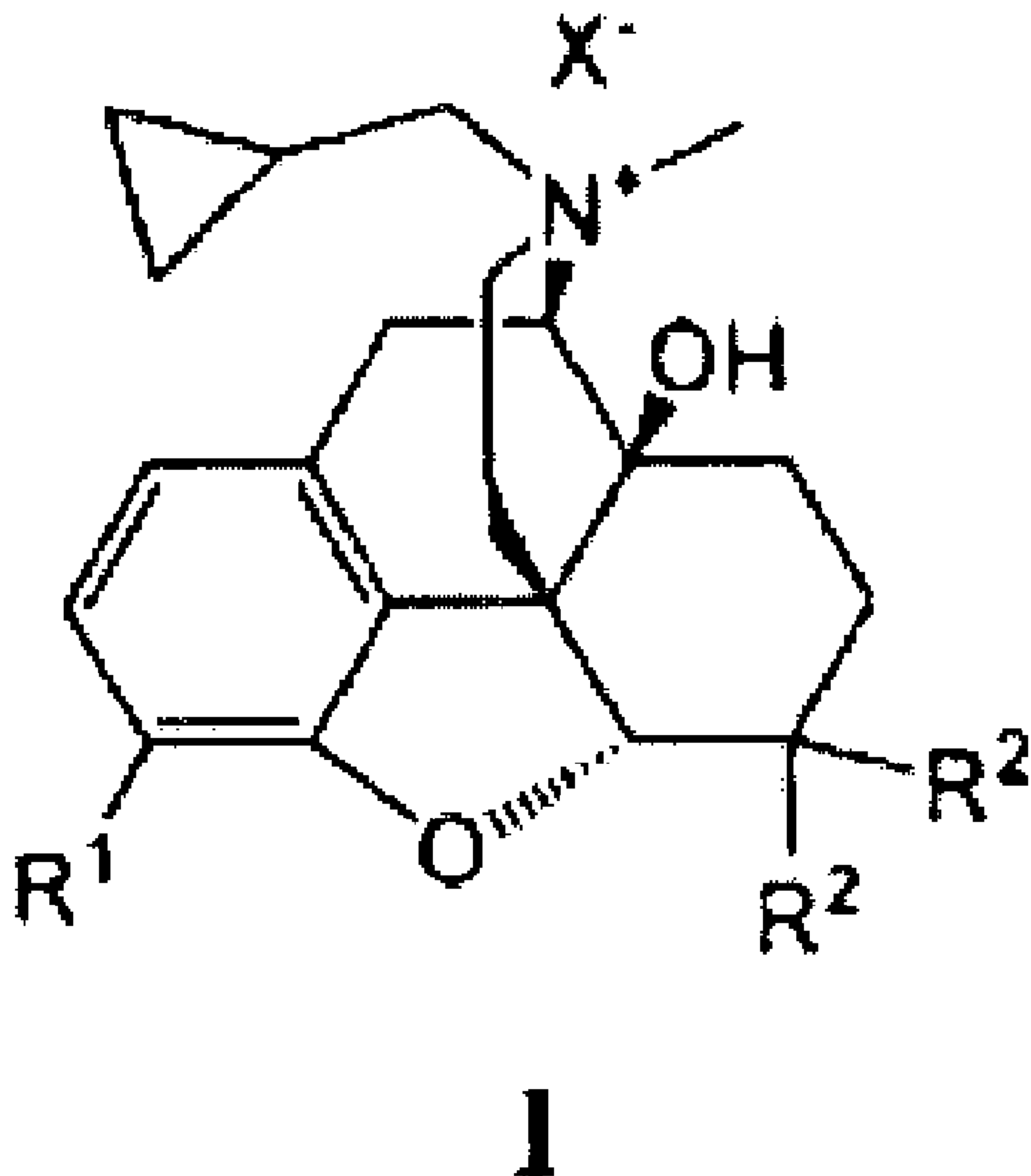




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(54) Titre : ANTAGONISTES DE RECEPTEURS OPIOIDES PERIPHERIQUES, ET LEURS UTILISATIONS
 (54) Title: PERIPHERAL OPIOID RECEPTOR ANTAGONISTS AND USES THEREOF



(57) **Abrégé/Abstract:**

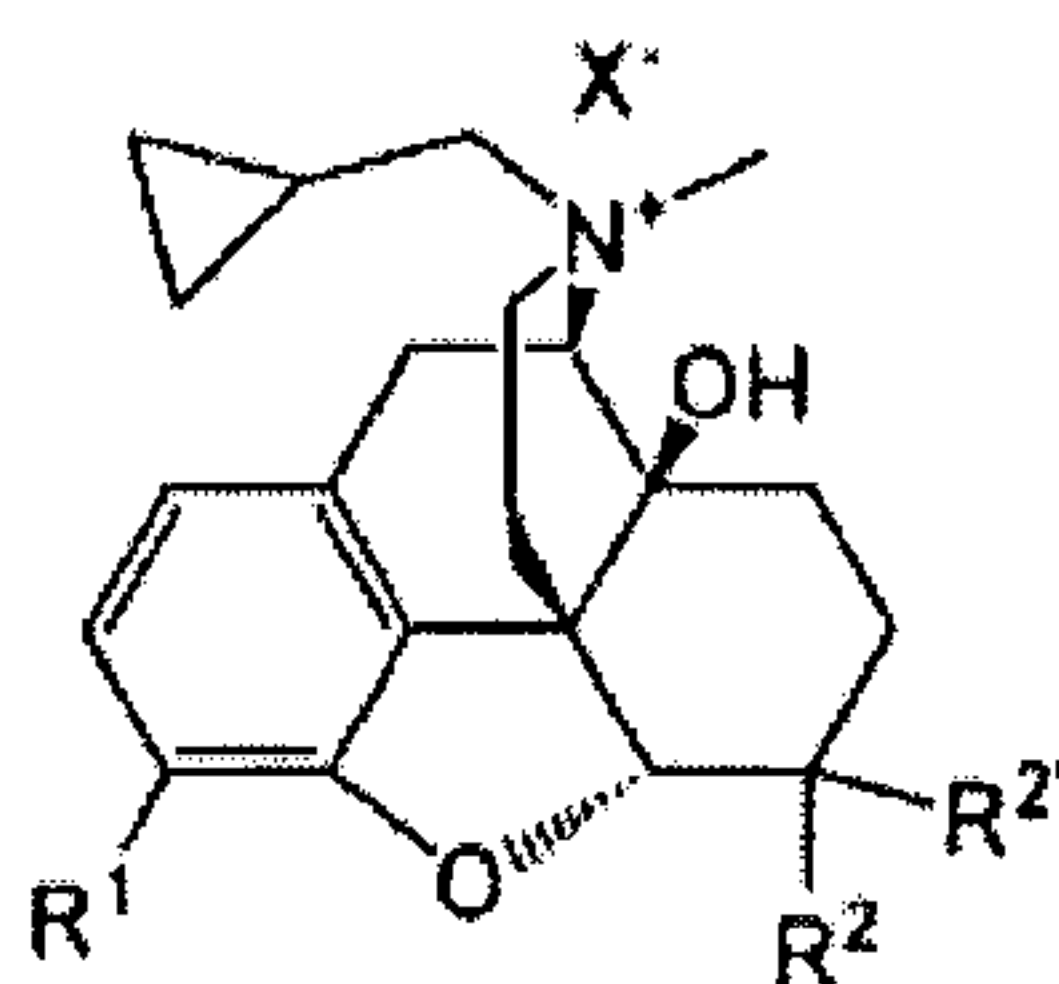
The present invention provides a compound of formula I: wherein R¹, R², R^{2'} and X' are as defined and described herein, methods of manufacture thereof and compositions thereof, useful for example as peripheral mu opioid receptor antagonists in treatment of side effects of opioid administration. (see above formula)

53795-23D1

Abstract

The present invention provides a compound of formula I: wherein R^1 , R^2 , $R^{2'}$ and X^1 are as defined and described herein, methods of manufacture thereof and compositions thereof, useful for example as peripheral mu opioid receptor antagonists in treatment of side

5 effects of opioid administration.

**I**

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PERIPHERAL OPIOID RECEPTOR ANTAGONISTS AND USES THEREOF

This application is a divisional of Canadian Patent Application No. 2,682,125, filed March 28, 2008.

It will be understood that any reference to "the present invention" or the like may refer to the subject matter of this divisional application and/or its parent.

BACKGROUND OF THE INVENTION

[0001] Opioids are widely used in patients with advanced cancers and other terminal diseases to lessen suffering. Opioids are narcotic medications that activate opioid receptors located in the central nervous system to relieve pain. Opioids, however, also react with receptors outside of the central nervous system, resulting in side effects including constipation, nausea, vomiting, urinary retention, and severe itching. Most notable are the effects in the gastrointestinal tract (GI) where opioids inhibit gastric emptying and propulsive motor activity of the intestine, thereby decreasing the rate of intestinal transit and producing constipation. The effectiveness of opioids for pain is often limited due to resultant side effects, which can be debilitating and often cause patients to cease use of opioid analgesics.

[0002] In addition to analgesic opioid induced side effects, studies have suggested that endogenous opioid compounds and receptors may also affect activity of the gastrointestinal (GI) tract and may be involved in normal regulation of intestinal motility and mucosal transport of fluids in both animals and man. (Koch, T. R, et al, Digestive Diseases and Sciences 1991, 36, 712-728; Schuller, A.G.P., et al., Society of Neuroscience Abstracts 1998, 24, 524, Reisine, T., and Pasternak, G., Goodman & Gilman's The Pharmacological Basis of Therapeutics Ninth Edition 1996, 521-555 and Bagnol, D., et al., Regul. Pept. 1993, 47, 259-273). Thus, an abnormal physiological level of endogenous compounds and/or receptor activity may lead to bowel dysfunction.

[0003] For example, patients who have undergone surgical procedures, especially surgery of the abdomen, often suffer from a particular bowel dysfunction, called post-operative (or post-surgical) ileus, that may be caused by fluctuations in natural opioid levels. Similarly, women who have recently given birth commonly suffer from post-partum ileus, which is thought to be caused by similar natural opioid fluctuations as a result of birthing stress. Gastrointestinal dysfunction associated with post-operative or post partum ileus can

typically last for 3 to 5 days, with some severe cases lasting more than a week. Administration of opioid analgesics to a patient after surgery, which is now an almost universal practice, may exacerbate bowel dysfunction, thereby delaying recovery of normal bowel function, prolonging hospital stays, and increasing medical care costs.

[0004] Opioid receptor antagonists such as naloxone, naltrexone, and nalmefene, have been studied as a means of antagonizing undesirable peripheral effects of opioids. However, these agents act not only on peripheral opioid receptors, but also on central nervous system sites, so that they sometimes reverse the beneficial analgesic effects of opioids, or cause symptoms of opioid withdrawal. Preferable approaches for use in controlling opioid-induced side effects include administration of peripheral opioid receptor antagonist compounds that do not readily cross the blood-brain barrier. For example, the peripheral μ opioid receptor antagonist compound methylnaltrexone and related compounds have been disclosed for use in curbing opioid-induced side effects in patients (e.g., constipation, pruritus, nausea, and/or vomiting). See, e.g., U.S. Pat. Nos. 5,972,954, 5,102,887, 4,861,781, and 4,719,215; and Yuan, C. -S. et al. Drug and Alcohol Dependence 1998, 52, 161. Similarly, peripherally selective piperidine-N-alkylcarboxylate and 3,4-dimethyl-4-aryl-piperidine opioid receptor antagonists have been described as being useful for treatment of opioid-induced side effects constipation, nausea or vomiting, as well as irritable bowel syndrome and idiopathic constipation. See, e.g., U.S. Pat. Nos. 5,250,542, 5,434,171, 5,159,081, and 5,270,328.

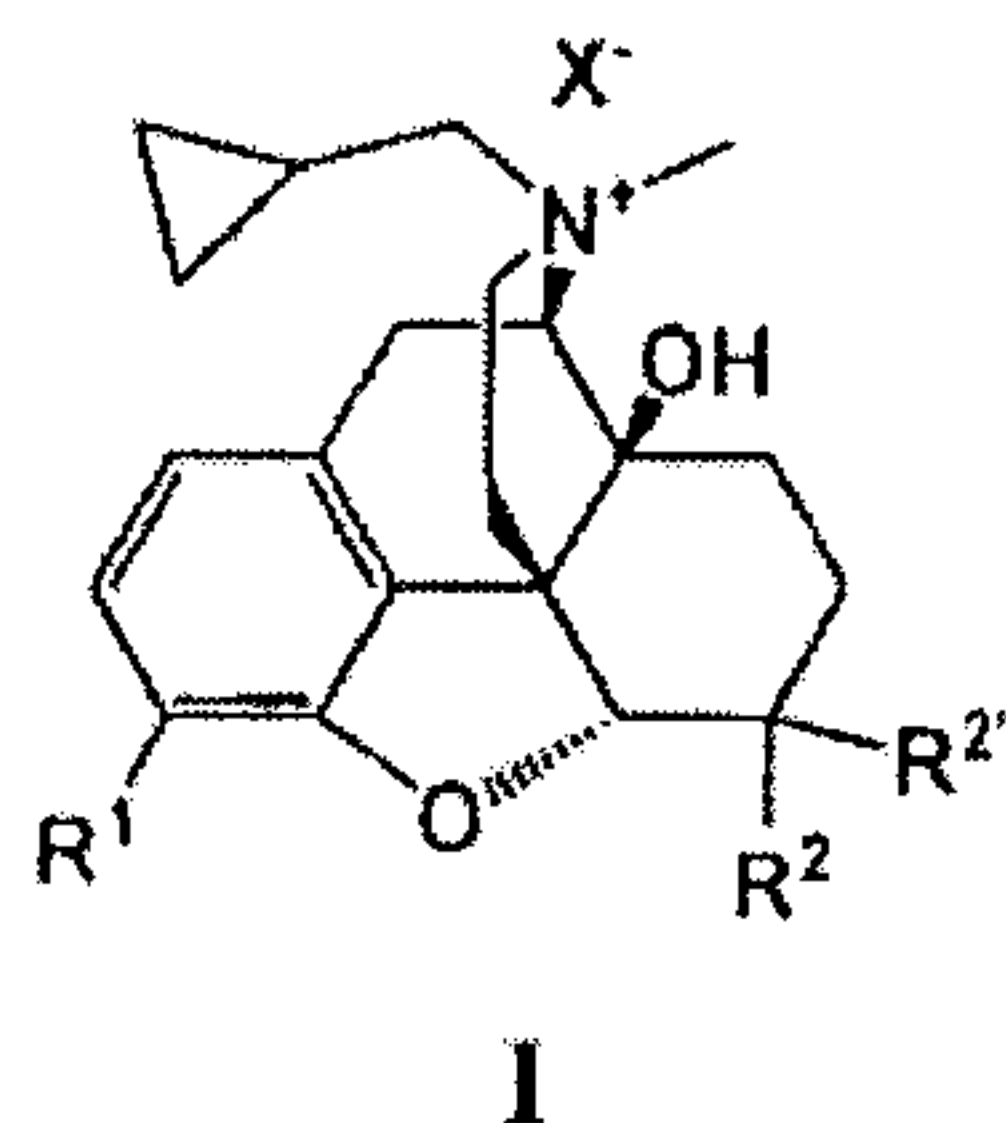
[0005] It would be desirable to provide peripheral μ opioid receptor antagonist compounds for administration to a patient in need of treatment for any of the above-mentioned disorders.

SUMMARY

[0006] The present invention provides compounds useful as peripheral μ opioid receptor antagonists, or prodrugs thereof, and are therefore useful for the treatment, prevention, amelioration, delay or reduction of severity and/or incidence of side effects associated with opioid administration, such as, for example, gastrointestinal dysfunction (e.g., inhibition of intestinal motility, constipation, GI sphincter constriction, nausea, emesis (vomiting), biliary spasm, opioid bowel dysfunction, colic), dysphoria, pruritus, urinary retention, depression of respiration, papillary constriction, cardiovascular effects, chest wall rigidity and cough suppression, depression of stress response, and immune suppression associated with administration of narcotic analgesia, etc, or combinations thereof. Other uses of provided compounds are set forth *infra*.

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[0006a] In one aspect, the present divisional application relates to an isolated compound of formula **I**:



wherein X^- is a suitable anion; R^1 is $-OS(O)_2OH$; and R^2 and $R^{2'}$ are taken together to form
5 oxo.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] Figure 1 depicts the competition curve obtained for 6-alpha-methylnaltrexol (I-1).

[0008] Figure 2 depicts the competition curve obtained for 6-beta-methylnaltrexol (I-2).

[0009] Figure 3 depicts the competition curve obtained for 3 sulfo-methylnaltrexone (I-3).

[0010] Figure 4 depicts the competition curve obtained for 6 alpha-methylnaltrexone (I-1) on the DAMGO-induced decrease in twitch contraction amplitude in guinea pig ileum.

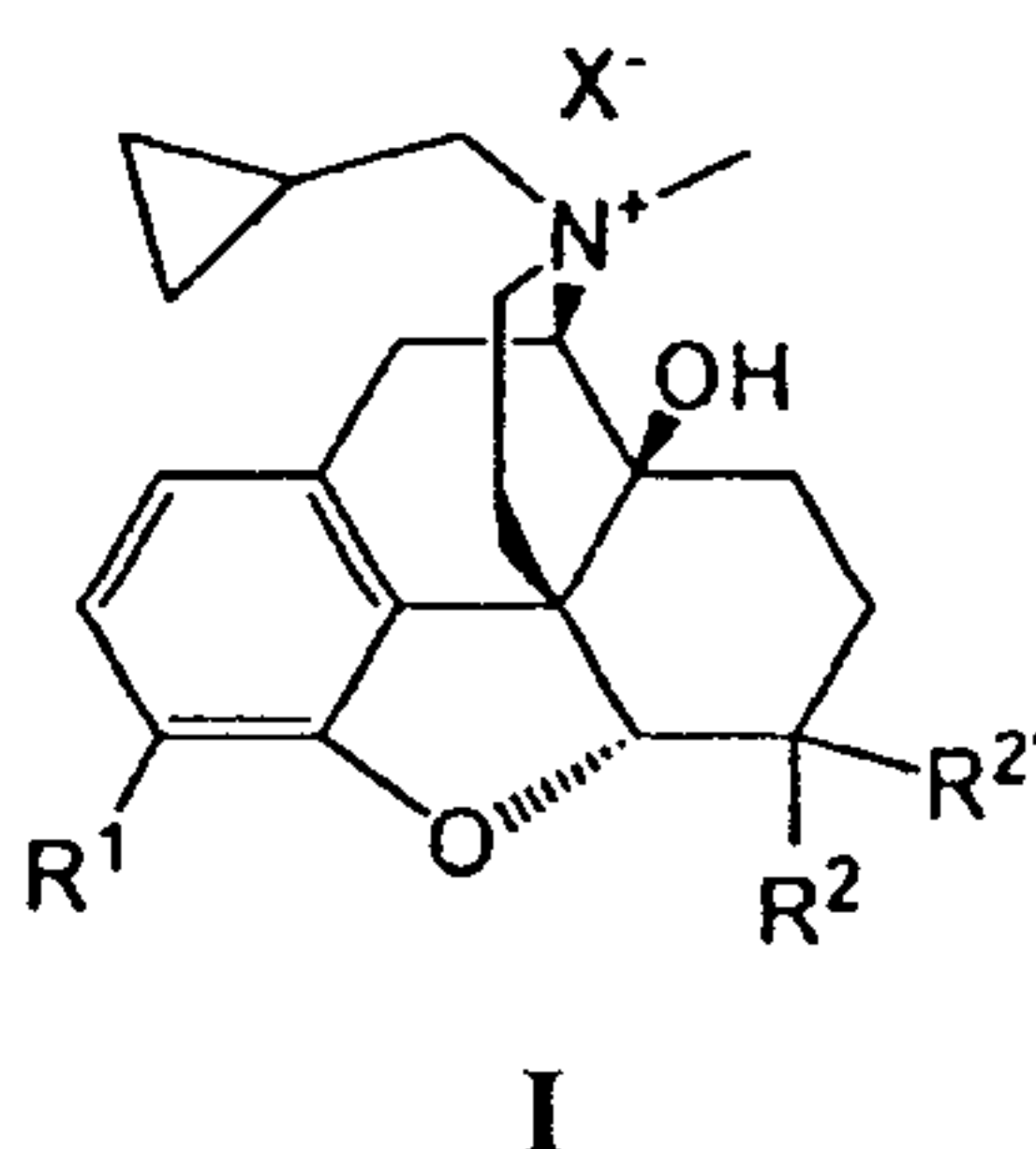
[0011] Figure 5 depicts the depicts the competition curve obtained for 6-beta-methylnaltrexol (I-2) on the DAMGO-induced decrease in twitch contraction amplitude in guinea pig ileum.

[0012] Figure 6 depicts the competition curve obtained for 3 sulfo-methylnaltrexone (I-3) on the DAMGO-induced decrease in twitch contraction amplitude in guinea pig ileum.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

1. Compounds and Definitions:

[0013] In certain embodiments, the present invention provides a compound of formula I:



wherein X^- is a suitable anion;

R^1 is $-OH$ or $-OS(O)_2OH$; and

R^2 is $-OH$; and

$R^{2'}$ is hydrogen; or R^2 and $R^{2'}$ are taken together to form oxo;

provided that, when R^2 and $R^{2'}$ are taken together to form oxo, then R^1 is $-OS(O)_2OH$.

