenyl, naphthyl, and biphenyl, wherein the ring is optionally substituted with one to three substituents selected from the group consisting of halogen, alkyl, NO_2, CN, CF_3, and lower alkoxy R_4 can be a five-membered heterocyclic ring having one or more heteroatoms selected from the group consisting of O, S, and N, wherein the heterocyclic ring is substituted with a lower alkyl or a substituted phenyl group; R_4 can be a pyridine ring wherein the pyridine ring is optionally substituted with halogen, alkyl, NO_2, CN, CF_3, OCH_3, or NR_1R_2, where R_1 and R_2 are each independently H or alkyl, or R_1 and R_2 together with the nitrogen to which they are bound jointly form ~~is~~ a cyclic ring, wherein the cyclic ring is a 3- to 7- membered alicyclic ring optionally having a double bond in the ring. R_4 can be quinoline. R_4 can be isoquinoline. R_4 can be 4-cyclohexylphenyl. R_4 can be a cyclic ring, wherein the cyclic ring is a 3- to 7-membered alicyclic ring optionally having a double bond in the ring.

Particularly preferred is nalmefene the compound where X is cyclopropylmethyl and R is hydrogen.

DETAILED DESCRIPTON OF THE INVENTION

Treatments or medicaments produced according to the invention include those for preventing or treating viral infections such as hepatitis B and hepatitis C and conditions such as septic shock, organ damage, neurological disorders, neurodegenerative diseases, cancer, and diseases associated with overproduction of superoxide anion radical, TNF-α, or iNOS.

According to other embodiments of the present invention, the present invention relates to methods of preventing or treating viral infections in patients with hepatitis B and hepatitis C and conditions such as septic shock, organ damage, neurological disorders, neurodegenerative diseases, cancer, and diseases associated with overproduction or superoxide anion radical, TNF-α, or iNOS, comprising administering to a subject in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of one or more of the specified compounds.

The methods of the invention may be of particular use in prevention or treatment of organ damage, specially damage of the liver, kidneys or lungs, cancers which may be treated including skin cancer, small cell lung cancer, testicular cancer, esophageal cancer, breast cancer, endometrial cancer, ovarian cancer, CNS cancer, liver cancer and prostate cancer.

The foregoing and other aspects of the present invention will now be described in more detail with respect to other embodiments described herein. It should be appreciated that the invention can be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

The terminology used in the description of the invention herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used in the description of the invention and the appended claims, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

All publications, patent applications, patents and other references cited herein are incorporated by reference in their entireties for the teachings relevant to the sentence and/or paragraph in which the reference is presented.

The term "alkyl" as used herein refers to C_1-C_{20} inclusive, linear, branched, or cyclic, saturated or unsaturated hydrocarbon chains, including for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, octyl, ethenyl, propenyl, butenyl, pentyl, hexenyl, octenyl, butadienyl, and allenyl groups. Alkyl groups can either be unsubstituted or substituted with one or more non-interfering substituents, e.g., halogen, alkoxy, acyloxy, hydroxy, mercapto, carboxy, benzyloxy, phenyl, benzyl, or other functionality which has been suitably blocked with a protecting group so as to render the functionality non-interfering. Each substituent may be optionally substituted with additional non-interfering substituents. The term "non-interfering" characterizes the substituents as not adversely affecting any reactions to be performed in accordance with the process of this invention.

The term "loweralkyl" as used herein refers to C_1 to C_8 alkyl, including C_1 to C_3, C_1 to C_4, C_1 to C_5, C_1 to C_6, and C_1 to C_7, which may be linear or branched and saturated or unsaturated.

The term "cycloalkyl" as used herein is typically C_3, C_4 or C_5 or C_6 or C_8 cycloalkyl.

The term "aryl" as used herein refers to C_6 to C_{10} cyclic aromatic groups such as phenyl, benzyl, naphthyl, and the like, and includes substituted aryl groups such as tolyl.

The term "heterocycle" as used herein refers to a monovalent saturated, unsaturated, or aromatic carbocyclic group having a single ring or multiple condensed ring and having at least one hetero atom, such as N, O, or S, within the ring, which can optionally be unsubstituted or substituted with hydroxy, alkyl, alkoxy, halo, mercapto, and other non-interfering substituents. Examples of nitrogen heterocycles include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline,

quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, and indoline.