[0014] As used herein, an “effective amount” of a compound or pharmaceutically acceptable composition can achieve a desired therapeutic and/or prophylactic effect. In some embodiments, an “effective amount” is at least a minimal amount of a compound, or composition containing a compound, which is sufficient for treating one or more symptoms of a disorder or condition associated with modulation of peripheral μ opioid receptors, such as side effects associated with opioid analgesic therapy (e.g., gastrointestinal dysfunction (e.g., dysmotility constipation, etc.), nausea, emesis, (e.g., nausea), etc.). In certain embodiments, an “effective amount” of a compound, or composition containing a compound, is sufficient for treating one or more symptoms associated with, a disease associated with aberrant endogenous peripheral opioid or μ opioid receptor activity (e.g., idiopathic constipation, ileus, etc.).

[0015] The term “subject”, as used herein, means a mammal and includes human and animal subjects, such as domestic animals (e.g., horses, dogs, cats, etc.).

[0016] The terms “suffer” or “suffering” as used herein refers to one or more conditions that a patient has been diagnosed with, or is suspected to have.

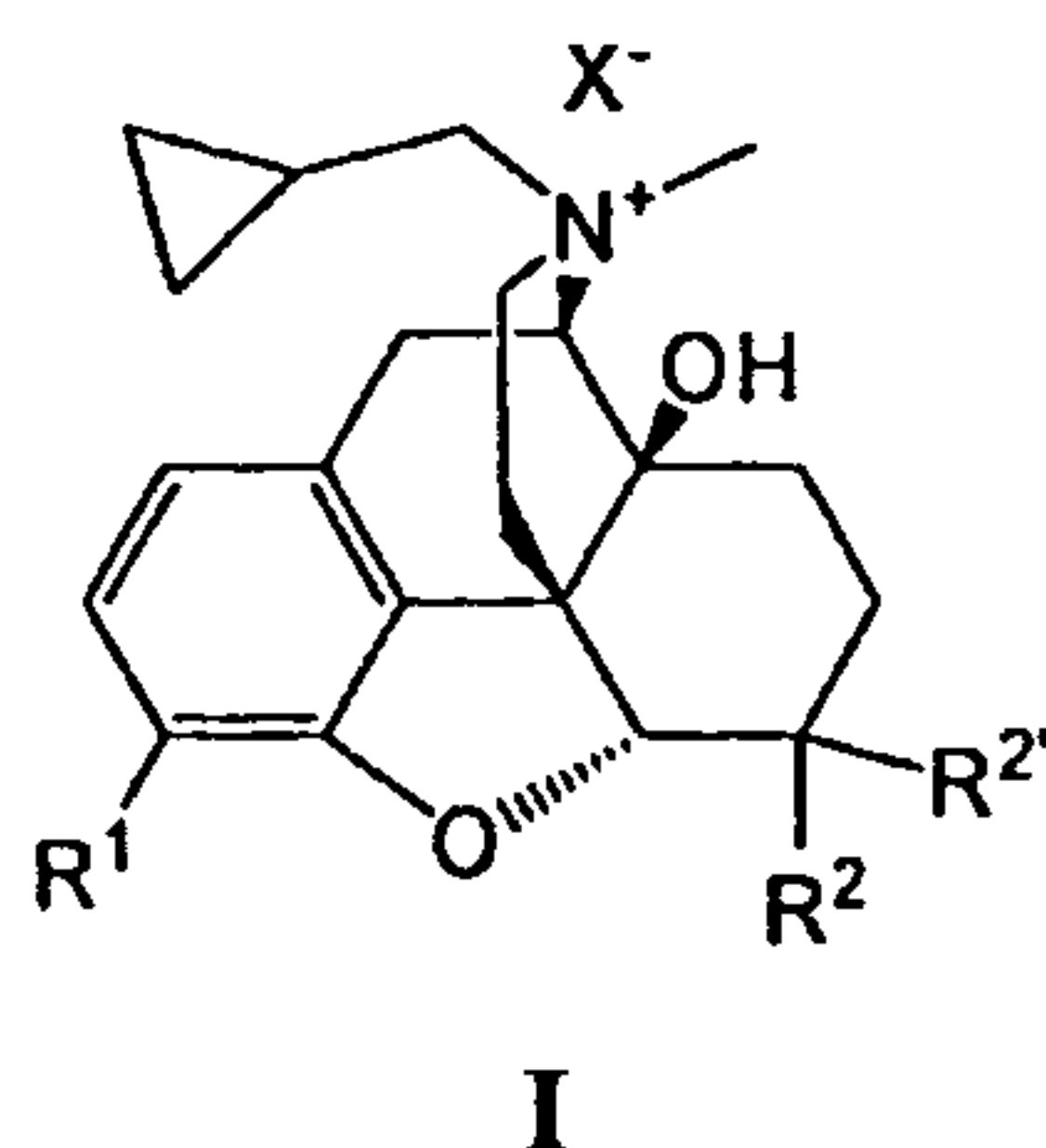
[0017] The terms “treat” or “treating,” as used herein, refers to partially or completely alleviating, inhibiting, delaying onset of, preventing, ameliorating and/or relieving a disorder or condition, or one or more symptoms of the disorder or condition.

[0018] “Therapeutically active agent” or “active agent” refers to a substance, including a biologically active substance, that is useful for therapy (e.g., human therapy, veterinary therapy), including prophylactic and therapeutic treatment. Therapeutically active agents include organic molecules that are drug compounds, peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoprotein, mucoprotein, lipoprotein, synthetic polypeptide or protein, small molecules linked to a protein, glycoprotein, steroid, nucleic acid, DNA, RNA, nucleotide, nucleoside, oligonucleotides, antisense oligonucleotides, lipid, hormone, and vitamin. Therapeutically active agents include any substance used as a medicine for treatment, prevention, delay, reduction or amelioration of a disease, condition, or disorder. Among therapeutically active agents useful in the formulations of the present invention are opioid receptor antagonist compounds, opioid analgesic compounds, and the like. Further detailed description of compounds useful as therapeutically active agents is provided below. A therapeutically active agent includes a compound that increases the effect or effectiveness of a second compound, for example, by enhancing potency or reducing adverse effects of a second compound.

[0019] The expression "unit dosage form" as used herein refers to a physically discrete unit of inventive formulation appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular subject or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of specific active agent employed; specific composition employed; age, body weight, general health, sex and diet of the subject; time of administration, and rate of excretion of the specific active agent employed; duration of the treatment; drugs and/or additional therapies used in combination or coincidental with specific compound(s) employed, and like factors well known in the medical arts.

2. *Description of Exemplary Compounds:*

[0020] As described generally above, the present invention provides a compound of formula I:



wherein X^- is a suitable anion;

R^1 is -OH or -OS(O)₂OH; and

R^2 is -OH; and

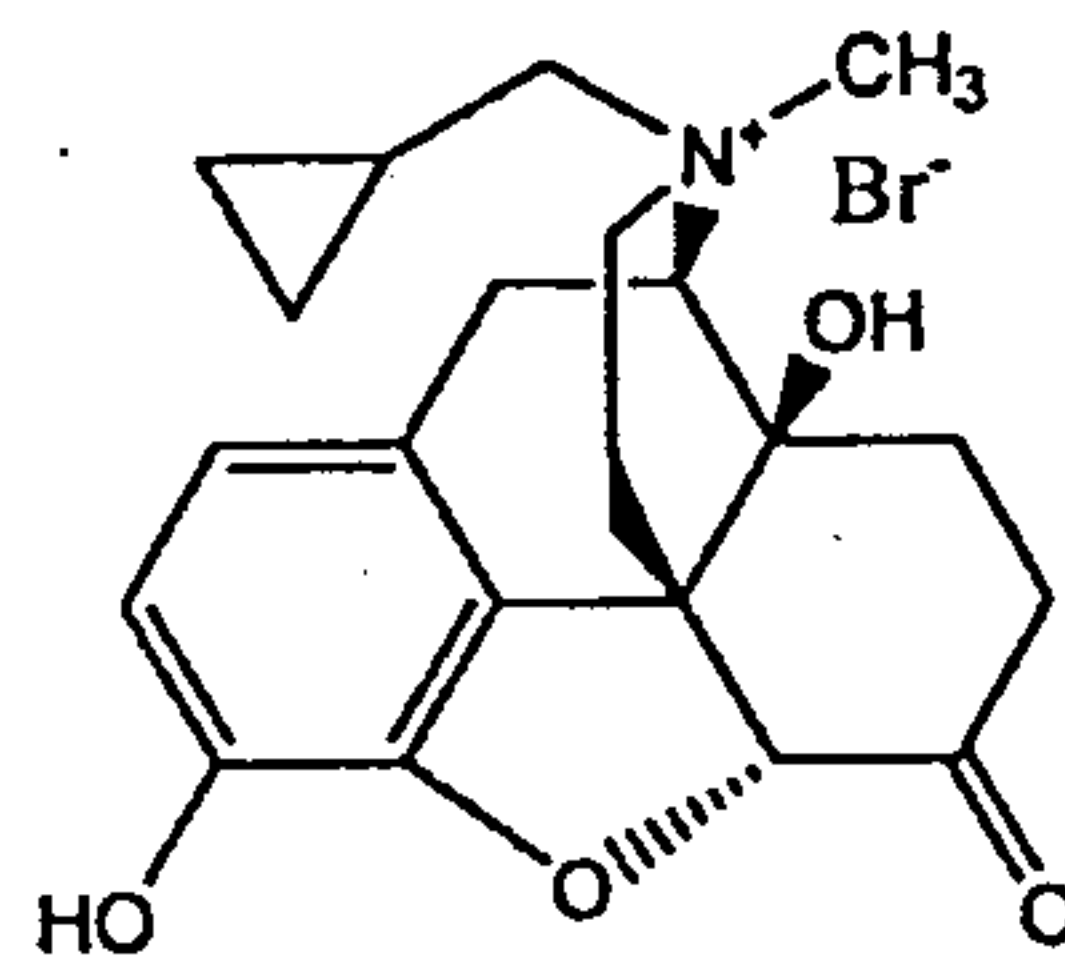
$R^{2'}$ is hydrogen; or R^2 and $R^{2'}$ are taken together to form oxo;

provided that, when R^2 and $R^{2'}$ are taken together to form oxo, then R^1 is -OS(O)₂OH.

[0021] One of ordinary skill in the art will recognize that the nitrogen atom depicted in formula I is a chiral center and, therefore, can exist in either the (R) or (S) configuration. According to one aspect, the present invention provides a compound of formula I wherein the compound is in the (R) configuration with respect to the nitrogen. In certain embodiments of the present invention, at least about 99.6%, 99.7%, 99.8%, 99.85%, 99.9%, or 99.95% of a compound of formula I is in the (R) configuration with respect to nitrogen.

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[0022] Provided compounds were discovered as a result of metabolic studies of peripheral mu opioid antagonists. Without wishing to be bound by theory, it is believed that the present compounds are metabolites of peripheral mu opioid antagonists, such as (R)-*N*-methylnaltrexone bromide (Compound 1), described in International patent application publication number WO2006/127899, which has the following structure:



Compound 1

where the compound is in the (R) configuration with respect to the nitrogen. In certain embodiments of the present invention, at least about 99.6%, 99.7%, 99.8%, 99.85%, 99.9%, or 99.95% of Compound 1 is in the (R) configuration with respect to nitrogen. Methods for determining the amount of (R)-*N*-methylnaltrexone bromide, present in a sample as compared to the amount of (S)-*N*-methylnaltrexone bromide present in that same sample, are described in detail in WO2006/127899.

In other embodiments, Compound 1 contains 0.15% or less (S)-*N*-methylnaltrexone bromide.

[0023] In certain embodiments, compounds of the present invention are useful for the study of peripheral mu opioid antagonists in biological and pathological phenomena and the comparative evaluation of peripheral mu opioid antagonists.

[0024] In certain embodiments, the present invention provides any compound of the present invention in isolated form. As used herein, the term "isolated" means that a compound is provided in a form that is separated from other components that might be present in that compound's biological environment. In certain embodiments, an isolated compound is in solid form. In some embodiments, an isolated compound is at least about 50% pure as determined by a suitable HPLC method. In certain embodiments, an isolated compound is at least about 60%, 70%, 80%, 90%, 95%, 98%, or 99% as determined by a suitable HPLC method.

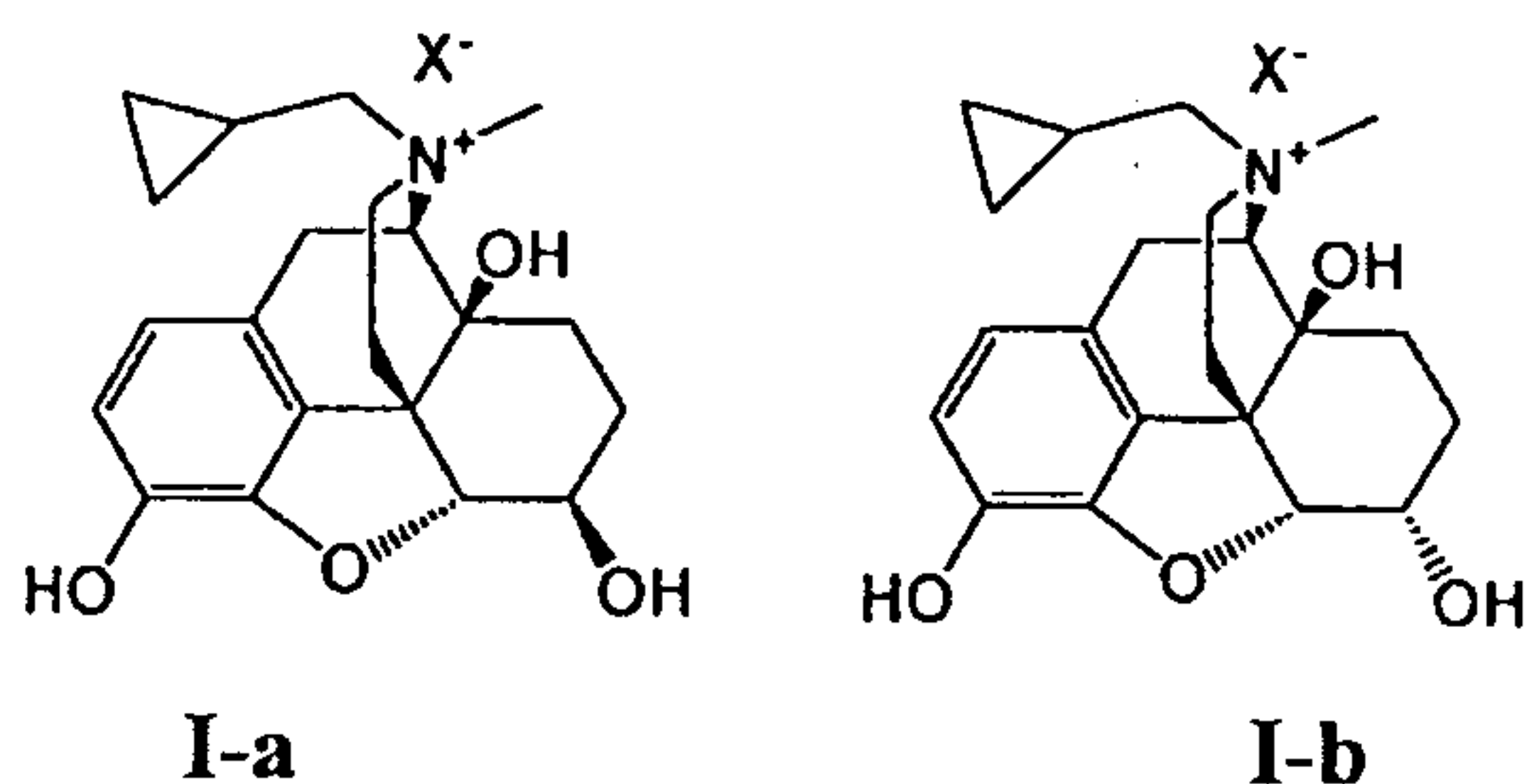
[0025] As defined generally above, the X⁻ group of formula I is a suitable anion. In certain embodiments, X⁻ is the anion of a suitable Brønsted acid. Exemplary Brønsted acids include hydrogen halides, carboxylic acids, sulfonic acids, sulfuric acid, and phosphoric acid.

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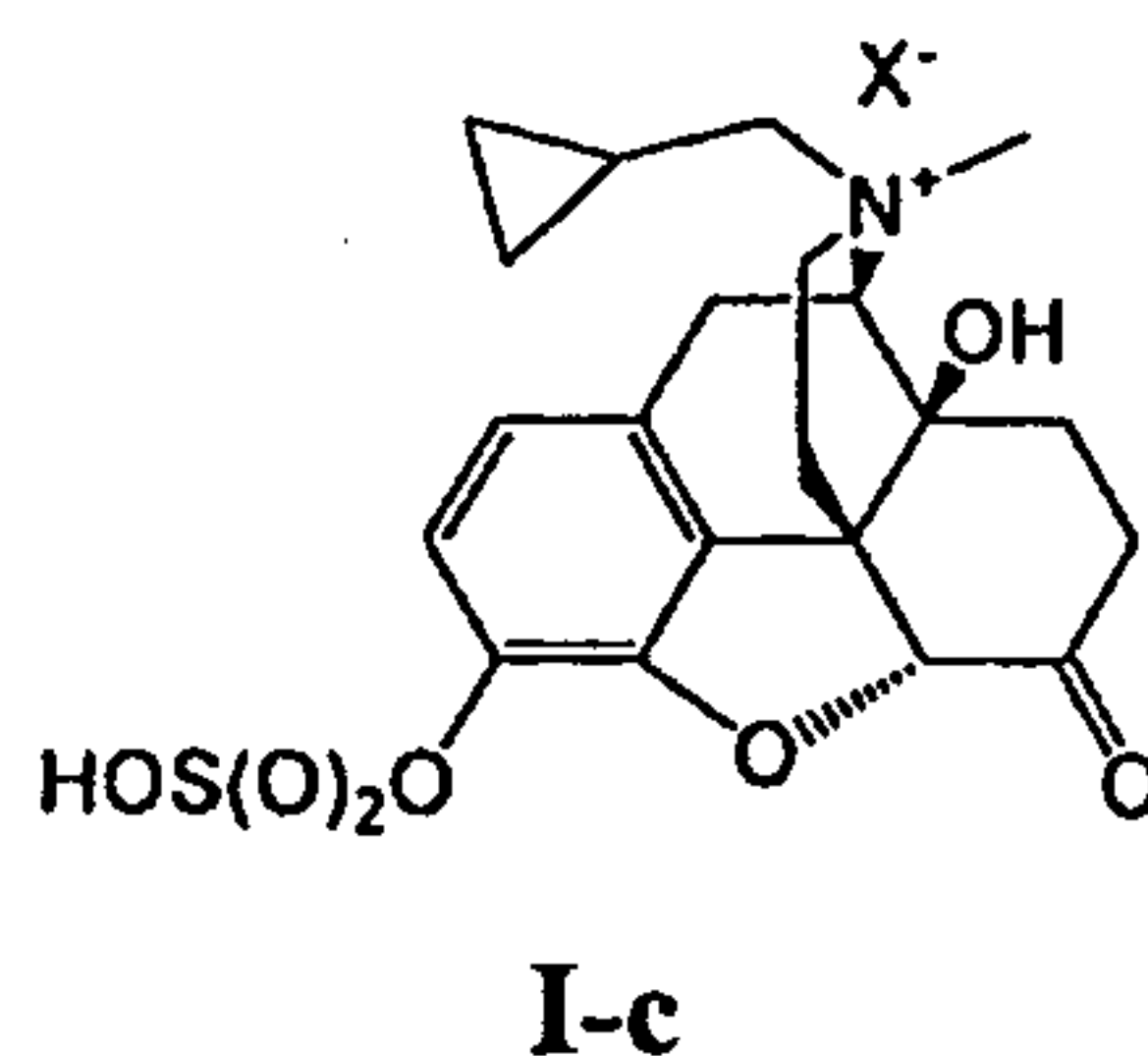
In certain embodiments, X^- is chloride, bromide, iodide, fluoride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, carbonate, phosphate, malate, maleate, fumarate sulfonate, methylsulfonate, formate, carboxylate, sulfate, methylsulfate or succinate. According to one aspect, X^- is bromide.

[0026] According to another aspect, the present invention provides a compound of formula I-a or I-b:



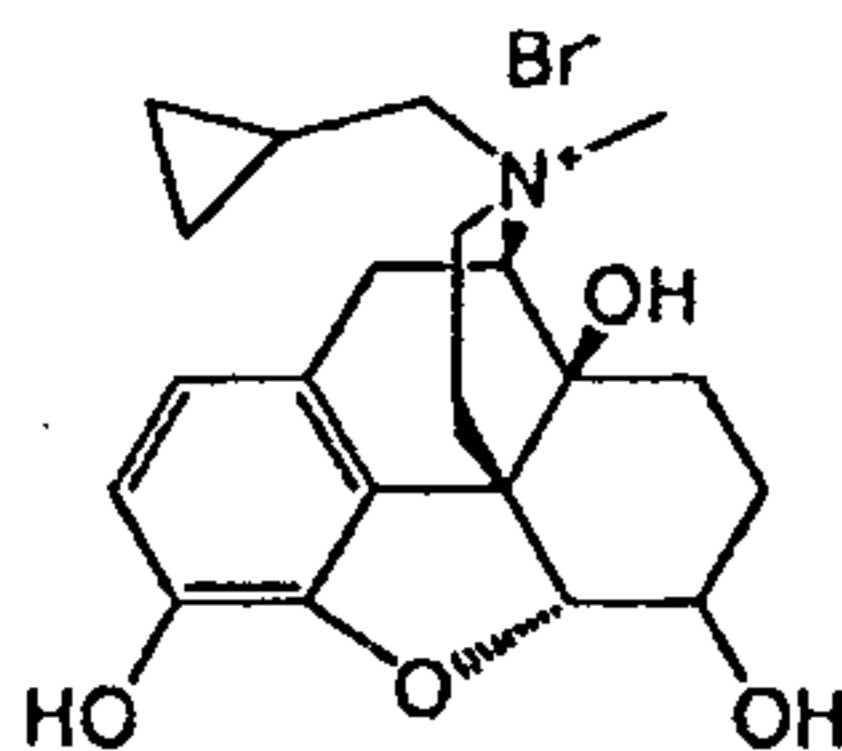
wherein each X^- is a suitable anion, as defined above and described herein.

[0027] In certain embodiments, the present invention provides a compound of formula I-c:



[0028] As defined generally above, the X^- group of formulae I-a, I-b, and I-c is a suitable anion. In certain embodiments, X^- is the anion of a suitable Brønsted acid. Exemplary Brønsted acids include hydrogen halides, carboxylic acids, sulfonic acids, sulfuric acid, and phosphoric acid. In certain embodiments, X^- is chloride, bromide, iodide, fluoride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, carbonate, phosphate, malate, maleate, fumarate sulfonate, methylsulfonate, formate, carboxylate, sulfate, methylsulfate or succinate. According to one aspect, X^- is bromide.

[0029] According to one embodiment, the present invention provides a compound of formula II:



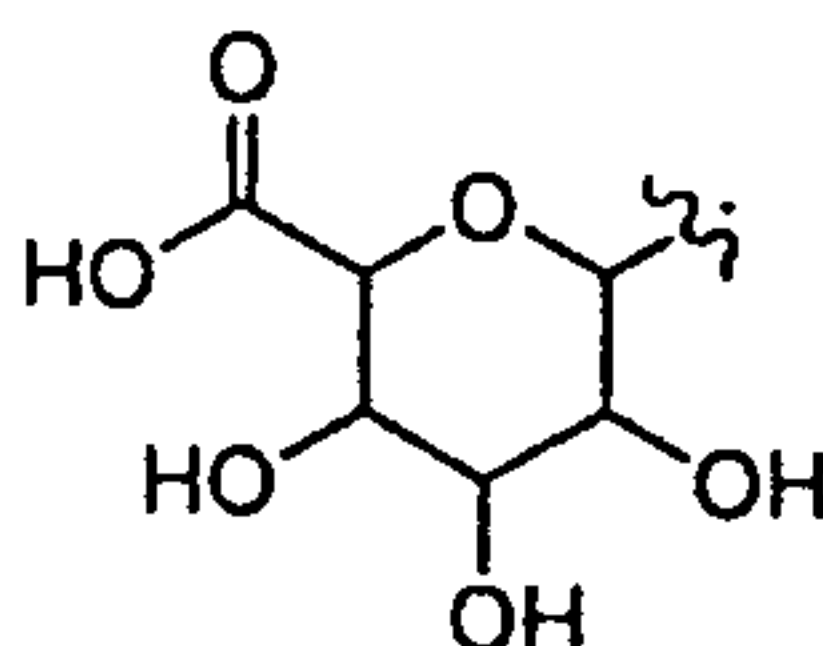
wherein X^- is a suitable anion;

R^1 is -OH, -OGlu, or -OS(O)₂OH;

R^2 is -OH or -OGlu, and $R^{2'}$ is hydrogen, or R^2 and $R^{2'}$ are taken together to form oxo; and each Glu is a glucuronyl moiety,

provided that at least one of R^1 and R^2 contains a glucuronyl moiety.

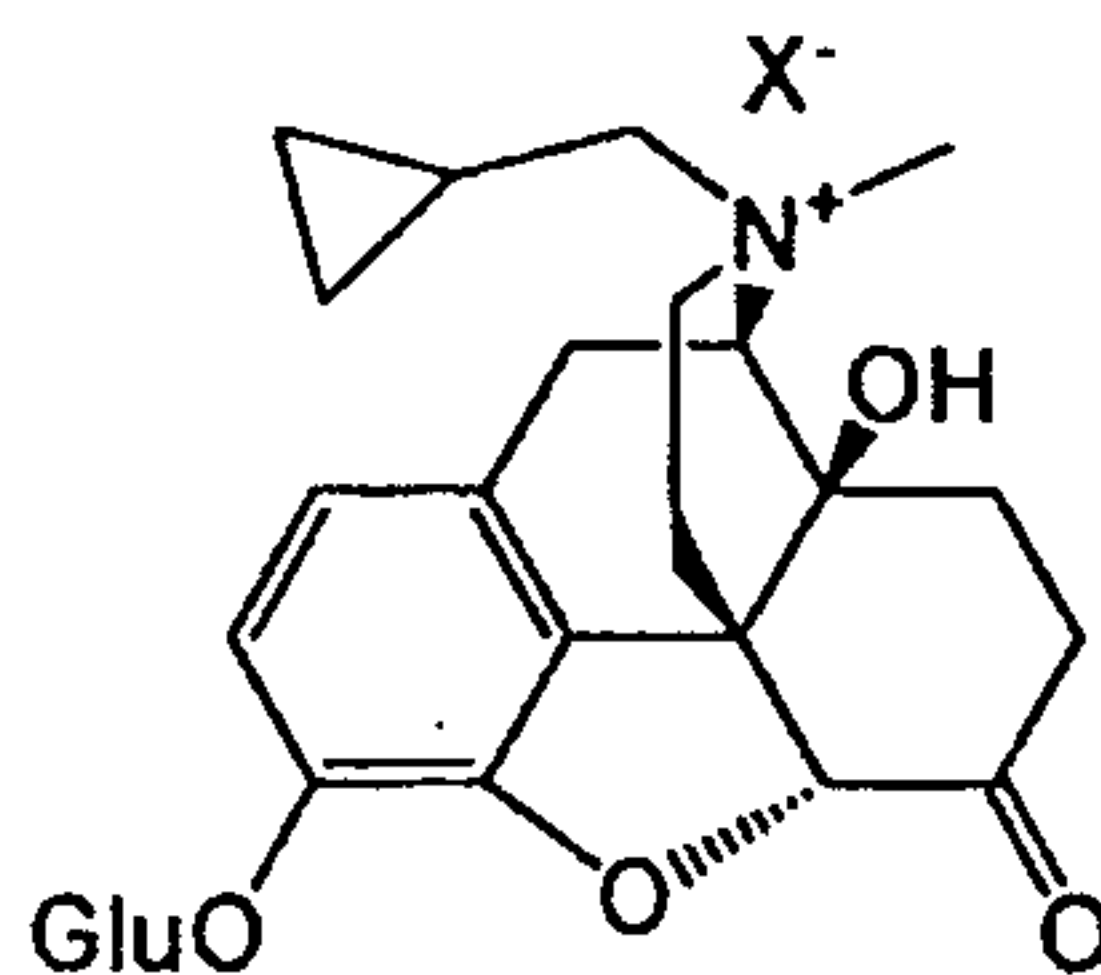
[0032] As used herein, the term "glucuronyl moiety" refers to a group having the structure:



wherein the wavy line depicted designated the point of attachment to a compound of formula III.

[0033] In certain embodiments, the R^1 group of formula III is -OH and R^2 is -OGlu. In other embodiments, the R^1 group of formula III is -OGlu and R^2 is -OH.

[0034] In certain embodiments, the R^1 group of formula III is -OGlu and R^2 and $R^{2'}$ are taken together to form oxo. Such compounds are of formula IV:

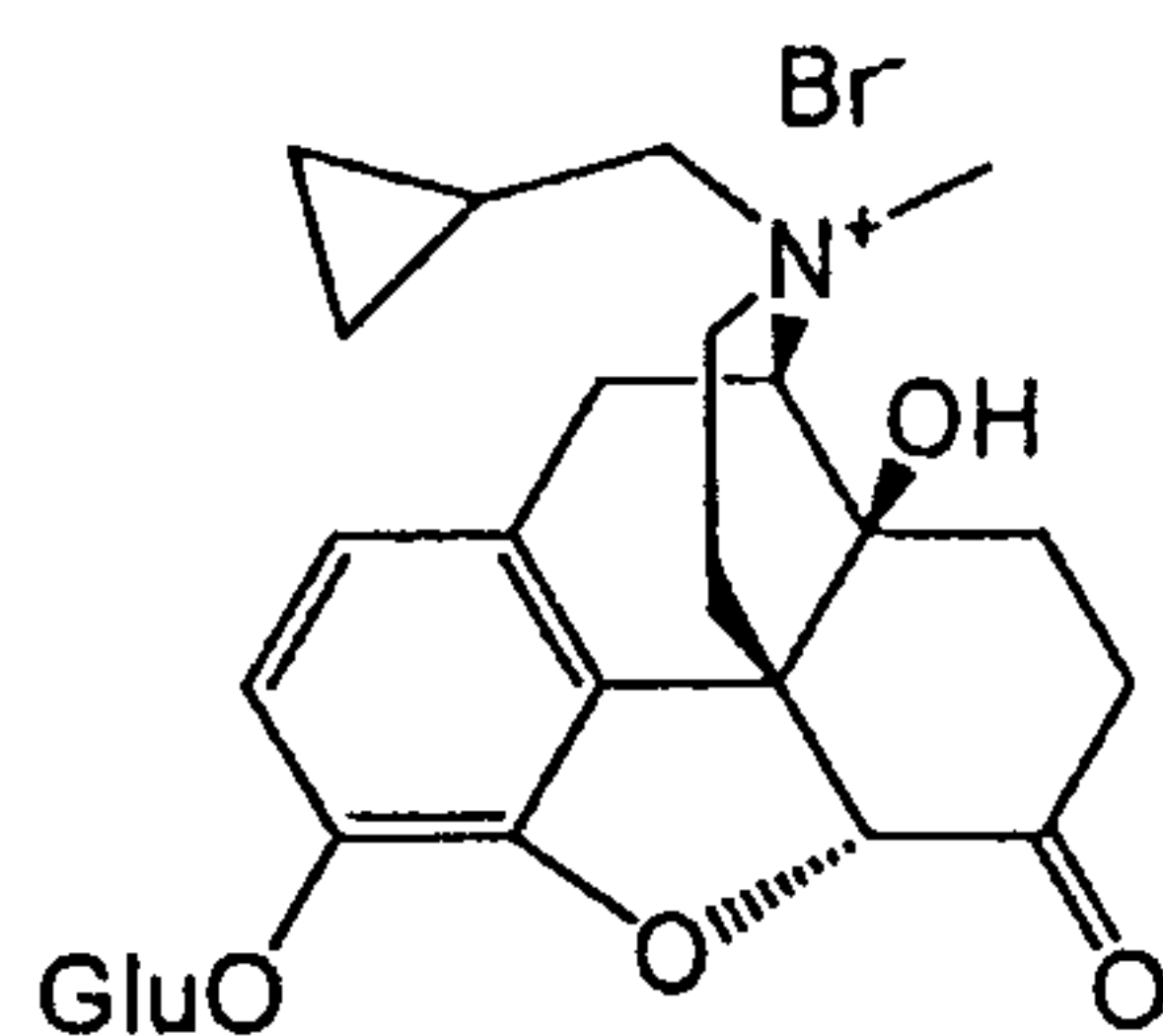


IV.

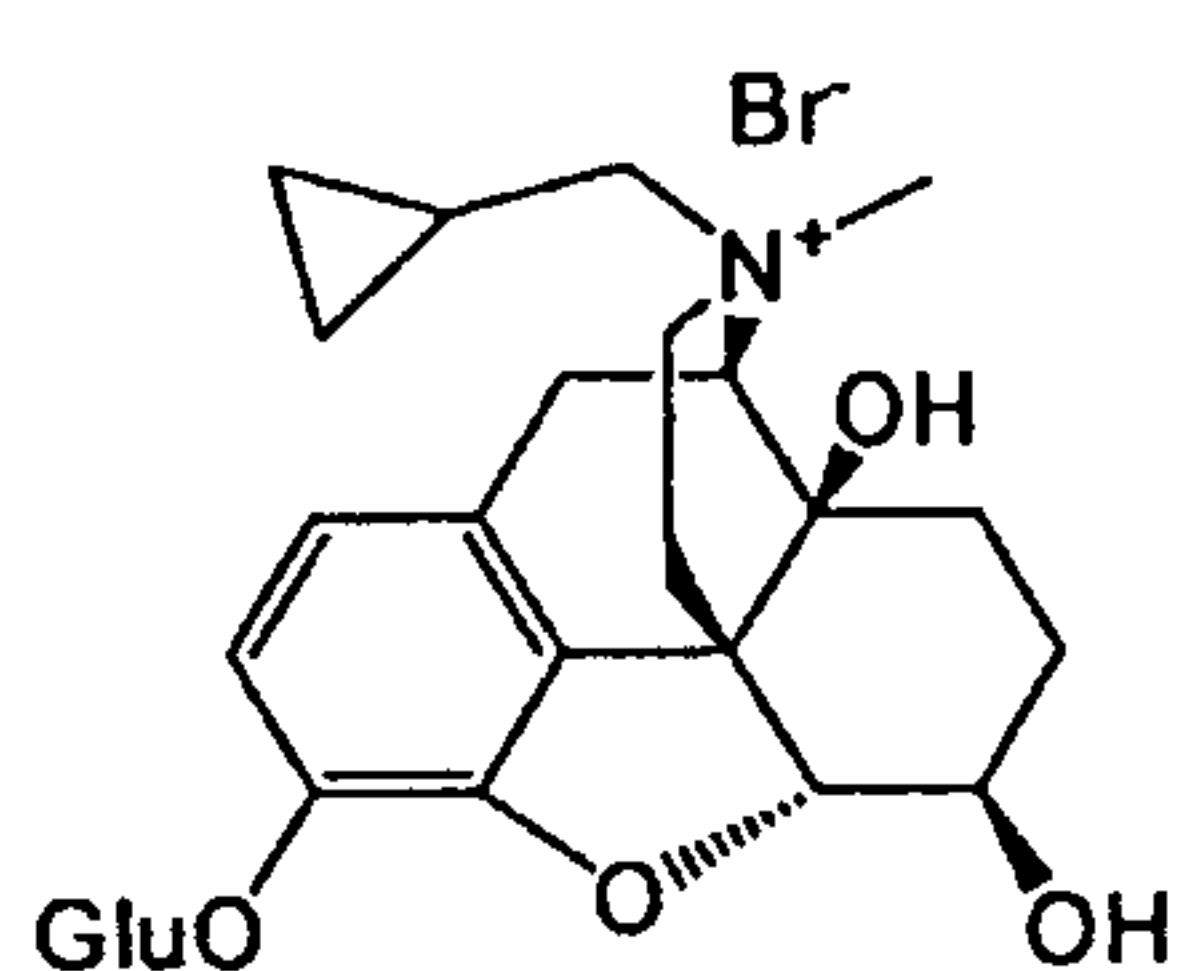
[0035] As defined generally above, the X^- group of formulae III and IV is a suitable anion. In certain embodiments, X^- is the anion of a suitable Brønsted acid. Exemplary Brønsted acids include hydrogen halides, carboxylic acids, sulfonic acids, sulfuric acid, and phosphoric acid. In certain embodiments, X^- is chloride, bromide, iodide, fluoride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, carbonate, phosphate, malate, maleate, fumarate sulfonate, methylsulfonate, formate, carboxylate, sulfate, methylsulfate or succinate. According to one aspect, X^- is bromide.

[0036] Exemplary compounds of formula III are set forth in Table 2, below.

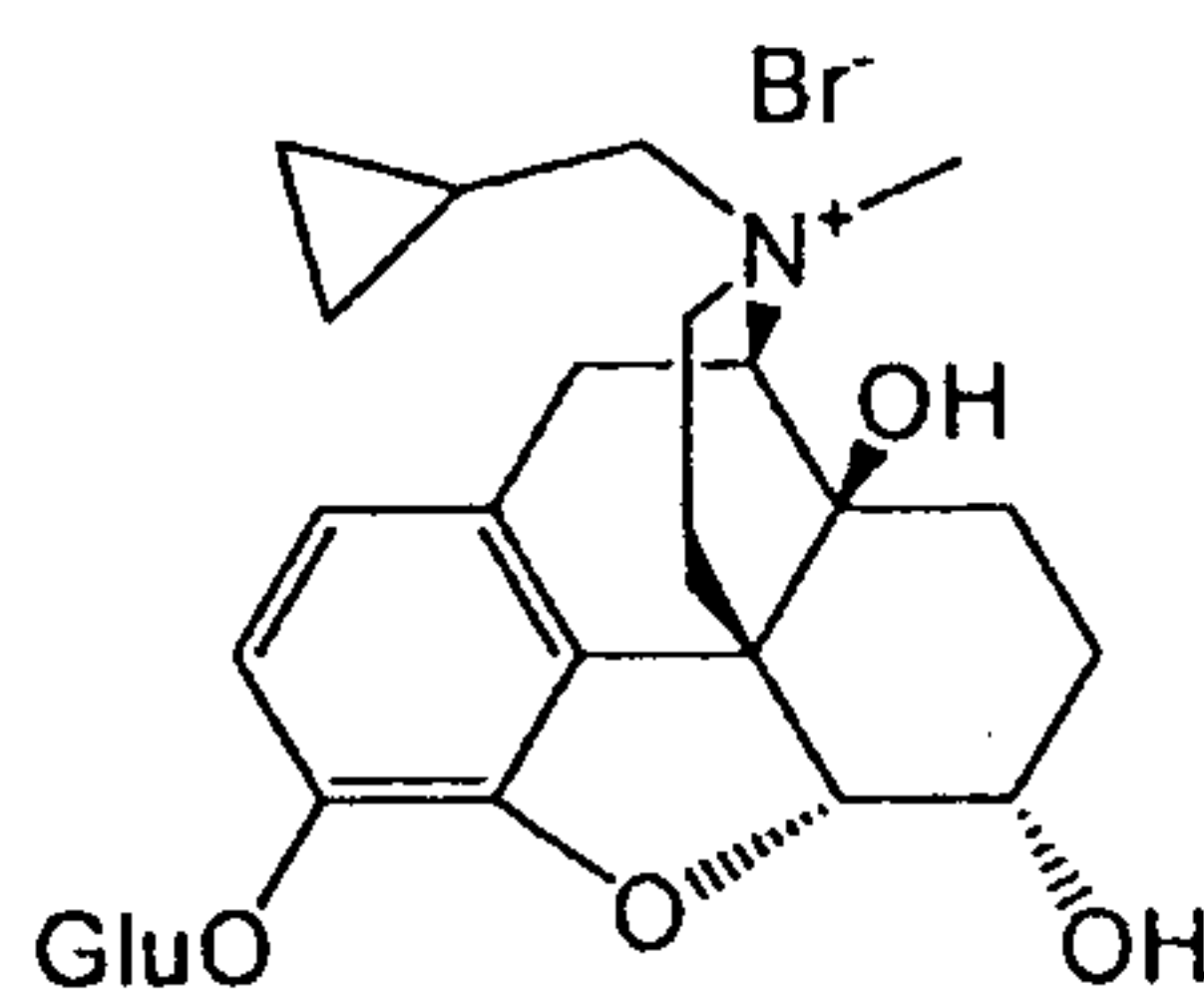
Table 2. Exemplary Compounds of Formula III