The term "halo" as used herein refers to any halogen group, such as chloro, fluoro, bromo, or iodo.

The term "opioid" as used herein refers to compounds that exhibit opium or morphine-like properties, including agonist and antagonist activity wherein such compounds can interact with stereospecific and saturable binding sites in the brain and other tissues. Pharmacological properties have previously included drowsiness, respiratory depression, changes in mood and mental clouding without a resulting loss of consciousness. The term "opioid-like" as used herein refers to compounds that are similar in structure and/or pharmacological profile to known opioid compounds.

"Treat" or "treating" as used herein refers to any type of treatment that imparts a benefit to a patient afflicted with a disease, including improvement in the condition of the patient (*e.g.*, in one or more symptoms), delay in the progression of the condition, prevention or delay of the onset of the disease, etc.

As used herein, a "pharmaceutically acceptable" component (such as a salt, carrier, excipient or diluent) means that the compound or composition is suitable for administration to a subject to achieve the treatments described herein, without unduly deleterious side effects in light of the severity of the disease and necessity of the treatment.

"Therapeutically effective amount" as used herein refers to an amount necessary to prevent, delay or reduce the severity of the condition of interest and also includes an amount necessary to enhance normal physiological functioning.

Some of the compounds of the present invention described above can possess narcotic and analgesic properties as well as antioxidant properties. However, certain therapeutic effects of the compounds of the present invention can be mediated through mechanisms other than through interaction with opiate receptors.

Active compounds of the present invention can be water soluble and can also comprise known water-soluble opioid and opioid-like derivatives.

Compounds of the present invention can possess an asymmetric carbon atom(s) and therefore are capable of existing as enantiomers or diastereoisomers. Thus, compounds of the present invention include enantiomers and diastereoisomers as well as pharmaceutically acceptable salts of the compounds of the present invention.

Active compounds of the present invention can be administered alone or in combination with other therapeutic agents. For example, active compounds of the present invention can be coadministered with compounds now known, or later identified, to be useful for the prevention and or treatment of viral infections and conditions such as septic shock, inflammation, organ damage, neurological disorders, neurodegenerative diseases, cancer, and cardiac disorders, and diseases associated with overproduction of superoxide anion radical, TNF-α, and iNOS, Exemplary compounds include, but are not limited to, analgesics, anesthetics, antifungals, antibiotics, antiinflammatories, anthelmintics, antidotes, antiemetics, antihistamines, antihypertensives, antimalarials, antimicrobials, antipsychotics, antipyretics, antiseptics, antiarthritics, antituberculotics, antitussives, antivirals, cardioactive drugs, cathartics, chemotherapeutic agents, corticoids (steroids), antidepressants, depressants, diagnostic aids, diuretics, enzymes, expectorants, hormones, hypnotics, minerals, nutritional supplements, parasympathomimetics, potassium supplements, sedatives, sulfonamides, stimulants, sympathomimetics, tranquilizers, urinary antiinfectives, vasoconstrictors, vasodilators, vitamins, xanthine derivatives, and the like.

Opioid compounds and opioid-like compounds can have unwanted side effects in the central nervous system. Therefore, compounds of the present invention in which undesirable side effects are minimal to non-existent are preferred.

As noted above, nalmefene is a well documented compound and commercially available. Other compounds of use in the present invention may be obtained by modification of nalmefene by routine chemical methods or by use of techniques analogous to those described in PCT Publication WO 03/097608.

The term "active agent" as used herein, includes the pharmaceutically acceptable salts of the compound. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart

undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (b) salts formed from elemental anions such as chlorine, bromine, and iodine. In other particular embodiments, pharmaceutically acceptable salts are formed with malic acid. In particular embodiments, pharmaceutically acceptable salts are formed with hydrochloric acid.

Active agents used to prepare compositions for the present invention may alternatively be in the form of a pharmaceutically acceptable free base of active agent. Because the free base of the compound is less soluble than the salt, free base compositions are employed to provide more sustained release of active agent to the target area. Active agent present in the target area which has not gone into solution is not available to induce a physiological response, but serves as a depot of bioavailable drug which gradually goes into solution.