III-1



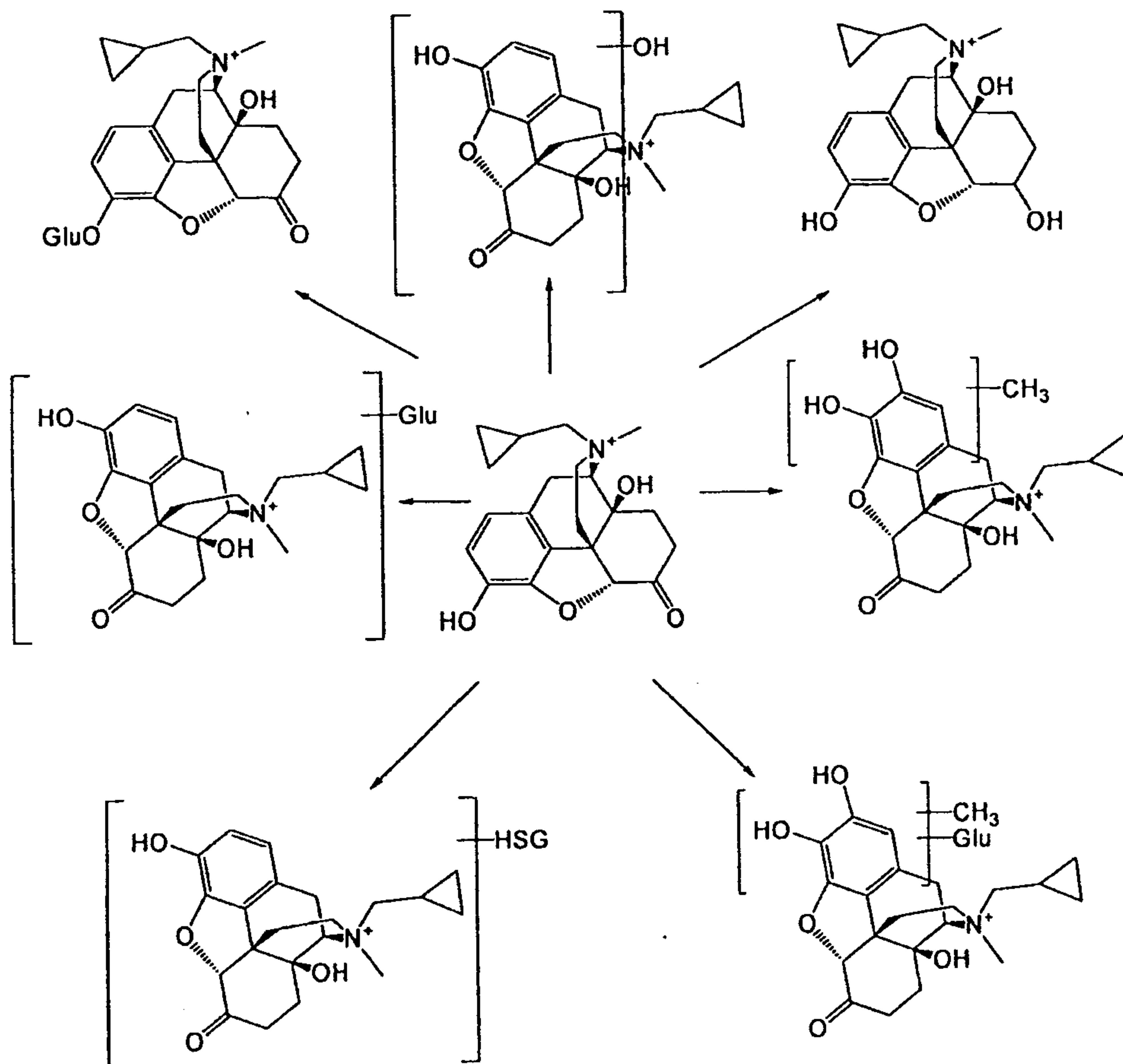
III-2



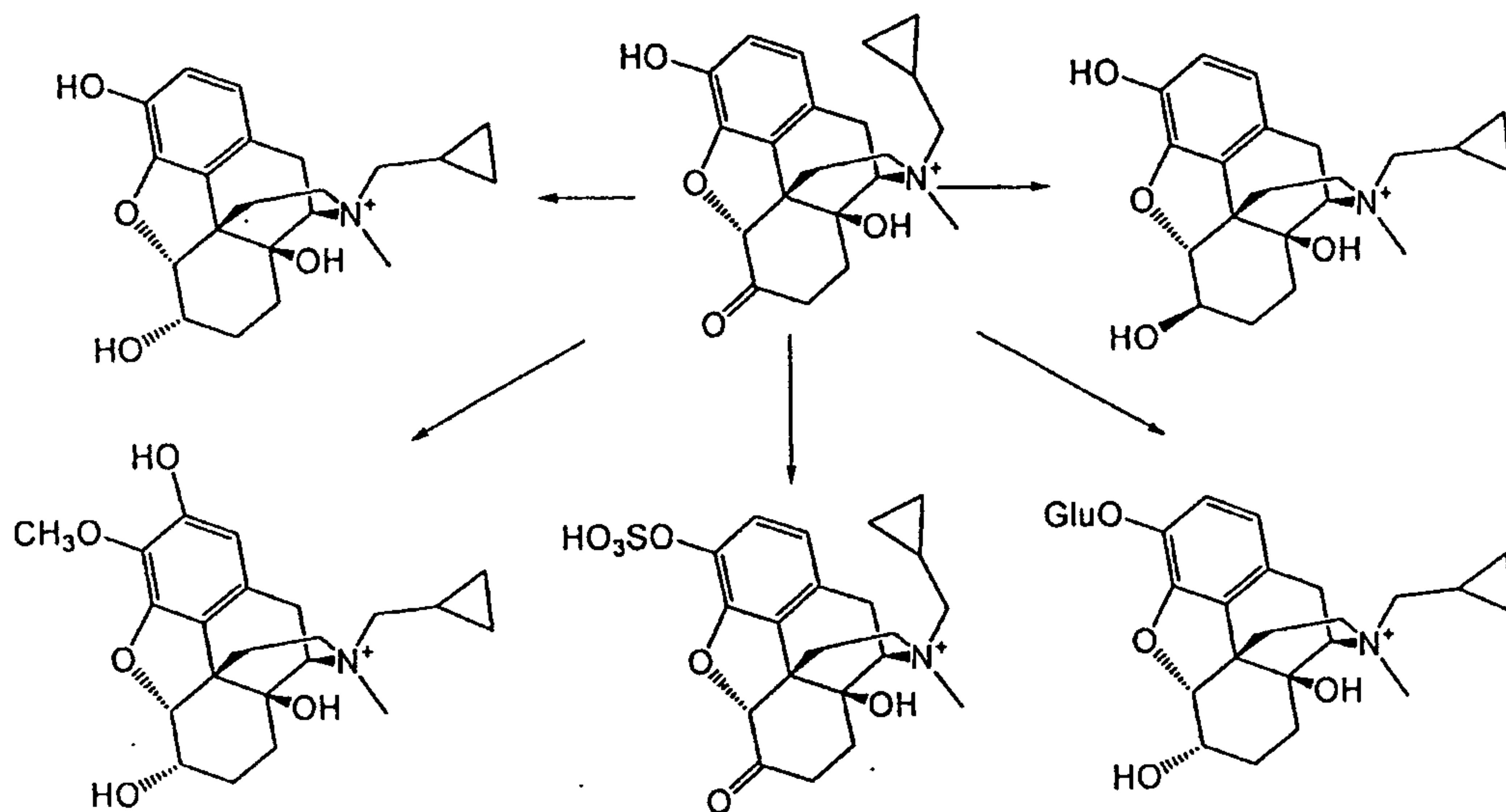
III-3

[0037] In other embodiments, the present invention provides a compound as depicted in Scheme 1, below:

Scheme 1.

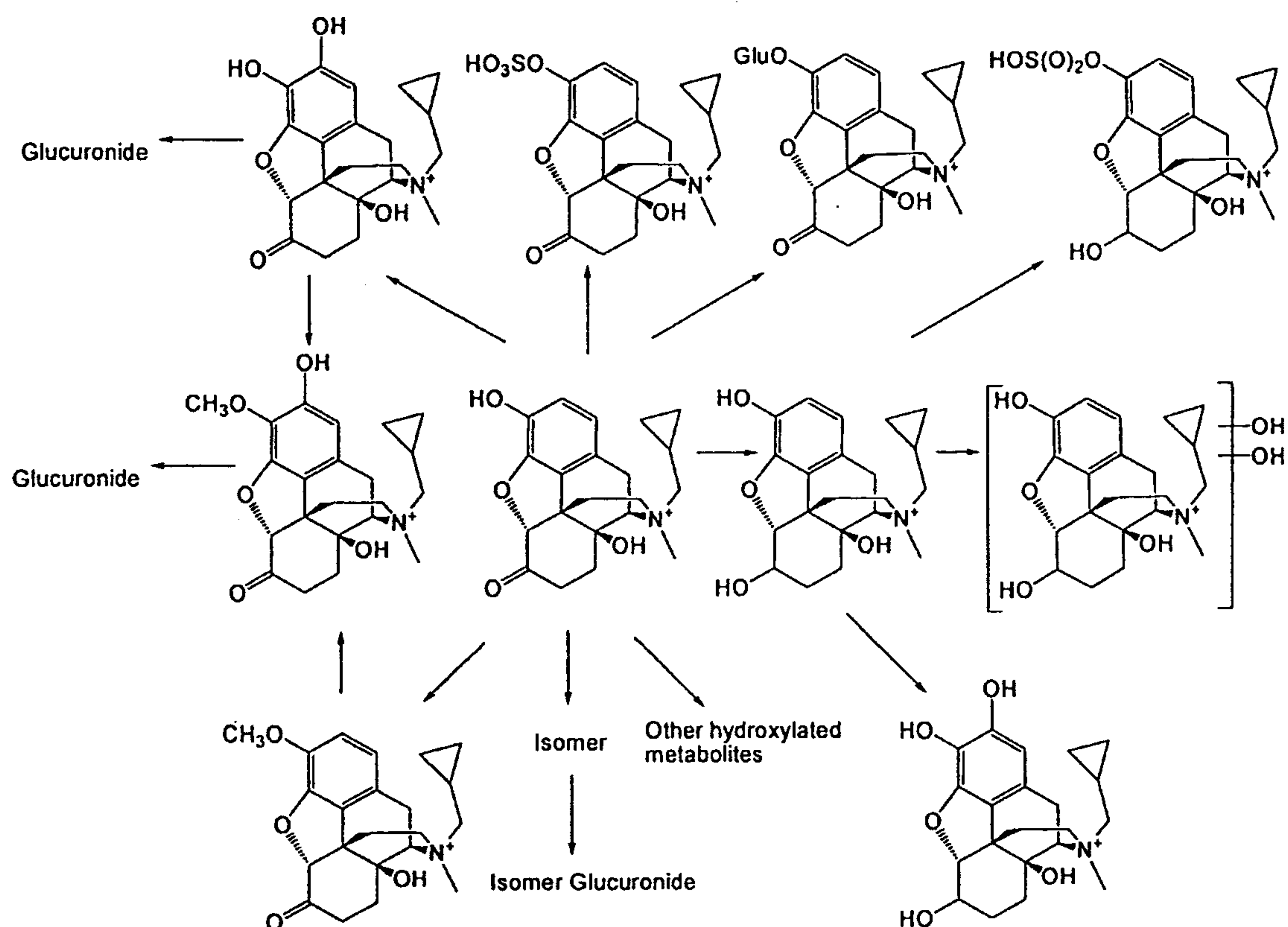


[0038] In certain embodiments, the present invention provides a compound as depicted in Scheme 2, below:

Scheme 2.

[0039] In some embodiments, the present invention provides a compound as depicted in Scheme 3, below:

Scheme 3.



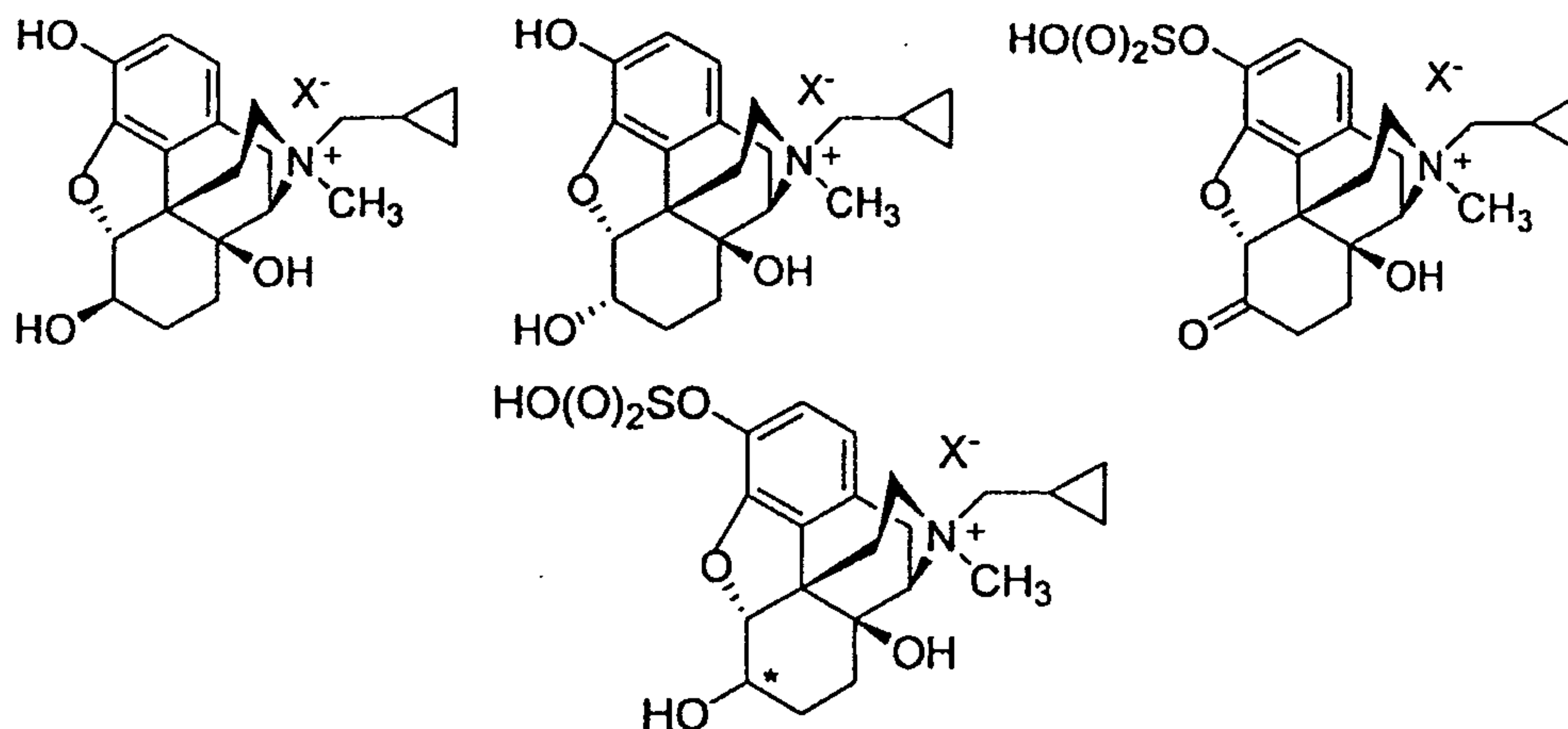
[0040] As depicted in Scheme 3, above, one metabolite of MNTX is its isomer. As used herein, the term "isomer" refers to a compound having the same mass as MNTX as determined by mass spectral analysis but, however, has a different retention time on HPLC.

[0041] To the extent that the foregoing Schemes 1, 2, and 3 would predict metabolites of compound 1, one of ordinary skill in the art would understand that a glucuronyl (-Glu), glutathione (-GSH or -HSG), or methyl group, depicted at a bracket would be attached to the bracketed structure at a hydroxyl moiety. It will be appreciated that a hydroxyl moiety includes both a depicted hydroxyl moiety and the hydroxyl moiety associated with an enol (formed by a ketone, if present).

[0042] In still other embodiments, the present invention provides a compound as depicted in any of Tables 3 through 7 below, wherein each X⁻ group is independently a suitable anion. In certain embodiments, each X⁻ is the anion of a suitable Brønsted acid. Exemplary Brønsted acids include hydrogen halides, carboxylic acids, sulfonic acids, sulfuric acid, and phosphoric acid. In certain embodiments, each X⁻ is chloride, bromide, iodide, fluoride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, carbonate, phosphate, malate,

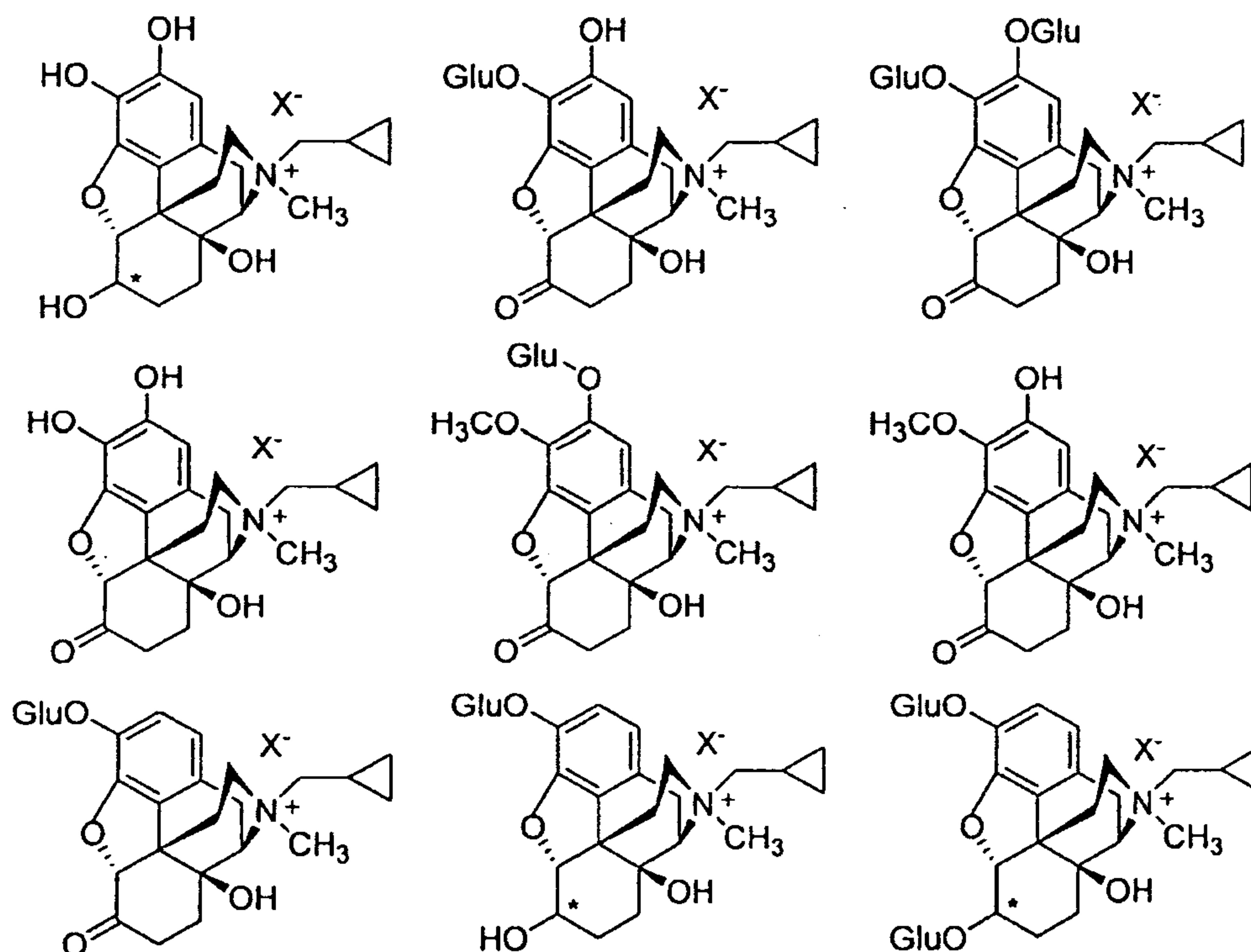
maleate, fumarate sulfonate, methylsulfonate, formate, carboxylate, sulfate, methylsulfate or succinate. According to one aspect, each X^- , as depicted in any of Tables 3 through 7 below, is bromide.

Table 3.



wherein each * denotes a stereo-center. In each case the substituent can either be in the (R) or (S) configuration.

Table 4.



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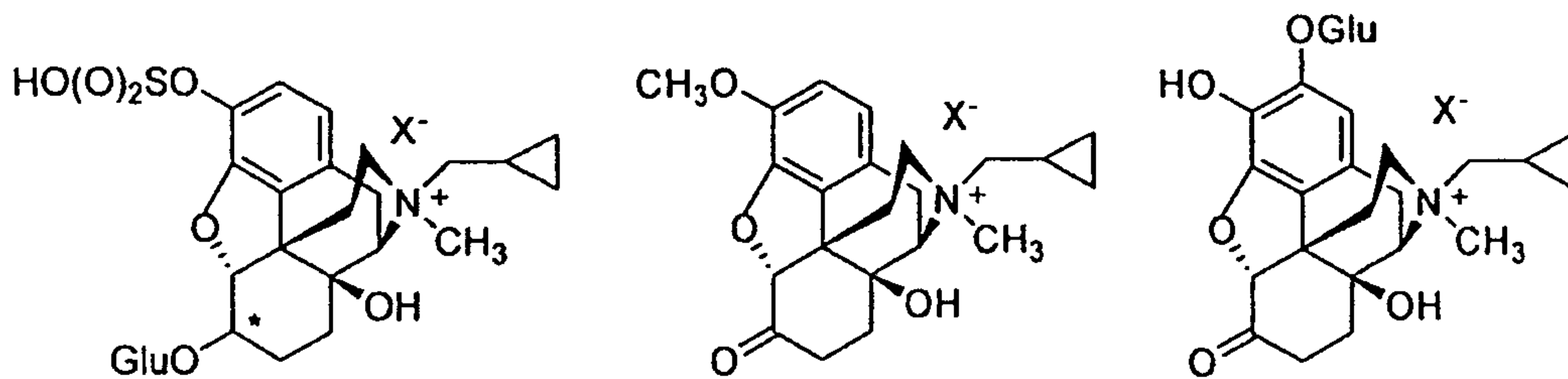


Table 5.