Pharmaceutical Formulations

The opioid and opioid-like compounds of the present invention are useful as pharmaceutically active agents and may be utilized in bulk form. More preferably, however, these compounds are formulated into pharmaceutical formulations for administration. Any of a number of suitable pharmaceutical formulations may be utilized as a vehicle for the administration of the compounds of the present invention.

It will be appreciated that certain compounds of the above formulas can possess an asymmetric carbon atom(s) and are thus capable of existing as enantiomers. Unless otherwise specified, this invention includes such enantiomers, including racemates. The separate enantiomers may be synthesized from chiral starting materials, or the racemates can be resolved by procedures that are well known in the art of chemistry such as chiral chromatography, fractional crystallization of diastereometric salts and the like.

The compounds of the present invention may be formulated for administration for the treatment of a variety of conditions. In the manufacture of a pharmaceutical formulation according to the invention, the compounds of the present invention and the physiologically acceptable salts thereof, or the acid derivatives of either (hereinafter referred to as the "active compound") are typically admixed with, *inter alia*, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.5% to 95% by weight of the active compound. In one particular embodiment, a pharmaceutical composition comprises less than 80% by weight of active compound. In other particular embodiments, a pharmaceutical composition comprises less than 50% by weight of active compound. One or more of each of the active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) and transdermal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, tablets, dragees, or syrups each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above).

In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a

tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations may be administered by means of subcutaneous, intravenous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration may also be delivered by iontophoresis (*see, for example, Pharmaceutical Research* 3(6):318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis\tris buffer (pH 6) or ethanol/water and contain from 0.01 to 0.2M active ingredient.

The present invention may also be formulated into a sustained-release preparation. A sustained-release composition includes, but is not limited to, those in which the active ingredient is bound to an ion exchange resin which is optionally coated with a diffusion barrier to modify the release properties of the resin.

Carriers and/or diluents which may be used include vaseline, lanoline, glycerin, vegetable oils, or fat emulsions, polyethylene glycols, alcohols, transdermal enhancers, natural or hardened oils or waxes, and combinations of two or more thereof.

Methods of Use

In addition to the compounds of the formulas described herein, the present invention also provides useful therapeutic methods. For example, the present invention provides a method of treating viral infections and septic shock, inflammation, organ damage, neurological disorders, neurodegenerative diseases, cancer, and cardiac disorders, and diseases associated with overproduction of superoxide anion radical, TNF-α, and iNOS. In some embodiments, viral infections include, but are not limited to, infections by Hepatitis B virus and Hepatitis C virus.

In particular embodiments, organ damage includes, but is not limited to, liver damage, kidney damage, and lung damage. Such damage may arise from causes that include, but are not limited to, alcohol abuse, cirrhosis, hepatitis, and septic shock such as sepsis arising from bacterial infections or environmental toxins such as carbon tetrachloride.

In other particular embodiments, neurological disorders include, but are not limited to seizure disorders such as epilepsy, Tourette Syndrome, stroke, and neurodegenerative diseases including, but not limited to, Parkinson's disease, Alzheimer's disease, cognition deficit disorder, memory loss, amyotrophic lateral sclerosis, and multiple sclerosis.

In particular embodiments, exemplary cancers include, but are not limited to, leukemia, lymphoma, colon cancer, renal cancer, liver cancer, breast cancer, lung cancer, prostate cancer, ovarian cancer, melanoma, small cell lung cancer, testicular cancer, esophageal cancer, stomach cancer, endometrial cancer, central nervous system cancer, and the like. The term "cancer" has its understood meaning in the art, for example, an uncontrolled growth of tissue that has the potential to spread to

distant sites of the body (*i.e.*, metastasize). Preferred are methods of treating and preventing tumor-forming cancers. The term "tumor" is also understood in the art, for example, as an abnormal mass of undifferentiated cells within a multicellular organism. Tumors can be malignant or benign. Preferably, the inventive compounds and methods disclosed herein are used to prevent and treat malignant tumors.

In still yet other particular embodiments, cardiac disorders include, but are not limited to, cardiac ischemia, congestive heart failure, and hypertension.

In other particular embodiments, diseases associated with overproduction of superoxide anion radical, TNF-α, or iNOS include, but are not limited to, Alzheimer's disease, Parkinson's disease, aging, cancer, myocardial infarction, atherosclerosis, autoimmune disease, radiation injury, emphysema, sunburn, joint disease, and oxidative stress. Suitable subjects to be treated according to the present invention include both avian and mammalian subjects, preferably mammalian. Mammals according to the present invention include but are not limited to canine, felines, bovines, caprines, equines, ovines, porcines, rodents (*e.g.* rats and mice), lagomorphs, primates, and the like, and encompass mammals *in utero*. Humans are preferred.

Illustrative avians according to the present invention include chickens, ducks, turkeys, geese, quail, pheasant, ratites (*e.g.*, ostrich) and domesticated birds (*e.g.*, parrots and canaries), and include birds *in ovo*. Chickens and turkeys are preferred.

Any mammalian subject in need of being treated according to the present invention is suitable. Human subjects are preferred. Human subjects of both genders and at any stage of development (*i.e.*, neonate, infant, juvenile, adolescent, adult) can be treated according to the present invention.

As noted above, the present invention provides pharmaceutical formulations comprising the compounds of formulae described herein, or pharmaceutically acceptable salts thereof, in pharmaceutically acceptable carriers for any suitable route of administration, including but not limited to, oral, rectal, topical, buccal, parenteral, intramuscular, intradermal, intravenous, and transdermal administration.

According to the present invention, methods of this invention comprise administering an effective amount of a composition of the present invention as described above to the subject. The effective amount of the composition, the use of which is in the scope of present invention, will vary somewhat from subject to subject, and will depend upon factors such as the age and condition of the subject and the route of delivery. Such dosages can be determined in accordance with routine pharmacological procedures known to those skilled in the art. For example, the compounds of the present invention can be administered to the subject in an amount ranging from a lower limit from about 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, or 10% to an upper limit ranging from about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% by weight of the composition. In some embodiments, the compounds comprise from about 0.05 to about 95% by weight of the composition. In other embodiments, the compounds comprise from about 0.05 to about 60% by weight of the composition. In still other embodiments, the compounds comprise from about 0.05 to about 10% by weight of the composition.

The therapeutically effective dosage of any specific compound will vary somewhat from compound to compound, patient to patient, and will depend upon the condition of the patient and the route of delivery. As a general proposition, a dosage from about 0.1 to about 50 mg/kg will have therapeutic efficacy, with still higher dosages potentially being employed for oral and/or aerosol administration. Toxicity concerns at the higher level may restrict intravenous dosages to a lower level such as up to about 10 mg/kg, all weights being calculated based upon the weight of the active base, including the cases where a salt is employed. Typically a dosage from about 0.5 mg/kg to about 5 mg/kg will be employed for intravenous or intramuscular administration. A dosage from about 10 mg/kg to about 50 mg/kg may be employed for oral administration.

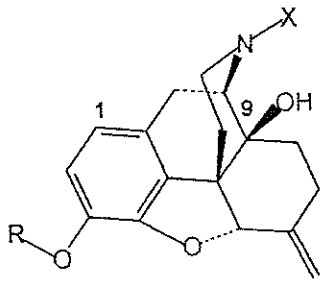
In particular embodiments, compounds of the present invention may be administered at a daily dosage of from about 0.1 mg to about 20 mg per kg of animal body weight, which can be given in divided doses q.d. to q.i.d. or in a sustained release form. For humans, the total daily dose may be in the range of from about 5 mg to

about 1,400 mg, and in other particular embodiments, the total daily dose is in the range of from about 10 mg to about 100 mg. In still other embodiments, the unit dosage forms suitable for oral administration may comprise about 2 mg to about 1,400 mg of the compound optionally admixed with a solid or liquid pharmaceutical carrier or diluent. The compounds of the present invention can be administered in any amount appropriate to administer to the subject for treatment of the condition desired to be treated as determined by one of ordinary skill in the art by reference to the pertinent texts and literature and/or by using routine experimentation. (*See*, for example, Remington, *The Science And Practice of Pharmacy* (9th Ed. 1995). However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg to about 20 mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

Claims

1. Use of a compound of the following formula XXVIII,



XXVIII

wherein R is H or alkyl, and X is hydrogen, allyl, cyclopropylmethyl, or alkyl, or a physiologically acceptable salt and/or acid derivative thereof, for the preparation of a medicament for treating or preventing a condition which is inflammatory organ damage, wherein said inflammatory organ damage is liver, lung or kidney damage, or a disease associated with overproduction of superoxide anion radical, TNF-α, and iNOS, wherein said disease is Crohn's disease, ulcerative colitis, or atherosclerosis.