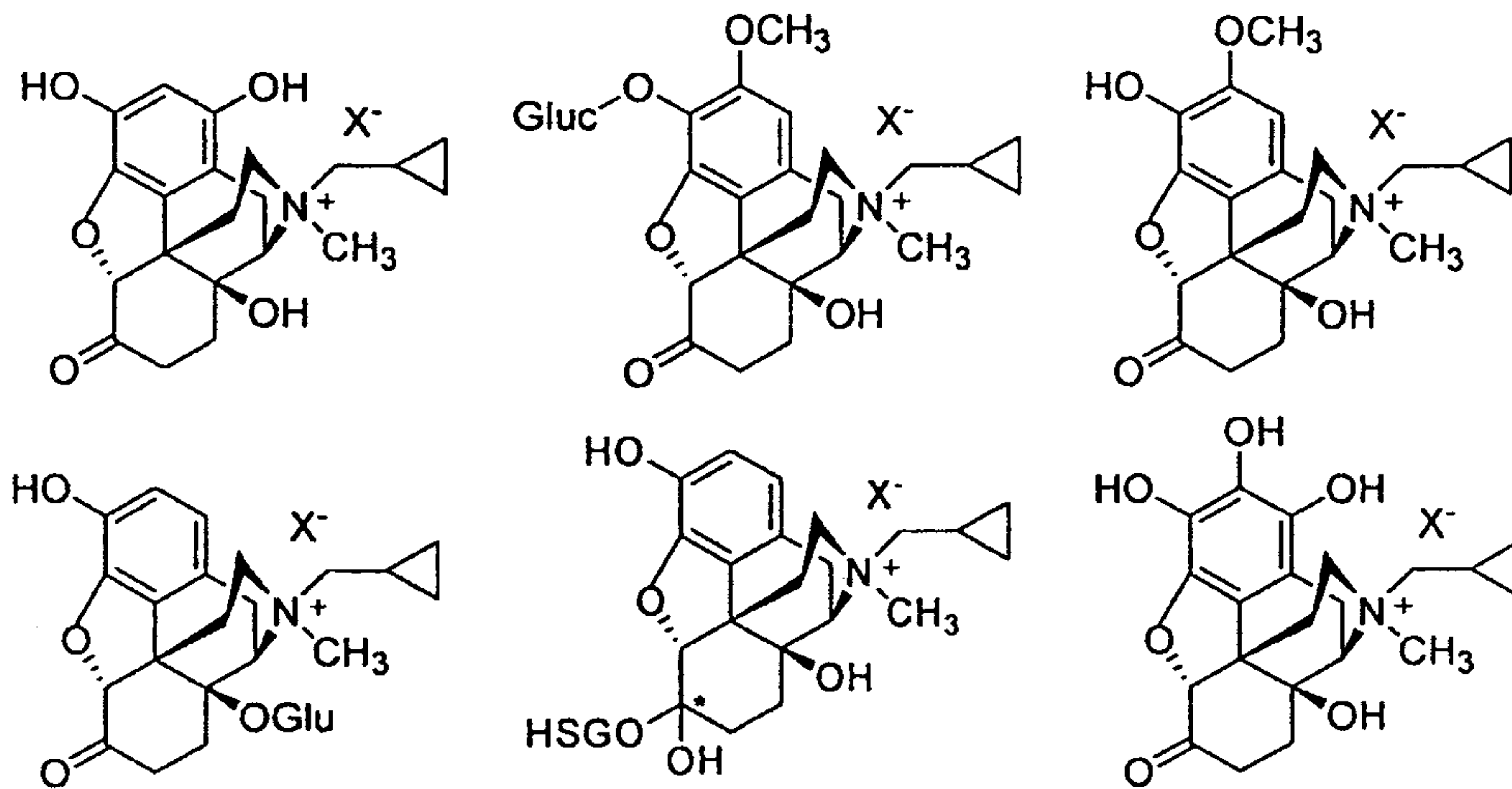
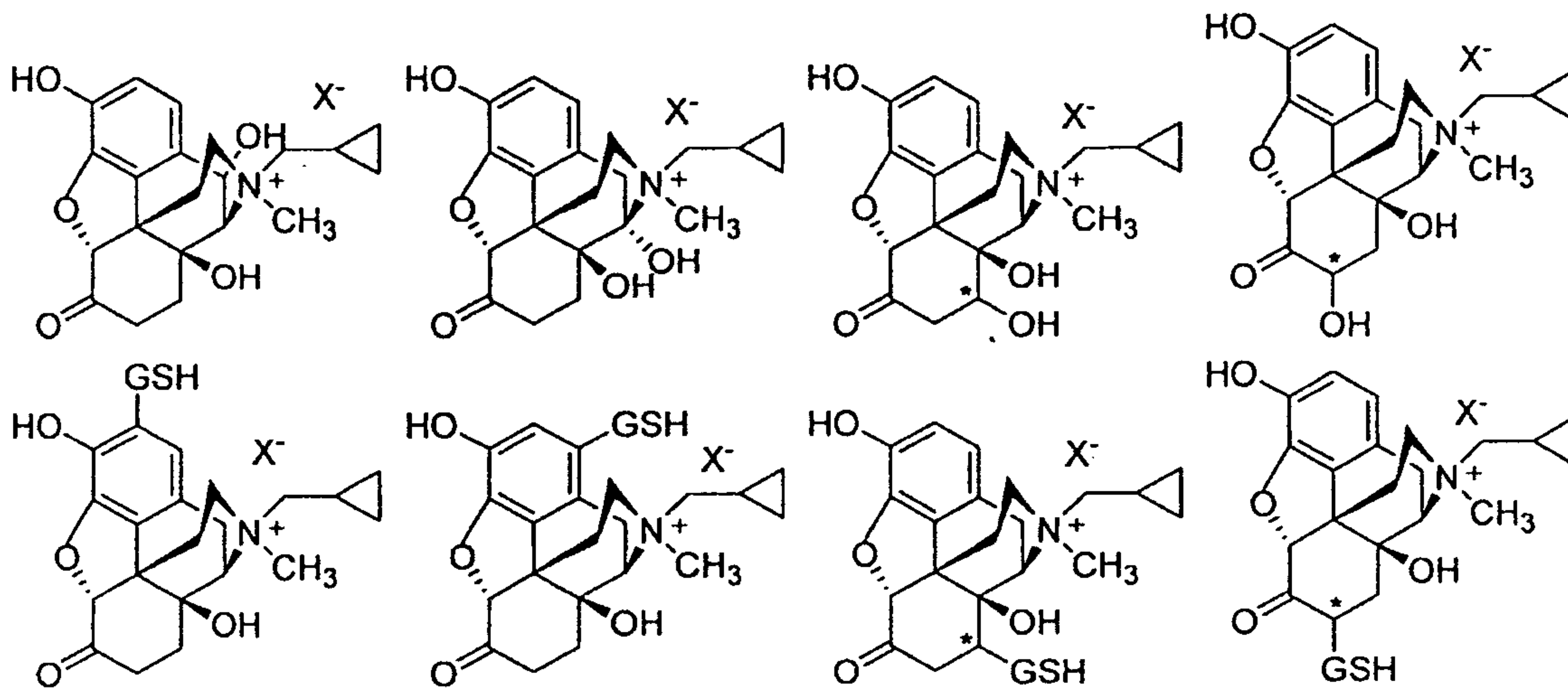
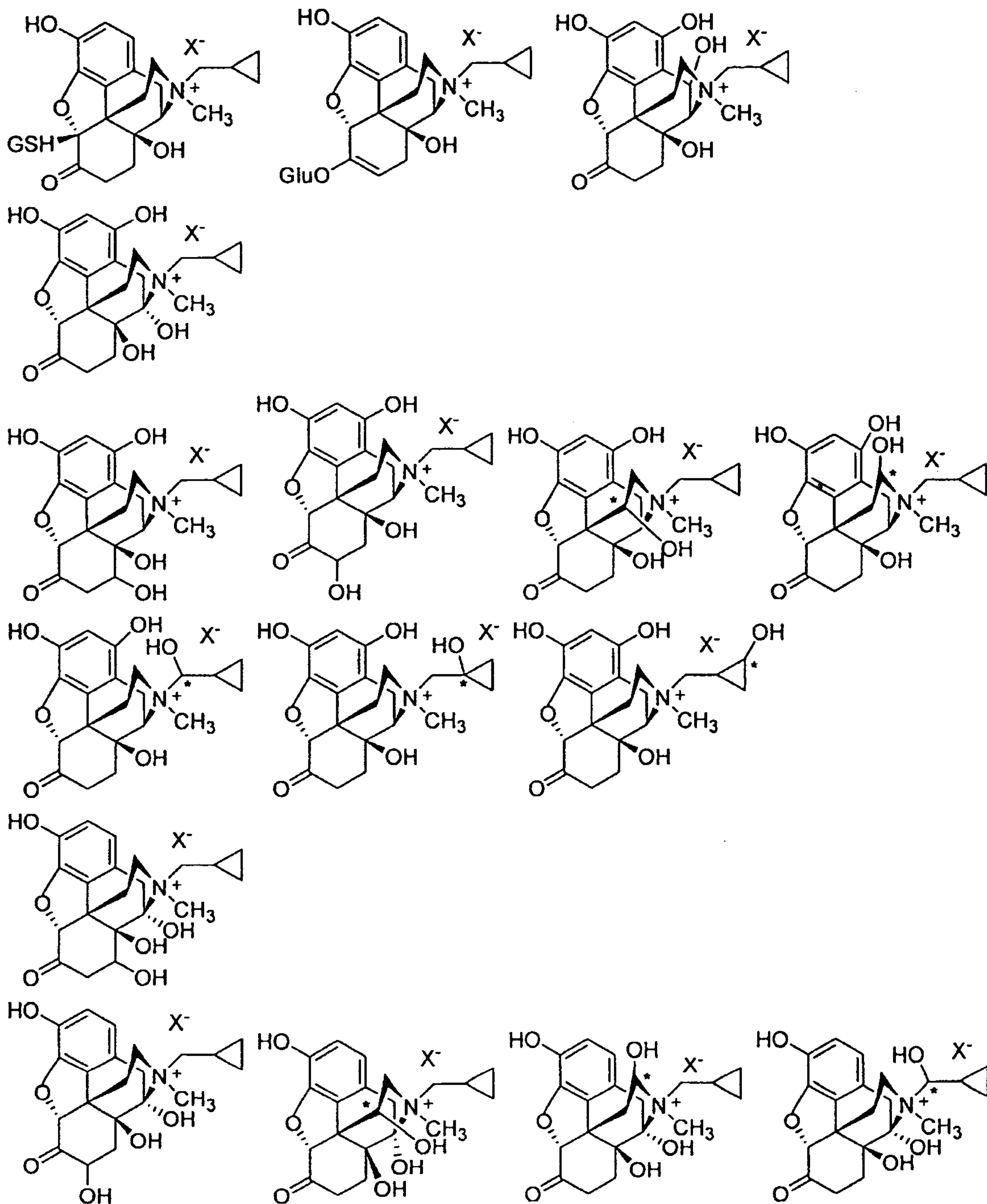


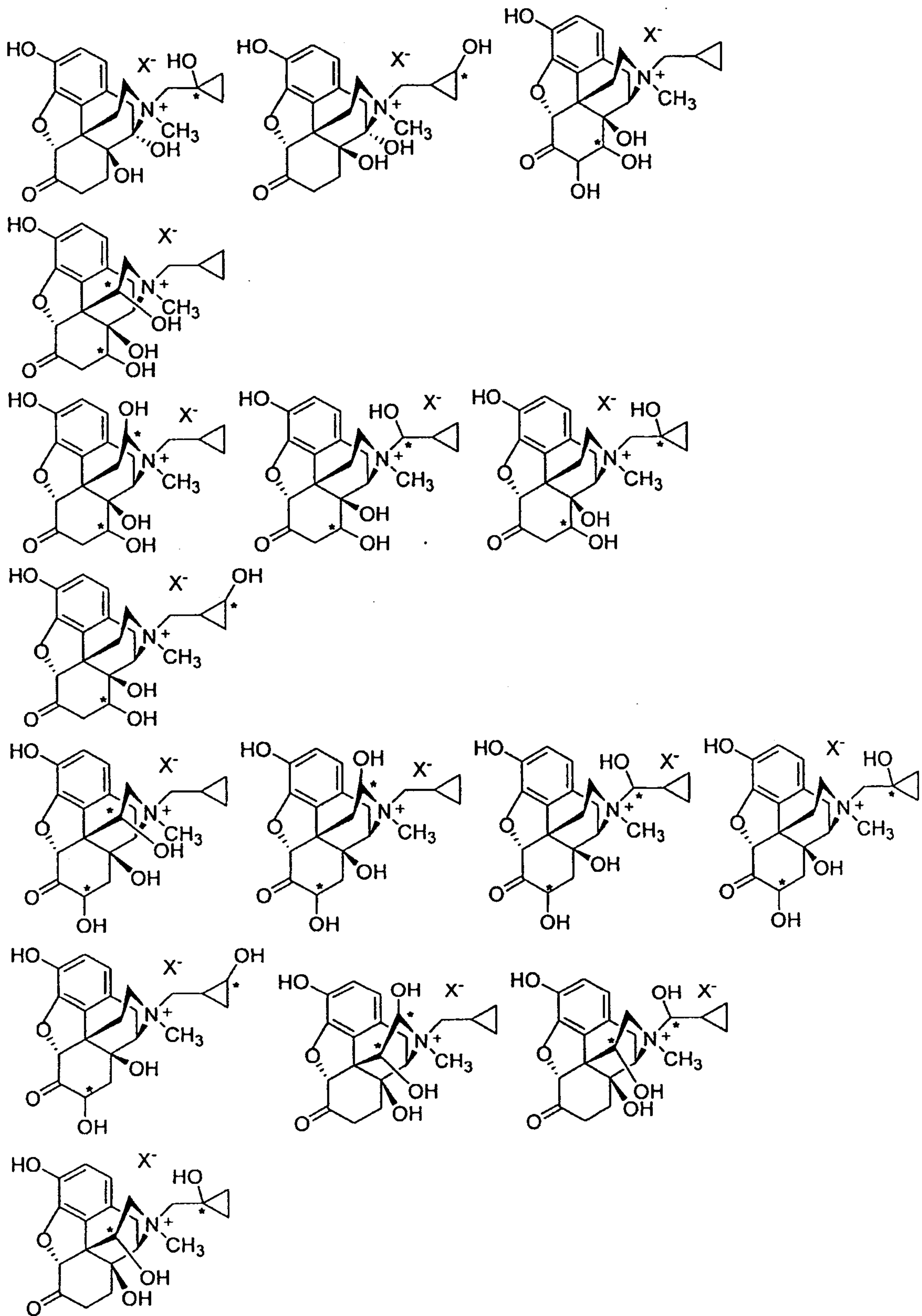
Table 6.



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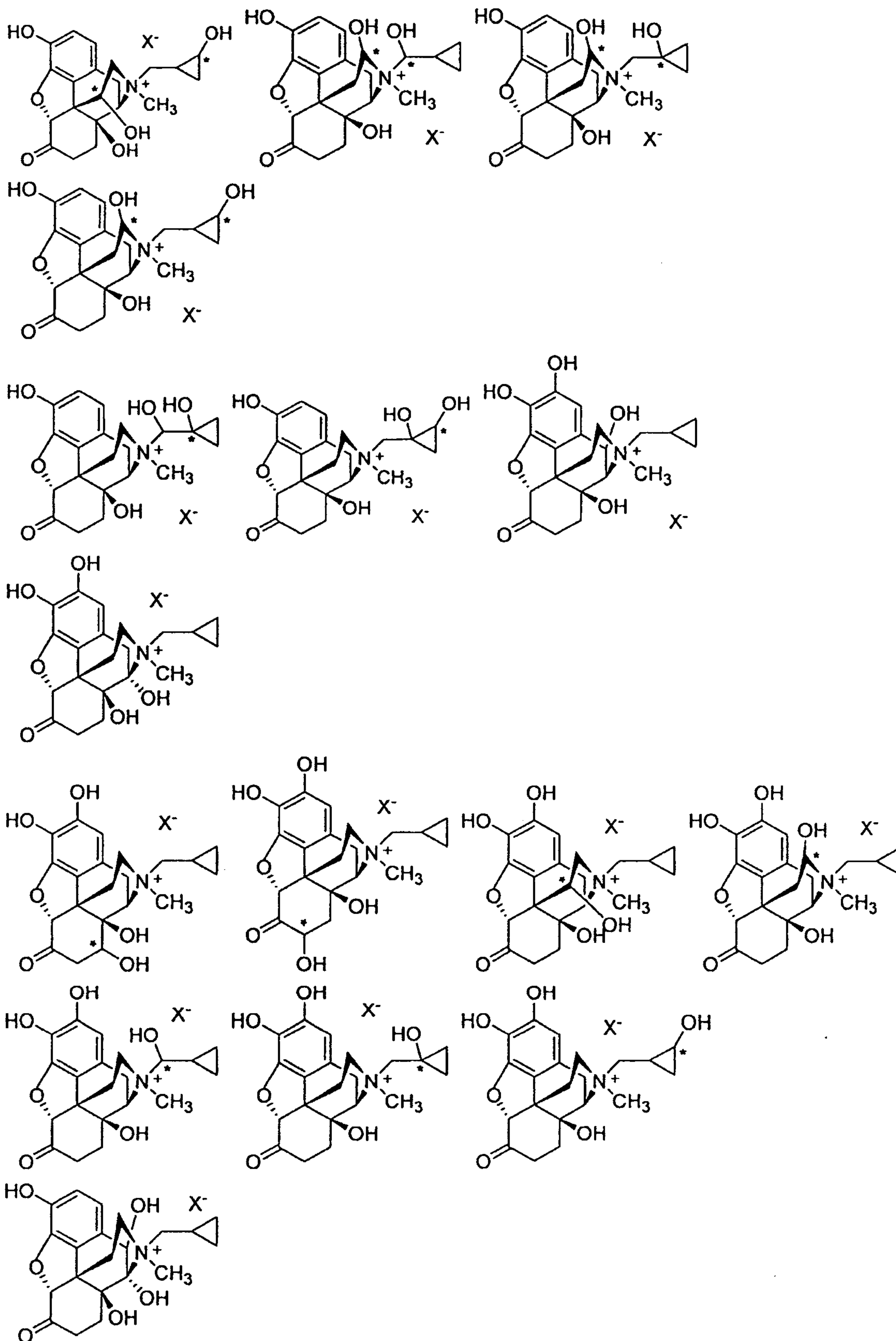
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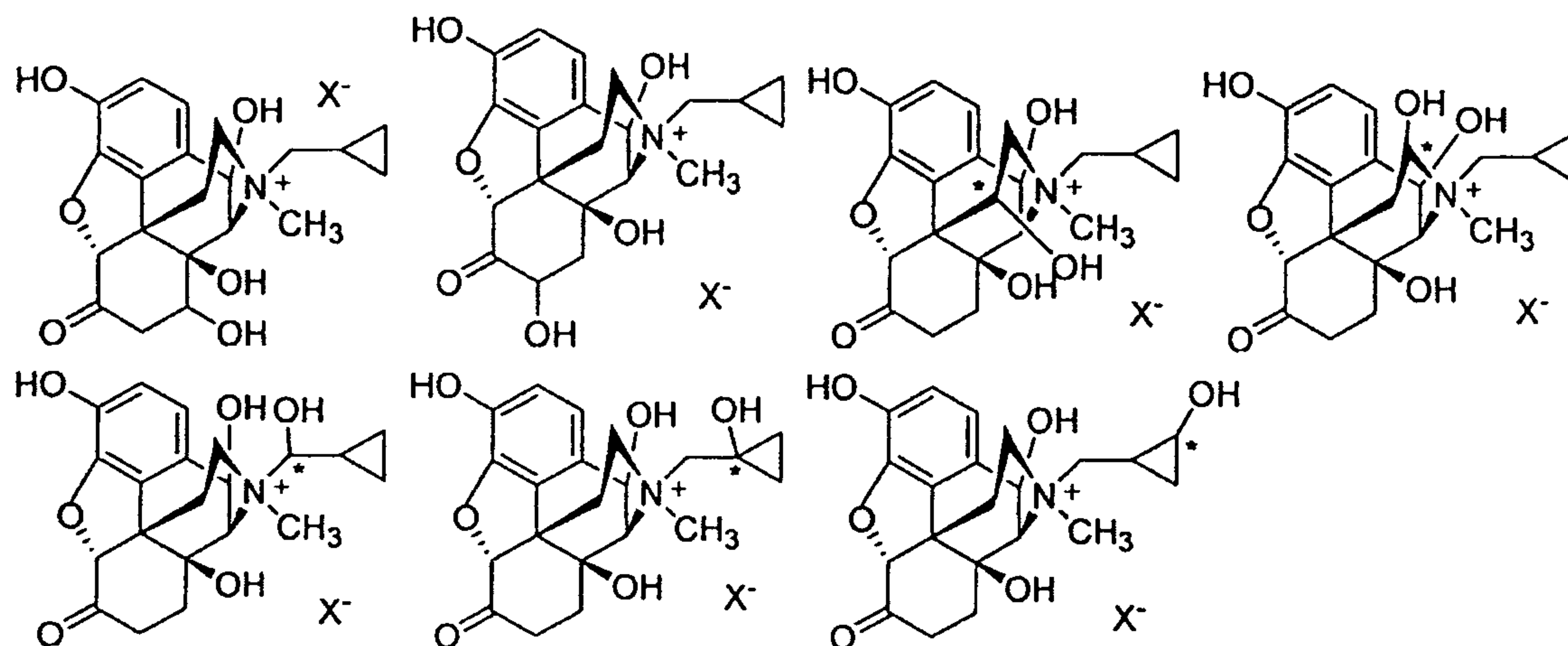
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[0043] It is readily apparent that certain compounds of the present invention contain both a quaternized nitrogen group and an acidic moiety (e.g. a phenolic hydroxyl, a sulfate, or a glucuronyl carboxylate). One of ordinary skill in the art will recognize that the acidic group of such compounds can form a salt with the quaternized nitrogen of such compounds. Such salts can form between two molecules *via* an intermolecular interaction or can form between those groups of the same compound *via* an intramolecular interaction (e.g. compound I-3a set forth in the Examples, below). The present invention contemplates both such salt forms.

[0044] In some embodiments, certain compounds of the present invention are useful as prodrugs of peripheral μ opioid receptor antagonists, as defined herein. In certain embodiments, a prodrug of the present invention comprises a glucuronyl moiety. As used herein, the term "prodrug" refers to a derivative of a parent drug molecule that requires transformation within the body in order to release the active drug, and that has improved physical and/or delivery properties over the parent drug molecule. Prodrugs are designed to enhance pharmaceutically and/or pharmacokinetically based properties associated with the parent drug molecule. The advantage of a prodrug lies in its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent drug, or it enhances absorption from the digestive tract, or it may enhance drug stability for long-term storage. In recent years several types of bioreversible derivatives have been exploited for utilization in designing prodrugs. Using esters as a prodrug type for drugs containing carboxyl or hydroxyl function is known in the art as described, for example, in "The Organic Chemistry of Drug Design and Drug Interaction" Richard Silverman, published by Academic Press (1992).

3. *Uses, Formulation and Administration*

Pharmaceutically Acceptable Compositions

[0045] As discussed above, the present invention provides new forms of Compound I, which is useful as a peripheral mu opioid receptor antagonist and shows utility in clinically relevant models for treating opioid-induced side effects. According to another aspect of the present invention, pharmaceutically acceptable compositions are provided, comprising a compound of formula I, II, or III, or other compound as described herein, and optionally comprising a pharmaceutically acceptable carrier, adjuvant, or vehicle. In certain embodiments of the present invention, such pharmaceutically acceptable compositions optionally further comprise one or more additional therapeutic agents.