2. The use according to claim 1, wherein said medicament comprises a compound of formula XXVIII, or a physiologically acceptable salt and/or acid derivative thereof, in a daily dose of from 2 mg to 100 mg.

3. The use according to claim 1 or 2, which is for prevention of inflammatory organ damage.

4. The use according to claim 3, wherein said inflammatory organ damage is liver damage.

5. The use according to claim 3, wherein said inflammatory organ damage is kidney damage.

6. The use according to claim 3, wherein the inflammatory organ damage is lung damage.

7. The use according to claim 1 or 2, wherein said condition is said disease associated with overproduction of superoxide anion radical, TNF-α, and iNOS consisting of Crohn's disease, ulcerative colitis, or atherosclerosis.

8. The use according to claim 2 or 4, wherein the condition is liver damage caused by alcohol abuse, bacterial infection, cirrhosis, hepatitis, or an environmental toxin.

9. The use according to any one of claims 1 to 8, wherein the medicament is formulated for oral administration.

10. The use according to claim 2 or 7, wherein the medicament is formulated for parenteral administration.

11. The use according to any one of claims 1 to 8, wherein the compound of formula XXVIII, or a physiologically acceptable salt and/or acid derivative thereof, is formulated for administration in combination with at least one other therapeutic agent which is an antibiotic, an antimicrobial, an antiviral which is anti-hepatitis or interferon, a vaccine, or a cardiovascular drug, or any combination thereof.

12. The use according to any one of claims 1 to 9 and 11, wherein the compound of formula XXVIII used is nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.

13. The use of claim 4, wherein said condition is liver damage, said compound of formula XXVIII is nalmefene, and said medicament comprises a daily oral dose of from 2mg to 100mg of said nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.

14. The use according to claim 8, wherein said liver damage is caused by hepatitis, said compound of formula XXVIII is nalmefene, and said medicament comprises a therapeutically effective amount of a daily oral dose of from 2mg to 100mg of said nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.

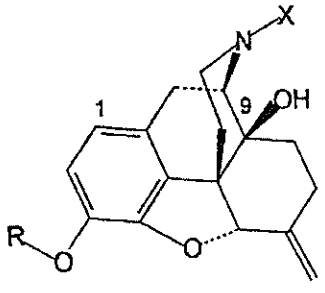
15. The use according to claim 8, wherein said liver damage is caused by bacterial infection, said compound of formula XXVIII is nalmefene, and said medicament comprises a therapeutically effective amount of a daily oral dose of from 2mg to 100mg of said nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.

16. The use according to claim 8, wherein said liver damage is caused by alcoholic abuse, said compound of formula XXVIII is nalmefene, and said medicament comprises a therapeutically effective amount of a daily oral dose of from 2mg to 100mg of said nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.

17. The use according to claim 8, wherein said liver damage is caused by cirrhosis, said compound of formula XXVIII is nalmefene, and said medicament comprises a therapeutically effective amount of a daily oral dose of from 2mg to 100mg of said nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.

18. The use according to claim 7, wherein said condition is Crohn's disease, said compound of formula XXVIII is nalmefene, and said medicament comprises a daily oral dose of from 2 mg to 100 mg of said nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.

19. A pharmaceutical composition for preventing or treating a condition which is inflammatory organ damage, wherein said inflammatory organ damage is liver, lung or kidney damage, or a disease associated with overproduction of superoxide anion radical, TNF-α, and iNOS, wherein said disease is Crohn's disease, ulcerative colitis, or atherosclerosis, comprising a compound of the formula XXVIII:



XXVIII

wherein R is H, or alkyl, and X is hydrogen, allyl, cyclopropylmethyl, or alkyl, or a physiologically acceptable salt and/or acid derivative thereof, and a pharmaceutically acceptable carrier.

20. The pharmaceutical composition according to claim 19, which comprises a daily dose of from 2 mg to 100 mg of a compound of formula XXVIII, or a physiologically acceptable salt and/or acid derivative thereof.

21. The pharmaceutical composition according to claim 19 or 20, which is for prevention of inflammatory organ damage.

22. The pharmaceutical composition according to claim 21, wherein said inflammatory organ damage is liver damage.

23. The pharmaceutical composition according to claim 21, wherein said inflammatory organ damage is kidney damage.

24. The pharmaceutical composition according to claim 21, wherein the inflammatory organ damage is lung damage.

25. The pharmaceutical composition according to claim 19 or 20, wherein said condition is said disease associated with overproduction of superoxide anion radical, TNF-α, and iNOS, consisting of Crohn's disease, ulcerative colitis, and atherosclerosis.

26. The pharmaceutical composition according to claim 20, wherein the condition is liver damage caused by alcohol abuse, a bacterial infection, cirrhosis, hepatitis, or an environmental toxin.

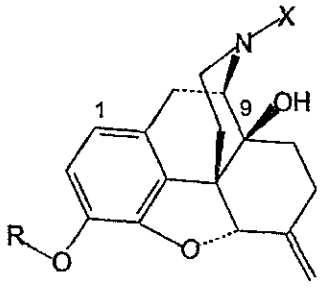
27. The pharmaceutical composition according to any one of claims 19 to 26, which is formulated for oral administration.

28. The pharmaceutical composition according to claim 20 or 25, which is formulated for parenteral administration.

29. The pharmaceutical composition according to any one of claims 19 to 28, wherein the compound of formula XXVIII, or a physiologically acceptable salt and/or acid derivative thereof, is formulated for administration in combination with at least one other therapeutic agent which is an antibiotic, an antimicrobial, an antiviral which is anti-hepatitis or interferon, a vaccine, or a cardiovascular drug, or any combination thereof.

30. The pharmaceutical composition according to any one of claims 19 to 27 and 29, wherein the compound of formula XXVIII is nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.

31. A commercial package comprising a compound of the formula XXVIII:



XXVIII

wherein R is H, or alkyl, and X is hydrogen, allyl, cyclopropylmethyl, or alkyl, or a physiologically acceptable salt and/or acid derivative thereof,

together with instructions for use for preventing or treating a condition which inflammatory organ damage, wherein said inflammatory organ damage is liver, lung or kidney damage, or a disease associated with overproduction of superoxide anion radical, TNF-α, and iNOS, wherein said disease is Crohn's disease, ulcerative colitis, or atherosclerosis.

32. The commercial package according to claim 31, which comprises a daily dose of from 2 mg to 100 mg of a compound of formula XXVIII, or a physiologically acceptable salt and/or acid derivative thereof.

33. The commercial package according to claim 31 or 32, which is for prevention of inflammatory organ damage.

34. The commercial package according to claim 33, wherein said inflammatory organ damage is liver damage.

35. The commercial package according to claim 33, wherein said inflammatory organ damage is kidney damage.

36. The commercial package according to claim 33, wherein the inflammatory organ damage is lung damage.

37. The commercial package according to claim 31 or 32, wherein said condition is said disease associated with overproduction of superoxide anion radical, TNF-α, and iNOS, consisting of Crohn' s disease, ulcerative colitis, or atherosclerosis.

38. The commercial package according to claim 32, wherein the condition is liver damage caused by alcohol abuse, a bacterial infection, cirrhosis, hepatitis, or an environmental toxin.

39. The commercial package according to any one of claims 31 to 38, wherein the compound of formula XXVIII, or a physiologically acceptable salt and/or acid derivative thereof, is formulated for oral administration.

40. The commercial package according to claim 32 or 37, wherein the compound of formula XXVIII, or a physiologically acceptable salt and/or acid derivative thereof, is formulated for parenteral administration.

41. The commercial package according to any one of claims 31 to 38, wherein the compound of formula XXVIII, or a physiologically acceptable salt and/or acid derivative thereof, is formulated for administration in combination with at least one other therapeutic agent which is an antibiotic, an antimicrobial, an antiviral which is anti-hepatitis or interferon, a vaccine, or a cardiovascular drug, or any combination thereof.

42. A commercial package according to any one of claims 31 to 39 and 41, wherein the active compound of formula XXVIII is nalmefene, or a physiologically acceptable salt and/or acid derivative thereof.