[0046] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with a compound of formula I, II, or III, or other compound of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut

oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0047] The term "formulation" refers to a preparation that includes a compound of formula I, II, or III, or other compound described herein, in combination with one or more excipients for administration to a subject. In general, particular pharmaceutical additives are selected with the aim of enabling an optimal release, distribution and development of activity of a compound of formula I, II, or III, or other compound described herein, for the respective applications.

[0048] A compound of formula I, II, or III, or other compound described herein, according to the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a disorder associated with modulation of peripheral μ opioid receptors. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. It will be understood, however, that the total daily usage of a compound of formula I, II, or III, or other compound described herein, will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[0049] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, nasally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or

drops), buccally, or the like, depending on the severity of the infection being treated. In certain embodiments, a compound of formula I, II, or III, or other compound described herein, may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0050] Liquid dosage forms for oral or nasal administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, aerosols, gels, syrups, and elixirs. In addition to a compound of formula I, II, or III, or other compound described herein, liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a pharmaceutically acceptable propellant. The aerosol dosage forms can also take the form of a pump-atomiser.

[0051] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including

synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0052] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0053] In order to prolong the effect of a compound of formula I, II, or III, or other compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0054] Typical parenteral compositions consist of a solution or suspension of the compound in a sterile aqueous carrier or non-aqueous or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

[0055] Compositions for rectal or vaginal administration are conveniently in the form of suppositories, pessaries, vaginal tabs, foams, or enemas. Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing a compound of formula I, II, or III, or other compound described herein, with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0056] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, a compound of formula I, II, or III, or other compound described herein, is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium salts, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0057] Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

[0058] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0059] A compound of formula I, II, or III, or other compound described herein, can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms a compound of

formula I, II, or III may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0060] Compositions for oral administration may be designed to protect the active ingredient against degradation as it passes through the alimentary tract, for example by an outer coating of the formulation on a tablet or capsule.

[0061] In another embodiment, a compound of formula I, II, or III, or other compound described herein, is provided in an extended (or "delayed" or "sustained") release composition. This delayed release composition comprises a compound of formula I, II, or III, or other compound described herein, in combination with a delayed release component. This composition allows targeted release of a compound of formula I, II, or III, or other compound described herein, into the lower gastrointestinal tract; for example into the small intestine, the large intestine, the colon and/or the rectum. In certain embodiments, the delayed release composition comprising a compound of formula I, II, or III, or other compound described herein, further comprises an enteric or pH dependent coating such as cellulose acetate phthalates and other phthalates (e.g. polyvinyl acetate phthalate, methacrylates (Eudragits)). Alternatively, the delayed release composition provides controlled release to the small intestine and/or colon by the provision of pH sensitive methacrylate coatings, pH sensitive polymeric microspheres, or polymers which undergo degradation by hydrolysis. The delayed release composition can be formulated with hydrophobic or gelling excipients or coatings. Colonic delivery can further be provided by coatings which are digested by bacterial enzymes such as amylose or pectin, by pH dependent polymers, by hydrogel plugs swelling with time (Pulsincap), by time dependent hydrogel coatings and/or by acrylic acid linked to azoaromatic bonds coatings.

[0062] In certain embodiments, the delayed release compositions of the present invention comprise hypromellose, microcrystalline cellulose, and a lubricant. The mixture of a compound of formula I, II, or III, or other compound described herein, hypromellose and

microcrystalline cellulose may be formulated into a tablet or capsule for oral administration. In certain embodiments, the mixture is granulated and pressed into tablets.

[0063] In other embodiments, the delayed release compositions of the present invention are provided in a multiparticulate formulation. A mixture of a compound of formula I, II, or III, or other compound described herein, and a suitable polymer is granulated to form pellets which are coated. In certain embodiments, the pellets are seal coated with a non-functional coating. In other embodiments, the pellets are first seal coated with a non-functional coating and then coated with a functional coating.

[0064] As used herein the term "non-functional coating" is a coating that does not effect the release rate of the drug. Examples of a non-functional coat include hydroxypropyl cellulose, hypromellose or polyvinyl alcohol. In certain embodiments, the non-functional coating is Opadry[®] Clear, which contains, hydroxypropyl methylcellulose and polyethylene glycol.

[0065] As used herein, the term "functional coating" is a coating that affects the release rate of the drug from the dosage form. Examples of a functional coating include ethylcellulose and polymethacrylate derivatives (Eudragits).

[0066] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0067] The compositions may contain from 0.1% to 99% (w/w) preferably from 0.1-60% (w/w), more preferably 0.2-20% by weight and most preferably 0.25 to 12% (w/w) of a compound of formula I, II, or III, or other compound described herein, depending on the method of administration.

Combination Products and Combined Administration

[0068] In certain embodiments, inventive compositions, and formulations thereof, may be administered alone to treat one or more disorders as described herein, or alternatively may be administered in combination with (whether simultaneously or sequentially) one or more other active agents useful to treat one or more disorders as described herein. Thus, an inventive composition, or formulation thereof, can be administered concurrently with, prior to, or subsequent to, one or more active agents.

[0069] In certain embodiments, inventive compositions include one or more other active agents in addition to a compound of formula I, II, or III, or other compound described herein, that is not a compound of formula I, II, or III, or other compound described herein. In certain embodiments, the present invention provides a formulation that delivers a compound of formula I, II, or III, or other compound described herein, and at least one additional active agent.

[0070] In some embodiments, inventive formulations comprise both an opioid and a compound of formula I, II, or III, or other compound described herein. Such combination products, containing both an opioid and a compound of formula I, II, or III, or other compound described herein, would allow simultaneous relief of pain and minimization of opioid-associated side effects (e.g., gastrointestinal effects (e.g., delayed gastric emptying, altered GI tract motility), etc.).

[0071] Opioids useful in treatment of analgesia are known in the art. For example, opioid compounds include, but are not limited to, alfentanil, anileridine, asimadoline, bremazocine, buprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, ethylmorphine, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, nicomorphine, opium, oxycodone, oxymorphone, papaveretum, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol. In some embodiments the opioid is at least one opioid selected from alfentanil, buprenorphine, butorphanol, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine (pethidine), methadone, morphine, nalbuphine, nicomorphine, oxycodone, oxymorphone, papaveretum, pentazocine, propiram, propoxyphene, sufentanil and/or tramadol. In certain embodiments of the present invention, the opioid is selected from morphine, codeine, oxycodone, hydrocodone, dihydrocodeine, propoxyphene, fentanyl,

tramadol, and mixtures thereof. In a particular embodiment, the opioid is loperamide. In other embodiments, the opioid is a mixed agonist such as butorphanol. In some embodiments, the subjects are administered more than one opioid, for example, morphine and heroin or methadone and heroin.

[0072] The amount of additional active agent(s) present in combination compositions of this invention will typically be no more than the amount that would normally be administered in a composition comprising that active agent as the only therapeutic agent. In certain embodiments of the present invention, the amount of additional active agent will range from about 50% to 100% of the amount normally present in a composition comprising that compound as the only therapeutic agent.

[0073] In certain embodiments, inventive formulations may also be used in conjunction with and/or in combination with conventional therapies for gastrointestinal dysfunction to aid in the amelioration of constipation and bowel dysfunction. For example, conventional therapies include, but may not be limited to functional stimulation of the intestinal tract, stool softening agents, laxatives (e.g., diphelymethane laxatives, cathartic laxatives, osmotic laxatives, saline laxatives, etc), bulk forming agents and laxatives, lubricants, intravenous hydration, and nasogastric decompression.

Uses and Kits of Inventive Formulations

[0074] As discussed above, the present invention provides a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, useful in antagonizing undesirable side effects of opioid analgesic therapy (e.g., gastrointestinal effects (e.g., delayed gastric emptying, altered GI tract motility), etc.). Furthermore, a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, may be used as to treat subjects having disease states that are ameliorated by binding μ opioid receptors, or in any treatment wherein temporary suppression of the μ opioid receptor system is desired (e.g., ileus, etc.). In certain embodiments of the present invention, methods of use of formulations are in human subjects.

[0075] Accordingly, administration of a compound of formula I, II, or III, or other compound described herein, or a pharmaceutically acceptable composition or formulation thereof, may be advantageous for treatment, prevention, amelioration, delay or reduction of side effects of opioid use, such as, for example, gastrointestinal dysfunction (e.g., inhibition

of intestinal motility, constipation, GI sphincter constriction, nausea, emesis (vomiting), biliary spasm, opioid bowel dysfunction, colic, dysphoria, pruritis, urinary retention, depression of respiration, papillary constriction, cardiovascular effects, chest wall rigidity and cough suppression, depression of stress response, and immune suppression associated with use of narcotic analgesia, etc, or combinations thereof. Use of a compound of formula I, II, or III, or other compound described herein, or a pharmaceutically acceptable composition or formulation thereof, may thus be beneficial from a quality of life standpoint for subjects receiving opioids, as well as to reduce complications arising from chronic constipation, such as hemorrhoids, appetite suppression, mucosal breakdown, sepsis, colon cancer risk, and myocardial infarction.

[0076] In some embodiments, a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, are useful for administration to a subject receiving acute opioid administration. In some embodiments, provided formulations are useful for administration to patients suffering from post-operative gastrointestinal dysfunction.

[0077] In other embodiments, a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, are also useful for administration to subjects receiving chronic opioid administration (e.g., terminally ill patients receiving opioid therapy such as an AIDS patient, a cancer patient, a cardiovascular patient; subjects receiving chronic opioid therapy for pain management; subjects receiving opioid therapy for maintenance of opioid withdrawal). In some embodiments, the subject is a subject using opioid for chronic pain management. In some embodiments, the subject is a terminally ill patient. In other embodiments the subject is a person receiving opioid withdrawal maintenance therapy.

[0078] Alternative or additional uses for a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, described herein may be to treat, reduce, inhibit, or prevent effects of opioid use including, e.g., aberrant migration or proliferation of endothelial cells (e.g., vascular endothelial cells), increased angiogenesis, and increase in lethal factor production from opportunistic infectious agents (e.g., *Pseudomonas aeruginosa*). Additional advantageous uses of a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, include treatment of opioid-induced immune suppression, inhibition of angiogenesis, inhibition of vascular

proliferation, treatment of pain, treatment of inflammatory conditions such as inflammatory bowel syndrome, treatment of infectious diseases and diseases of the musculoskeletal system such as osteoporosis, arthritis, osteitis, periostitis, myopathies, and treatment of autoimmune diseases.

[0079] In certain embodiments, a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, of the invention may be used in methods for preventing, inhibiting, reducing, delaying, diminishing or treating gastrointestinal dysfunction, including, but not limited to, irritable bowel syndrome, opioid-induced bowel dysfunction, colitis, post-operative or postpartum ileus, nausea and/or vomiting, decreased gastric motility and emptying, inhibition of the stomach, and small and/or large intestinal propulsion, increased amplitude of non-propulsive segmental contractions, constriction of sphincter of Oddi, increased anal sphincter tone, impaired reflex relaxation with rectal distention, diminished gastric, biliary, pancreatic or intestinal secretions, increased absorption of water from bowel contents, gastro-esophageal reflux, gastroparesis, cramping, bloating, abdominal or epigastric pain and discomfort, constipation, idiopathic constipation, post-operative gastrointestinal dysfunction following abdominal surgery (e.g., colectomy (e.g., right hemicolectomy, left hemicolectomy, transverse hemicolectomy, colectomy takedown, low anterior resection)), and delayed absorption of orally administered medications or nutritive substances.

[0080] Provided forms of a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, are also useful in treatment of conditions including cancers involving angiogenesis, immune suppression, sickle cell anemia, vascular wounds, and retinopathy, treatment of inflammation associated disorders (e.g., irritable bowel syndrome), immune suppression, chronic inflammation.

[0081] In still further embodiments, veterinary applications (e.g., treatment of domestic animals, e.g. horse, dogs, cats, etc.) of use of a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, are provided. Thus, use of provided formulations in veterinary applications analogous to those discussed above for human subjects is contemplated. For example, inhibition of equine gastrointestinal motility, such as colic and constipation, may be fatal to a horse. Resulting pain suffered by the horse with colic can result in a death-inducing shock, while a long-term case of constipation may also cause a horse's death. Treatment of

equines with peripheral opioid receptor antagonists has been described, e.g., in U.S. Patent Publication No. 20050124657 published January 20, 2005.

[0082] It will also be appreciated that a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, can be employed in combination therapies, that is, a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. Particular combination therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that therapies employed may achieve a desired effect for the same disorder (for example, a formulation may be administered concurrently with another compound used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic compounds which are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0083] In other embodiments, a compound of formula I, II, or III, or other compound described herein, and pharmaceutically acceptable compositions and formulations thereof, and unit dose forms are useful in preparation of medicaments, including, but not limited to medicaments useful in the treatment of side effects of opioid use (e.g., gastrointestinal side effects (e.g., inhibition of intestinal motility, GI sphincter constriction, constipation) nausea, emesis, (vomiting), dysphoria, pruritis, etc.) or a combination thereof. Compounds of the present invention, and pharmaceutically acceptable compositions and formulations thereof, are useful for preparations of medicaments, useful in treatment of patients receiving acute opioid therapy (e.g., patients suffering from post-operative gastrointestinal dysfunction receiving acute opioid administration) or subjects using opioids chronically (e.g., terminally ill patients receiving opioid therapy such as an AIDS patient, a cancer patient, a cardiovascular patient; subjects receiving chronic opioid therapy for pain management; or subjects receiving opioid therapy for maintenance of opioid withdrawal). Still further, preparation of medicaments useful in the treatment of pain, treatment of inflammatory conditions such as inflammatory bowel syndrome, treatment of infectious diseases, treatment of diseases of the musculoskeletal system such as osteoporosis, arthritis, osteitis, periostitis, myopathies, treatment of autoimmune diseases and immune suppression, therapy of post-

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operative gastrointestinal dysfunction following abdominal surgery (e.g., colectomy (e.g., right hemicolectomy, left hemicolectomy, transverse hemicolectomy, colectomy takedown, low anterior resection), idiopathic constipation, and ileus (e.g., post-operative ileus, post-partum ileus), and treatment of disorders such as cancers involving angiogenesis, chronic inflammation and/or chronic pain, sickle cell anemia, vascular wounds, and retinopathy.

[0084] Still further encompassed by the invention are pharmaceutical packs and/or kits comprising a compound of formula I, II, or III, or other compound described herein, or a pharmaceutically acceptable composition or formulation thereof, and a container (e.g., a foil or plastic package, or other suitable container). Optionally instructions for use are additionally provided in such kits.

[0085] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[0086] All features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*.

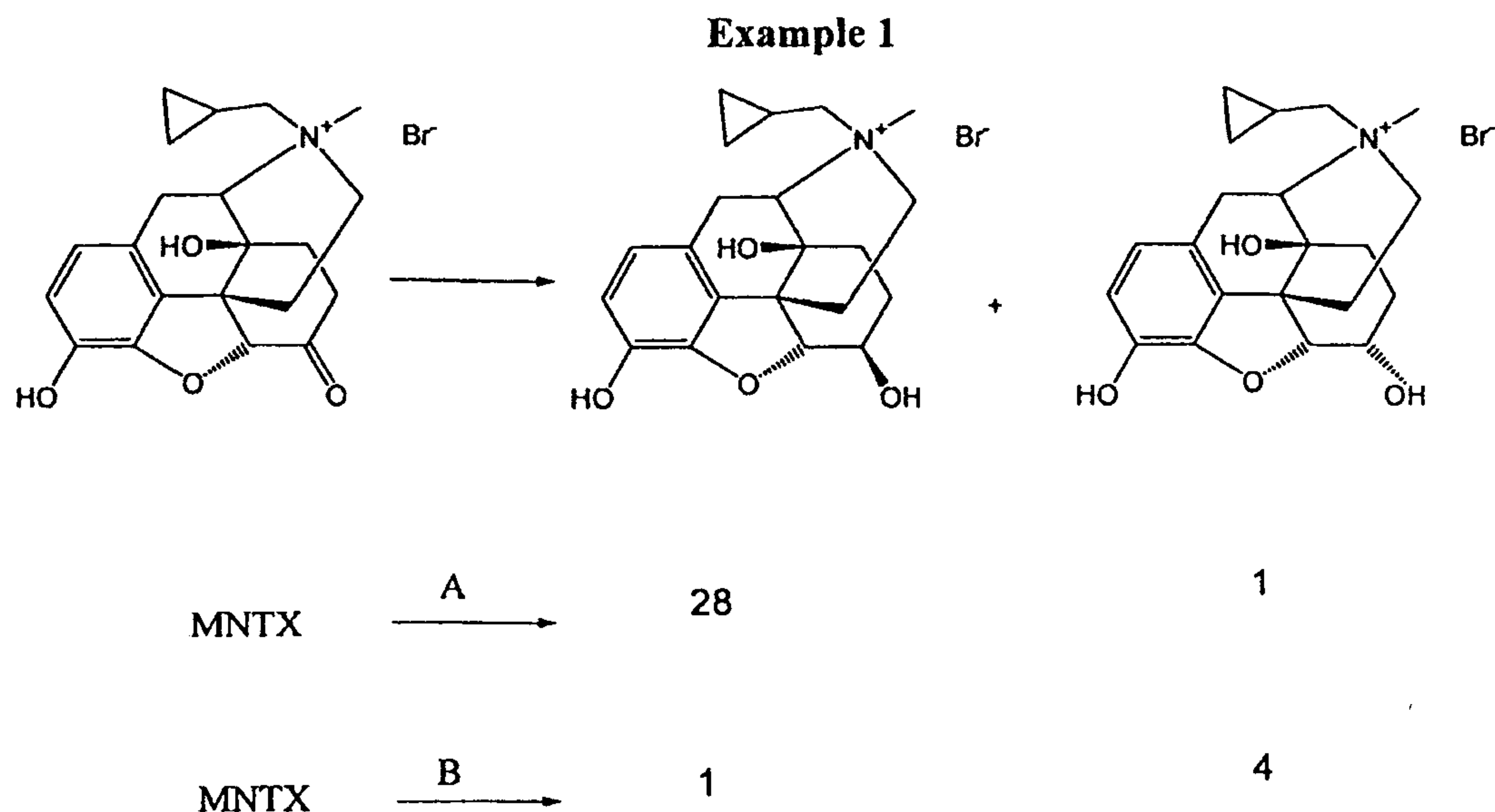
EXEMPLIFICATION

General Procedures

[0087] Compound 1 is prepared according to the methods described in detail in International Patent Application publication number WO2006/127899.

WO 2008/121348

PCT/US2008/004109



A = formamidinesulfonic acid in water with an excess of sodium hydroxide

B = sodium borohydride in DMF

General Methods

[0088] Compound 1 ("MNTX") was reduced using formamidinesulfonic acid in hot aqueous alkali in a method substantially similar to that described in Chatterjie, N., *et al.* J. Med. Chem. 18, 1975,490-492. The beta- and alpha-alcohols were formed in a 28:1 ratio. While a large amount of solid formed upon treatment of the cooled reaction mixture with hydrobromic acid and concentrating it, a second crop of higher purity provided the β -alcohol (I-2).

[0089] Sodium borohydride reduction of MNTX in aqueous alkali yielded a mixture of 1 and 2, with the former predominating. Reduction in a suitable solvent (e.g., dimethylformamide or methanol) resulted in formation of the above alcohols in a 1:4 ratio. Pure alpha alcohol (I-1) was obtained by preparative reverse phase chromatography. A solid sample of 99% purity (HPLC) was obtained as the iodide salt.

HPLC conditions:

Hewlett Packard 1100 series.

Column: Alltech Alltima column (C18, 5 μ , 250 X 4.6 mm)

Flow rate: 1.0 mL/min.

Column temperature: 40 °C.

Detector: diode array detector monitoring @ 215, 240, 270, and 280 nm.

Elution: isocratic. Various mixtures of water, buffer*, and methanol.

* 700 ml of water, 300 mL methanol, 3 mL triethylamine and sufficient phosphoric acid to give a pH of 3.4.

or alternatively:

Column: Phenomenex Intersil ODS 3 column (C18, 5 μ , 150 X 4.6 mm)

Flow rate: 1 mL/min.

Column temperature: 50 °C.

Detector: diode array detector monitoring @ 280nm.

Elution: gradient.

<i>Time min</i>	<i>Methanol</i>	<i>Water</i>	<i>Mix^a</i>	<i>Curve</i>
0	0%	90%	10%	<i>initial</i>
25	15%	75%	10%	<i>linear</i>
30	45%	45%	10%	<i>linear</i>
30.1	0%	90%	10%	<i>hold</i>
35	0%	90%	10%	<i>end</i>

^a(49.5% water, 49.5% methanol, 1% trifluoroacetic acid)

[0090] (5 α ,6 α)-17-cyclopropylmethyl-17-methyl-4,5-epoxy-3,6,14-trihydroxy-morphinan bromide ("alpha" I-1):

Method A:

[0091] MNTX (8.72 g, 0.020 mol) was suspended in 200 mL of DMF in a flask equipped with magnetic stirring and an argon blanket. To this was added NaBH₄ (1.0 g, 0.026 mol) as a single pellet. After 15 min, HPLC analysis confirmed the absence of any starting ketone. The alcohols, beta and alpha, were present in a ratio of 18: 81.

[0092] The solvent was removed *in vacuo*, and the residue was taken up into water. Hydrobromic acid was used to bring the pH to a value of 2, and the mixture was scratched vigorously with a glass rod. No crystal formed. The mixture was again concentrated, and the syrupy residue was again dissolved in water. The pH was brought to 10.5 with NaOH, and the mixture was left standing overnight. A waxy residue was removed, and the mixture was adjusted to pH 5 with TFA and concentrated to ca. 20 mL. The crystals that deposited had the same composition as the supernatant.

[0093] A sample of the supernatant was fractionated on a Biotage 65i C18 column (65 X 150 mm). The mobile phase was an 80:20:0.1 mixture of water, methanol, and TFA. Fractions containing only the desired product were combined and concentrated. This solution was mixed with a large excess of NaI, and the product was recovered by extractions into 2:1 dichloromethane:isopropanol and 2:1 chloroform:isopropanol followed by concentration *in*

vacuo. After the residue was triturated with boiling isopropanol and with ethyl acetate, a solid with a purity of 99% was obtained.

Method B:

[0094] To a 3 L 3-necked flask fitted with a condenser, thermometer, and a glass stopper was added naltrexone methobromide (MNTX) (100 g, 0.23 mol) and glacial acetic acid (1.2 L). The flask was immersed in a room temperature water bath and the slurry magnetically stirred. To this slurry was added ca. 1 g pellets sodium borohydride (30g, 0.79 mol) one at a time waiting for complete dissolution of the previous pellet before adding the next. The addition of the first 20 g of sodium borohydride took 4 hr and after this time most of the MNTX had dissolved. Analysis of the reaction mixture by HPLC showed 71.6% α -OH, 27.9% MNTX, and 0.4% β -OH. The water bath was warmed by a temperature controlled hot plate to 41 °C and the remaining sodium borohydride was added over a period of 2 hr, as described above. The reaction mixture was stirred at 41 °C overnight after which time the reaction mixture was a thick white mass. The reaction was cooled to room temperature and charged with concentrated hydrobromic acid (88 mL, 0.79 mol). The solid slowly dissolved and the reaction mixture was filtered. The solvent was then removed on a rotary evaporator. The resulting residue was dissolved in 250 mL methanol and the methanol was removed on a rotary evaporator. This procedure was repeated 3 times to remove boric acid as methyl borate. The residue was then placed under high vacuum to give 200 g of white solid. The solid was dissolved in 400 mL of boiling water and hot filtered. Analysis of the filtrate by HPLC showed 99.2% α -OH, 0.4% MNTX, and 0.36% β -OH. The filtrate was seeded with 6- α naltrexol methobromide, allowed to cool to room temperature, and stored over the weekend. The crystals were harvested and air dried to give 80 g (80%) of white crystals. Analysis of the product by HPLC showed 99.78% product with 0.10% MNTX and 0.12% β -OH. The HPLC method utilized for this analysis is set forth below:

Hewlett Packard 1100 series.

Column: Phenomenex Synergi hydro RP column (C18, 5 μ , 150 X 4.6 mm)

Flow rate: 1.5 mL/min.

Column temperature: 50 °C.

Detector: diode array detector monitoring @ 220 and 280nm.

Elution: gradient.

<i>Time min</i>	<i>Methanol</i>	<i>Water</i>	<i>Mix^a</i>	<i>Curve</i>
0	0%	90%	10%	<i>initial</i>
15	30%	60%	10%	<i>linear</i>

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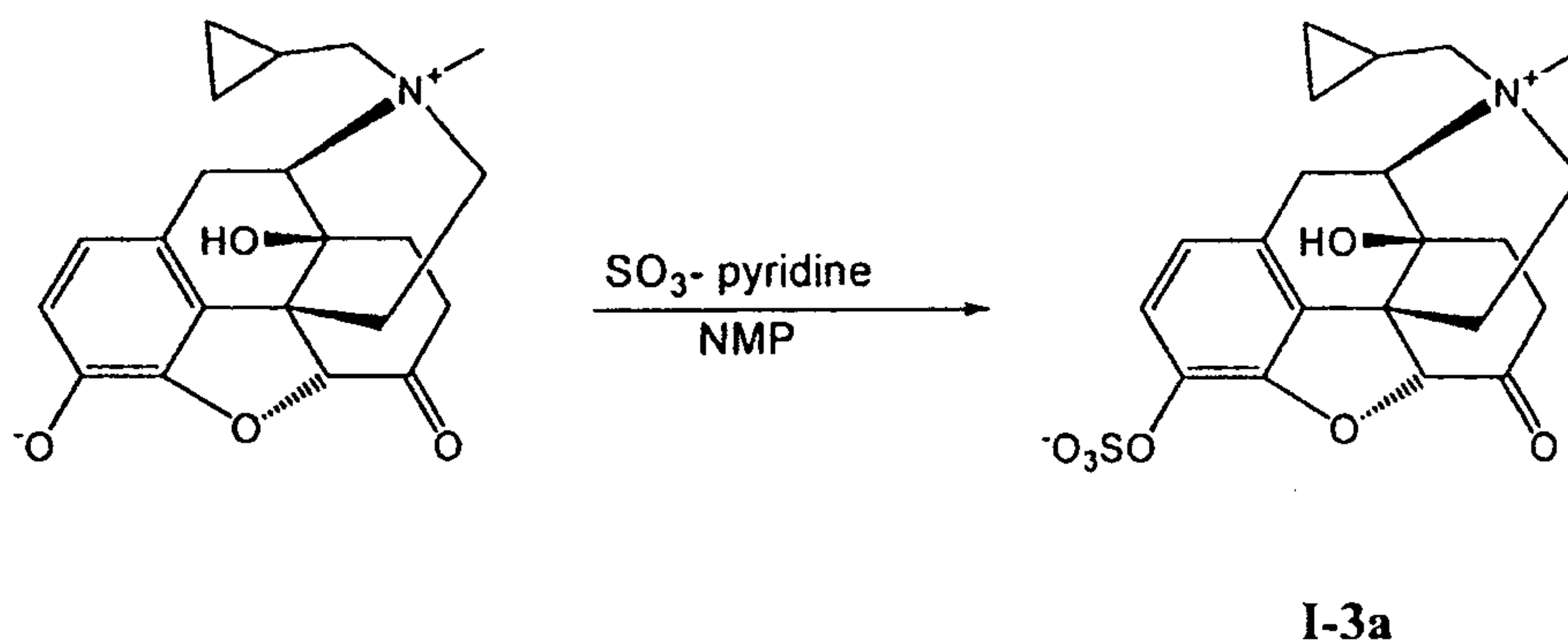
15.1	0%	90%	10%	linear
20	0%	90%	10%	hold

^a(49.5% water, 49.5% methanol, 1% trifluoroacetic acid)

[0095] **(5 α ,6 β)-17-cyclopropylmethyl-17-methyl-4,5-epoxy-3,6,14-trihydroxymorphinan bromide** ("beta" I-2) MNTX (8.72g, 0.020 mol) was dissolved in 500 mL of water in a flask equipped with magnetic stirring and an argon sweep. Formamidinesulfinic acid (8.64 g, 0.080 mol) in a solution of NaOH (6.4 g, 0.16 mol) in 500 mL of water was added, and the flask was immersed in an 80° bath. The heating was continued (total of ca. 2 hr) until HPLC analysis indicated the presence of only a trace of the starting ketone. The mixture was brought to pH 9.4 with hydrobromic acid, and the volume was reduced to 200 mL in vacuo. A solid formed slowly. The solid was collected and washed with 2 X 10 mL water.

[0096] The filtrate was concentrated to ca. 150 mL, and a second crop of crystals was allowed to form overnight. HPLC analysis of the 2.1 g of product showed the presence only of bromide ion, 1, and 2. The latter two were in a ratio of 99:1.

Example 2



[0097] **(5 α)-17-Cyclopropylmethyl-17-methyl-4,5-epoxy-14-hydroxymorphinan-6-one-3-sulfate internal salt (I-3a)** MNTX was converted to the internal salt by base treatment followed by crystallization from water. This material was dried several days over phosphorus pentoxide in a vacuum dessicator.

[0098] The internal salt (3.55 g, 0.010 mol) was dissolved in 40 mL anhydrous NMP in a flask equipped with magnetic stirring and argon blanket. The sulfur trioxide-pyridine complex (3.18 g, 0.020 mol) was added in one portion. The flask was immersed in an oil bath, and the bath temperature was slowly raised to 60° C. At this point, HPLC analysis (280

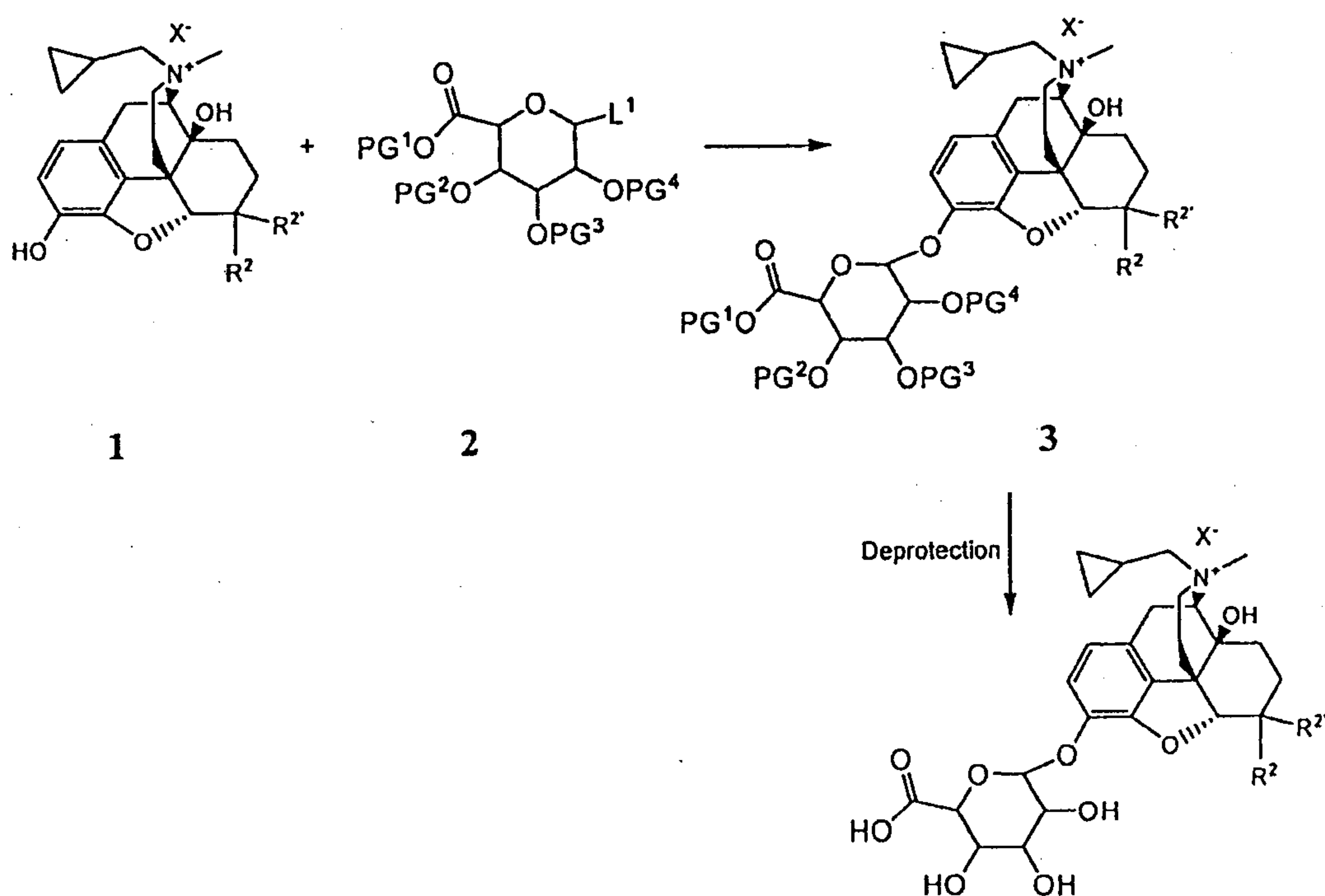
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nm) showed a composition of 84:8:8 product:starting material:impurity. The mixture was cooled to room temperature and diluted with 100 mL ether. The liquid phase was discarded, and the gummy residue was mixed with 10 mL of saturated aqueous sodium bicarbonate and 30 g ice. After the material became freely dispersed, it was collected. The isolated solid was triturated successively with boiling ethanol-water and hot 1:1 NMP:water. A sample of the resultant solid was recrystallized from water and triturated with NMP. The product was > 99% pure.

Example 3

[0099] Compounds of formula III are prepared by the general Scheme 2 depicted below.

Scheme 2



[00100] Scheme 2 above depicts a general method for preparing compounds of formula III. As shown above, the hydroxyl compound 1 is treated with a suitably protected glucuronidate compound 2 having a suitable leaving group to enable the desired coupling to form 3. For compounds of formula 2, each of PG², PG³, and PG⁴ is a suitable hydroxyl protecting group. Suitable hydroxyl protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

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Examples of suitable hydroxyl protecting groups further include, but are not limited to, esters, allyl ethers, ethers, silyl ethers, alkyl ethers, arylalkyl ethers, and alkoxyalkyl ethers. Examples of such esters include formates, acetates, carbonates, and sulfonates. Specific examples include formate, benzoyl formate, chloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, pivaloate (trimethylacetyl), crotonate, 4-methoxy-crotonate, benzoate, p-benylbenzoate, 2,4,6-trimethylbenzoate, carbonates such as methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, vinyl, allyl, and p-nitrobenzyl. Examples of such silyl ethers include trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, and other trialkylsilyl ethers. Alkyl ethers include methyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, trityl, t-butyl, allyl, and allyloxycarbonyl ethers or derivatives. Alkoxyalkyl ethers include acetals such as methoxymethyl, methylthiomethyl, (2-methoxyethoxy)methyl, benzyloxymethyl, beta-(trimethylsilyl)ethoxymethyl, and tetrahydropyranyl ethers. Examples of arylalkyl ethers include benzyl, p-methoxybenzyl (MPM), 3,4-dimethoxybenzyl, O-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, 2- and 4-picolyl.

[00101] It will be understood that each of PG^2 , PG^3 , and PG^4 may be different or the same. In certain embodiments, each of PG^2 , PG^3 , and PG^4 is the same such that they are removed by the same conditions. The removal of such protecting groups, also known as "deprotection", is achieved by methods known in the art, including those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

[00102] For compounds of formula 2, the PG^1 group is a suitable carboxylate protecting group. Such protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999.

Suitable carboxylate protecting groups further include, but are not limited to, substituted C_{1-6} aliphatic esters, optionally substituted aryl esters, silyl esters, activated esters, amides, hydrazides, and the like. Examples of such ester groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, benzyl, and phenyl wherein each group is optionally substituted.

[00103] After coupling the glucoronidate compound 2 with the compound 1, a protected compound 3 is obtained. This compound is then deprotected to form compounds of formula III.

[00104] It will be appreciated that in certain circumstances, it will be advantageous to remove all protecting groups at the same time. In such situations, the choice of PG¹, PG², PG³, and PG⁴ will be such that each protecting group is removed under the same conditions, e.g. by treatment with acid or base, by reduction, or by ultra-violet light, to name but a few. Such choice of protecting groups is well known to one of ordinary skill in the art.

Example 4

[00105] Compounds of the invention were assayed for activity at the human mu opioid receptor by methods substantially similar to those described in Zhang, et al., (1998) "Dynorphin A as a potential endogenous ligand for four members of the opioid receptor gene family." *J. Pharmacol. Exp. Ther.*, 286: 136-141.

[00106] IC₅₀ values (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficients (nH) were determined by non-linear regression analysis of the competition curves using Hill equation curve fitting.

[00107] Inhibition constants (K_i) were calculated from the Cheng Prusoff equation: (K_i = IC₅₀/(1+(L/KD))), where L = concentration of radioligand in the assay, and KD = affinity of the radioligand for the receptor).

[00108] Results are expressed as a percent of control specific binding obtained in the presence of compounds 6-alpha-methylnaltrexol, 6-beta-methylnaltrexol and 3-sulfo-methylnaltrexone. Individual and mean values are set forth in Table 7, below:

Table 7. Results

Compound	IC ₅₀ (M)	K _i (M)	n _H
6 alpha-methylnaltrexol (I-1)	1.1E-07	3.0E-08	0.8
6 beta-methylnaltrexol (I-2)	2.3E-07	6.0E-08	0.9
3 sulfo-methylnaltrexone (I-3)	8.3E-06	2.2E-06	0.8

[00109] Corresponding competition curves obtained with compounds 6-alpha-methylnaltrexol (I-1), 6-beta-methylnaltrexol (I-2), and 3 sulfo-methylnaltrexone (I-3) are shown in Figures 1, 2, and 3, respectively.

Example 5

[00110] Compounds of the invention were assayed for functional activity at the μ -opioid receptors in the guinea pig ileum by methods substantially similar to those described in Hutchinson, et al., (1975) "Assessment in the guinea-pig ileum and mouse vas deferens of benzomorphans which have strong antinociceptive activity but do not substitute for morphine in the dependent monkey." Br J Pharmacol. 1975 Dec;55(4):541-6.

[00111] The IC_{50} values (concentration causing a half-maximal inhibition of DAMGO-induced decrease of twitch contraction amplitude) were determined by non-linear regression analysis of the dose-response curves.

[00112] Results are expressed as a concentration causing a half-maximal inhibition of DAMGO-induced decrease of twitch contraction amplitude of guinea-pig ileum in the presence of compounds 6-alpha-methylnaltrexol, 6-beta-methylnaltrexol and 3-sulfo-methylnaltrexone. Individual values are set forth in Table 8:

Table 8. Results

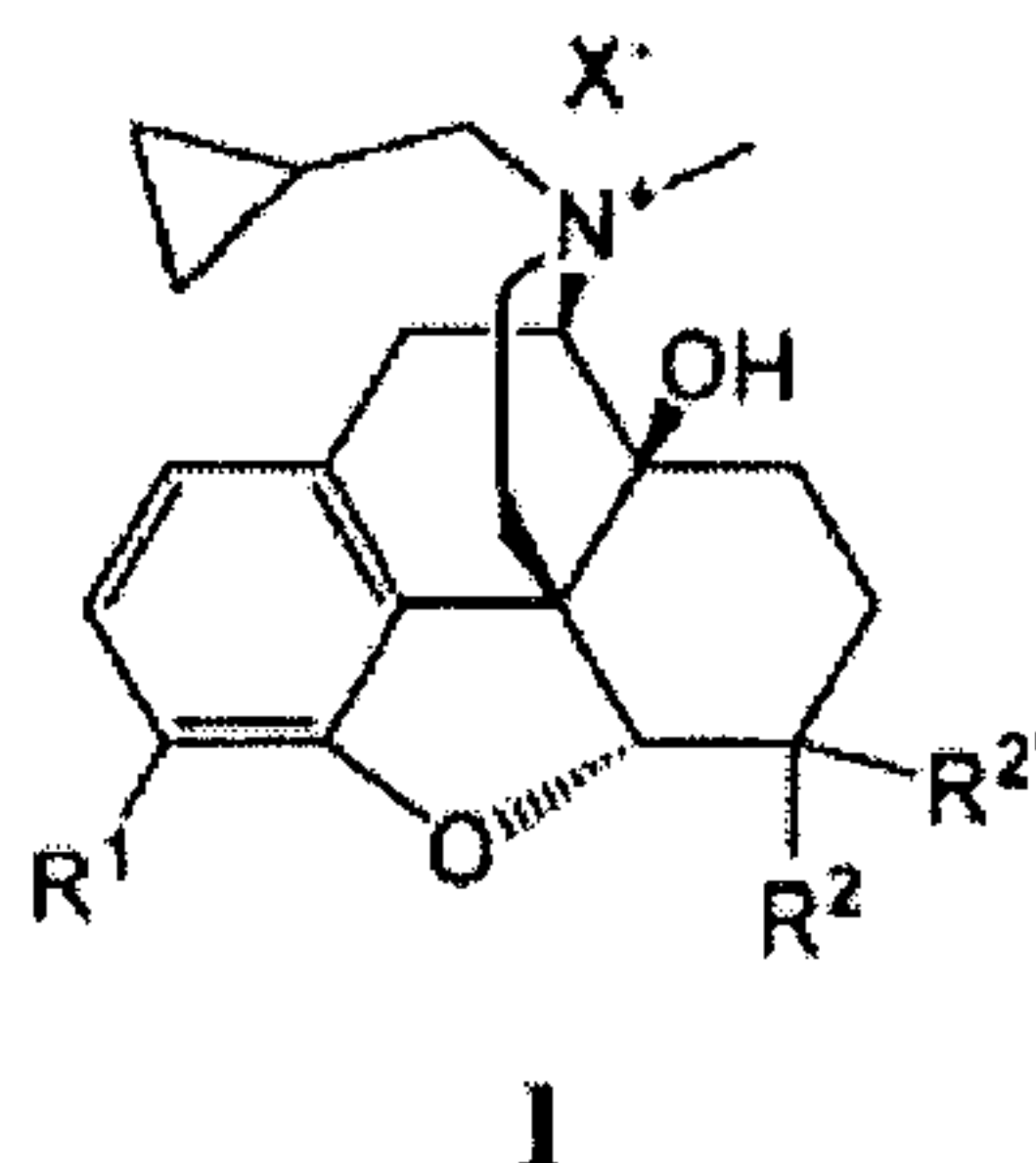
<i>Compound</i>	<i>IC₅₀ Value (M)</i>
<i>6 alpha-methylnaltrexol</i>	<i>1.7E-07 M</i>
<i>6 beta-methylnaltrexol</i>	<i>1.4E-07 M</i>
<i>3 sulfo-methylnaltrexone</i>	<i>1.0E-05 M</i>

[00113] The corresponding inhibition curves obtained with compounds 6-alpha-methylnaltrexol (I-1), 6-beta-methylnaltrexol (I-2), and 3 sulfo-methylnaltrexone (I-3) are shown in Figures 4, 5, and 6, respectively.

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CLAIMS:

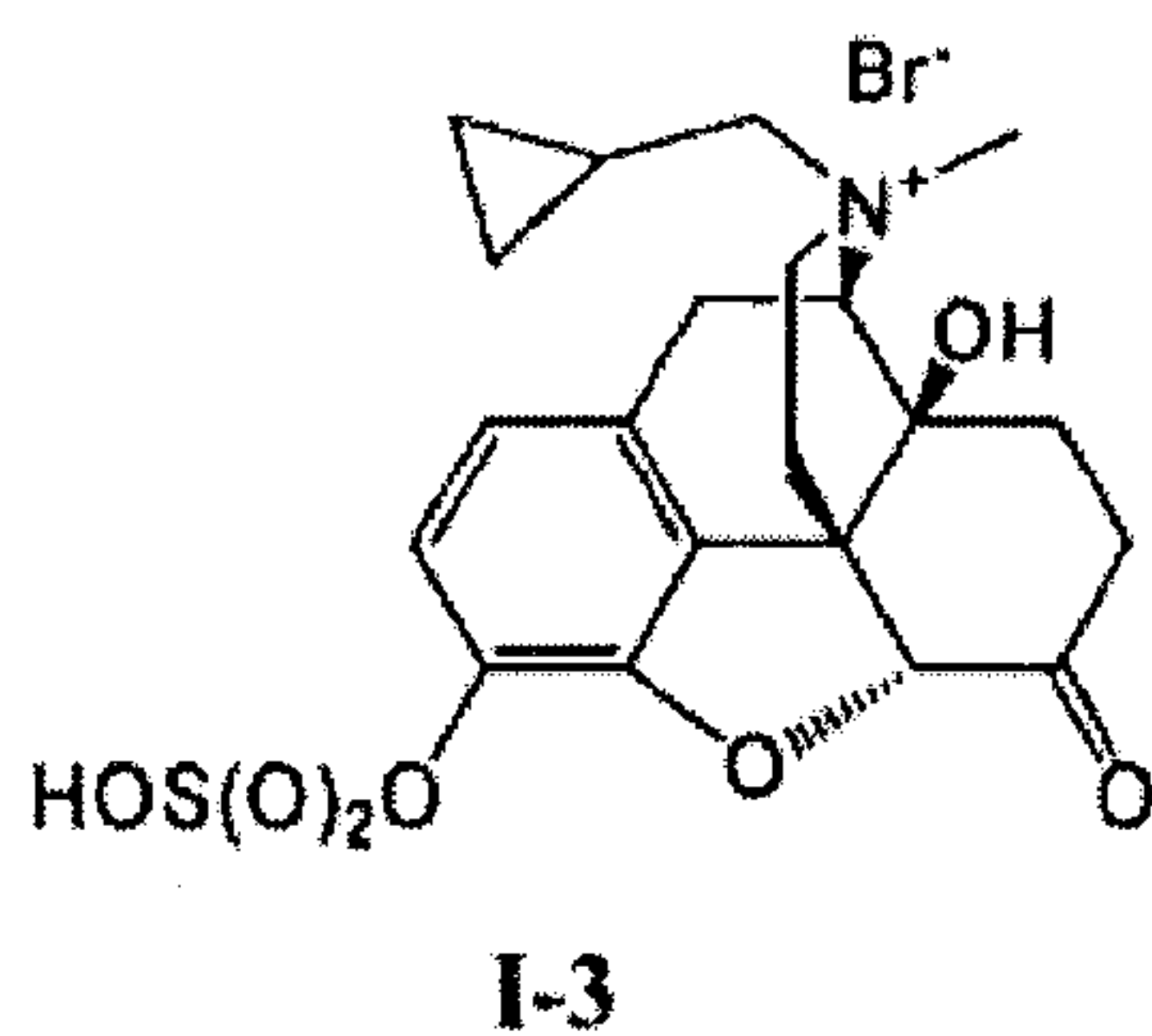
1. An isolated compound of formula I:



wherein X^- is a suitable anion;

- 5 R^1 is $-OS(O)_2OH$; and
 R^2 and $R^{2'}$ are taken together to form oxo.

2. The compound according to claim 1, wherein X^- is the anion of a suitable Brønsted acid.
3. The compound according to claim 2, wherein X^- is chloride, bromide, iodide,
 10 fluoride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, carbonate, phosphate, malate, maleate, fumarate, sulfonate, methylsulfonate, formate, carboxylate, methylsulfate or succinate.
4. The compound according to claim 1, which is



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5. A pharmaceutical composition comprising:

the compound defined in any one of claims 1-4; and

a pharmaceutically acceptable carrier, adjuvant, or vehicle.
6. An oral formulation comprising the pharmaceutical composition defined in
5 claim 5.
7. The pharmaceutical composition according to claim 5 for use in the reduction
of a side effect of opioid therapy in a subject receiving opioid treatment.
8. The pharmaceutical composition according to claim 7, wherein the side effect
is caused, mediated, or exacerbated by opioid receptor activity.
- 10 9. The pharmaceutical composition according to claim 5 for use in the reduction
of a peripheral effect of endogenous opioid activity in a subject.
10. The pharmaceutical composition according to claim 7, wherein the side effect is
selected from the group consisting of inhibition of intestinal motility, gastrointestinal
dysfunction, constipation, bowel hypomotility, impaction, gastric hypomotility, gastrointestinal
15 sphincter constriction, increased sphincter tone, inhibition of gastrointestinal motility, inhibition
of gastric emptying, delayed gastric emptying, incomplete evacuation, nausea, emesis, cutaneous
flushing, bloating, abdominal distension, sweating, dysphoria, pruritis, and urinary retention.
11. The pharmaceutical composition according to claim 10, wherein the subject is
a patient receiving short term opioid administration.
- 20 12. The pharmaceutical composition according to claim 9, wherein the effect
comprises at least one condition or disorder selected from the group consisting of ileus,
post-operative ileus, paralytic ileus, postpartum ileus, gastrointestinal dysfunction developing
following abdominal surgery, and idiopathic constipation.
13. The pharmaceutical composition according to claim 10, wherein the subject is
25 a patient receiving chronic opioid administration.

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COMPETITION CURVE OBTAINED WITH
COMPOUND 3 alpha-methylnaltrexol
AT THE HUMAN MU RECEPTOR

IC₅₀ = 1.1E-07 M

nH = 0.8

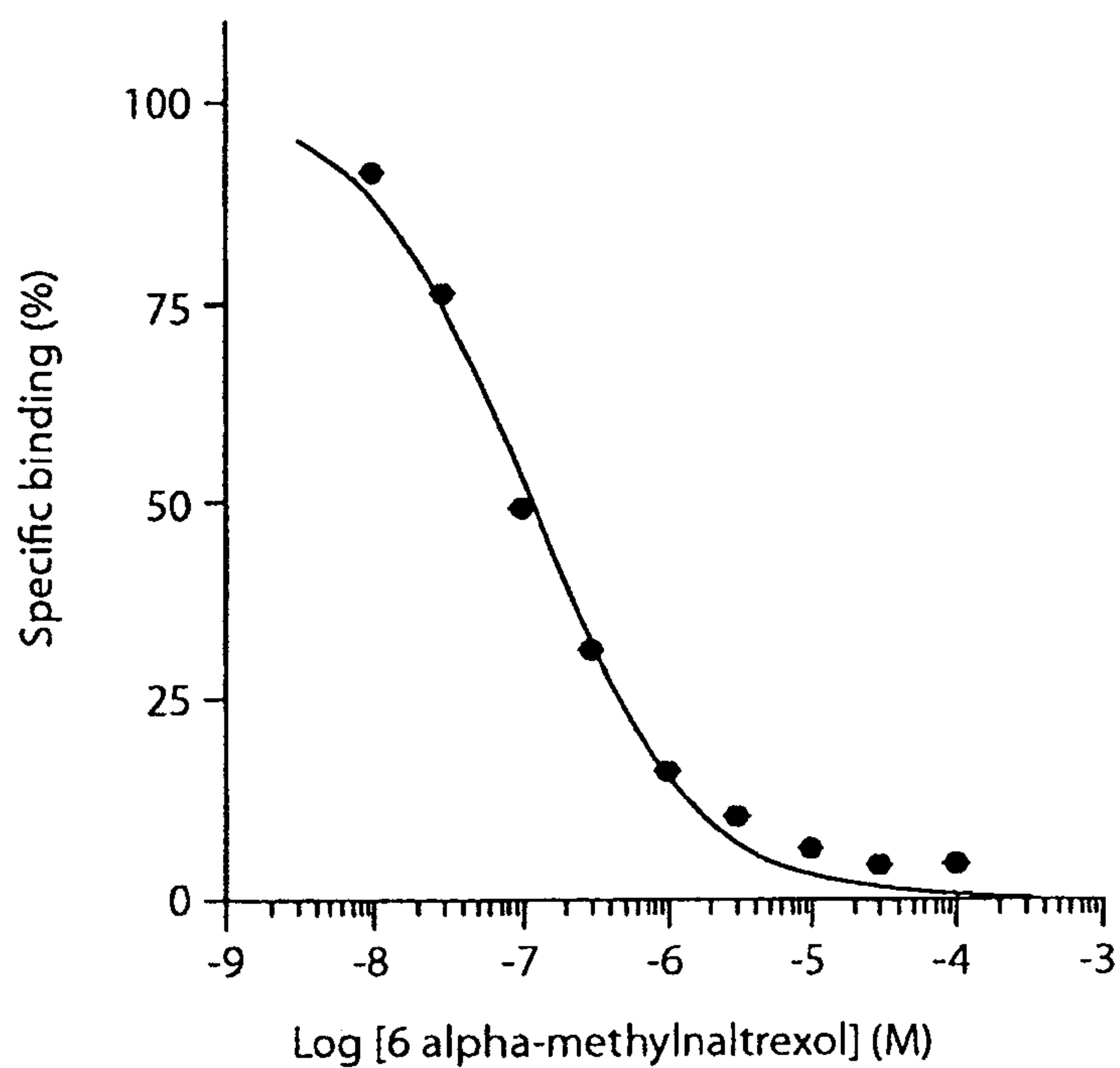


Fig. 1

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COMPETITION CURVE OBTAINED WITH
COMPOUND 6 beta-methylnaltrexol
AT THE HUMAN MU RECEPTOR

IC50 = 2.3E-07 M
nH = 0.9

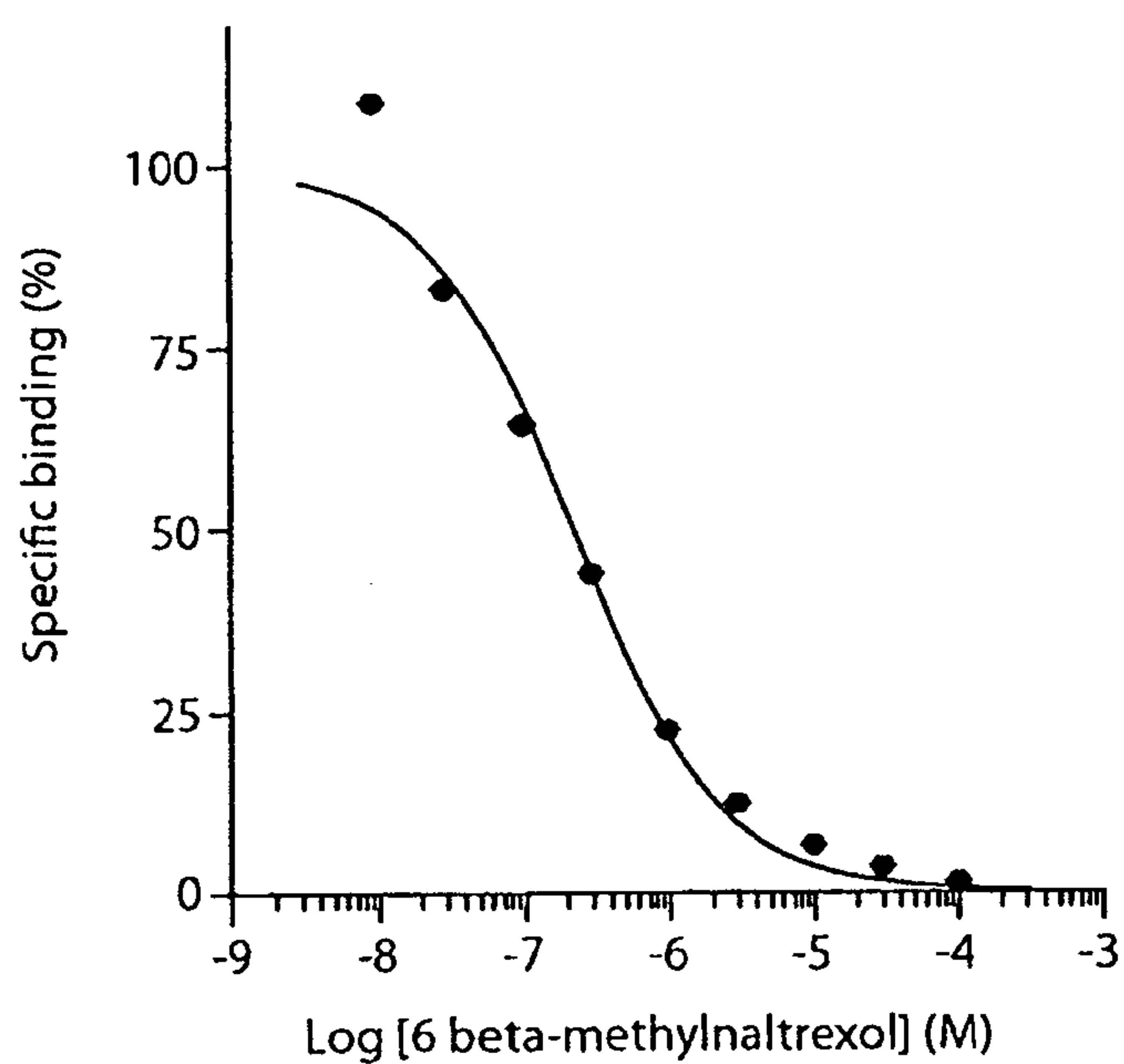


Fig. 2

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COMPETITION CURVE OBTAINED WITH
COMPOUND 3 sulfo-methylnaltrexone
AT THE HUMAN MU RECEPTOR

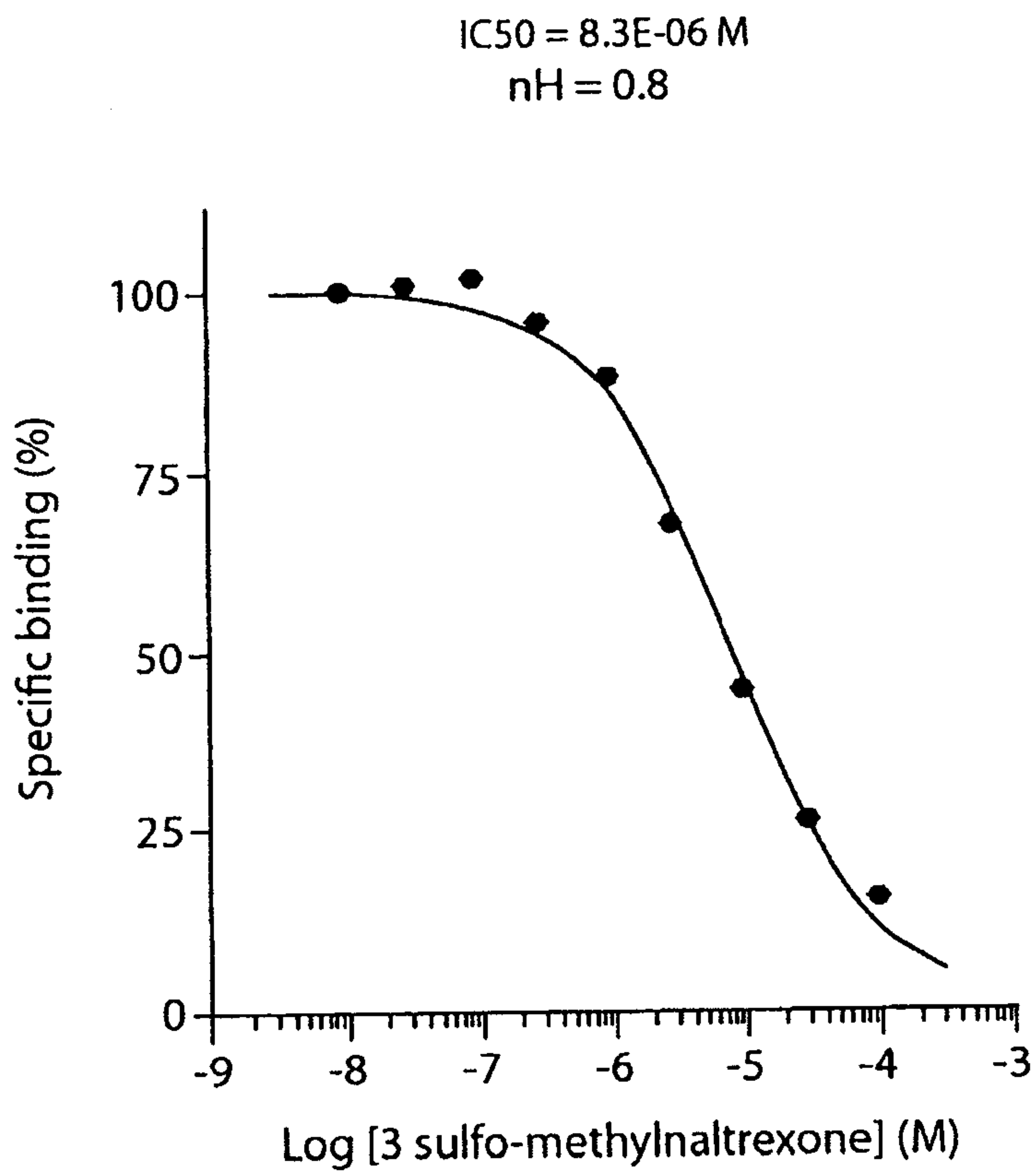


Fig. 3

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Concentration-response curve for the effects of 6 alpha-methylnaltrexol on the DAMGO-induced decrease in twitch contraction amplitude in the guinea pig ileum

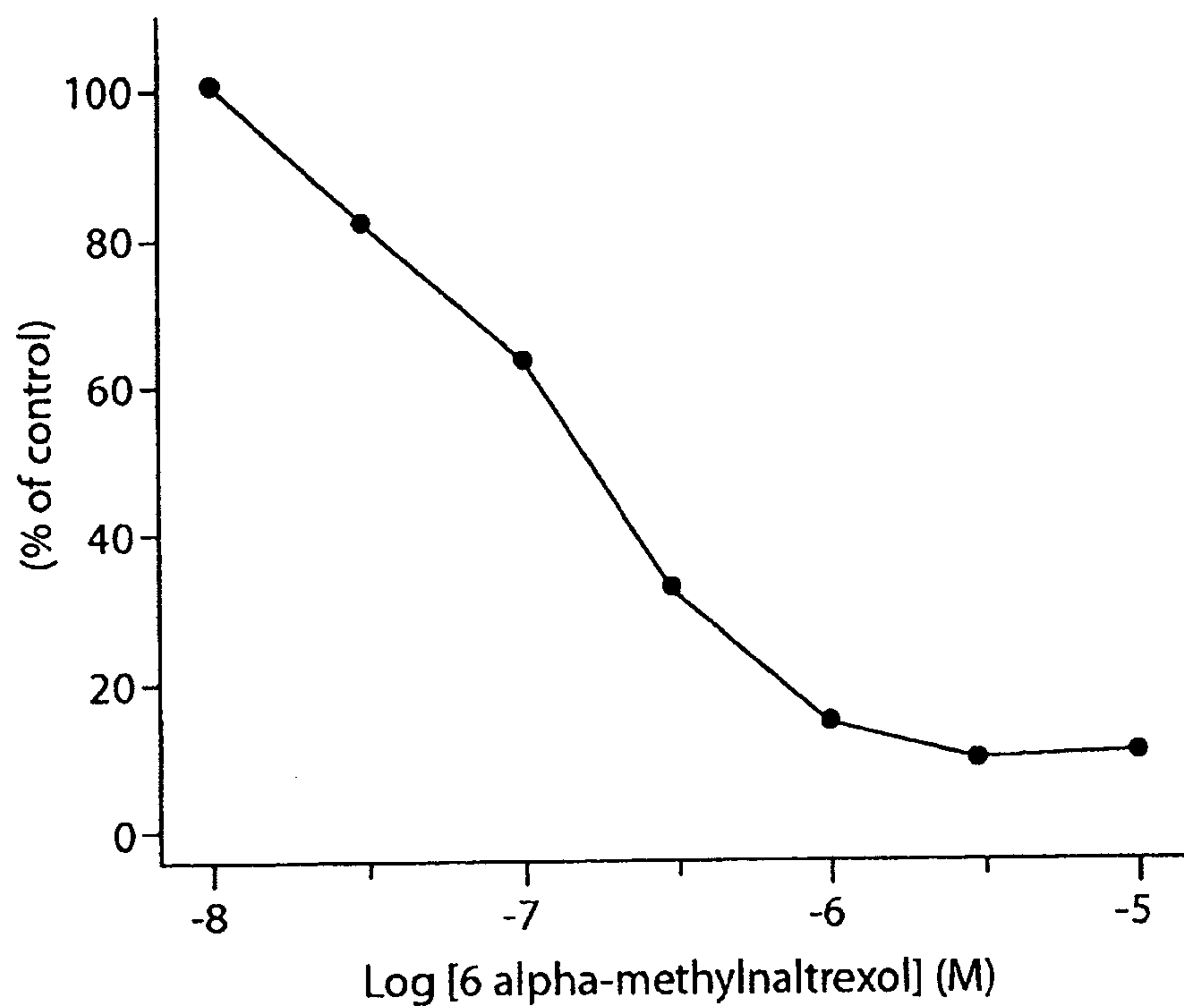


Fig. 4

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Concentration-response curve for the effects of 6 beta-methylnaltrexol on the DAMGO-induced decrease in twitch contraction amplitude in the guinea pig ileum

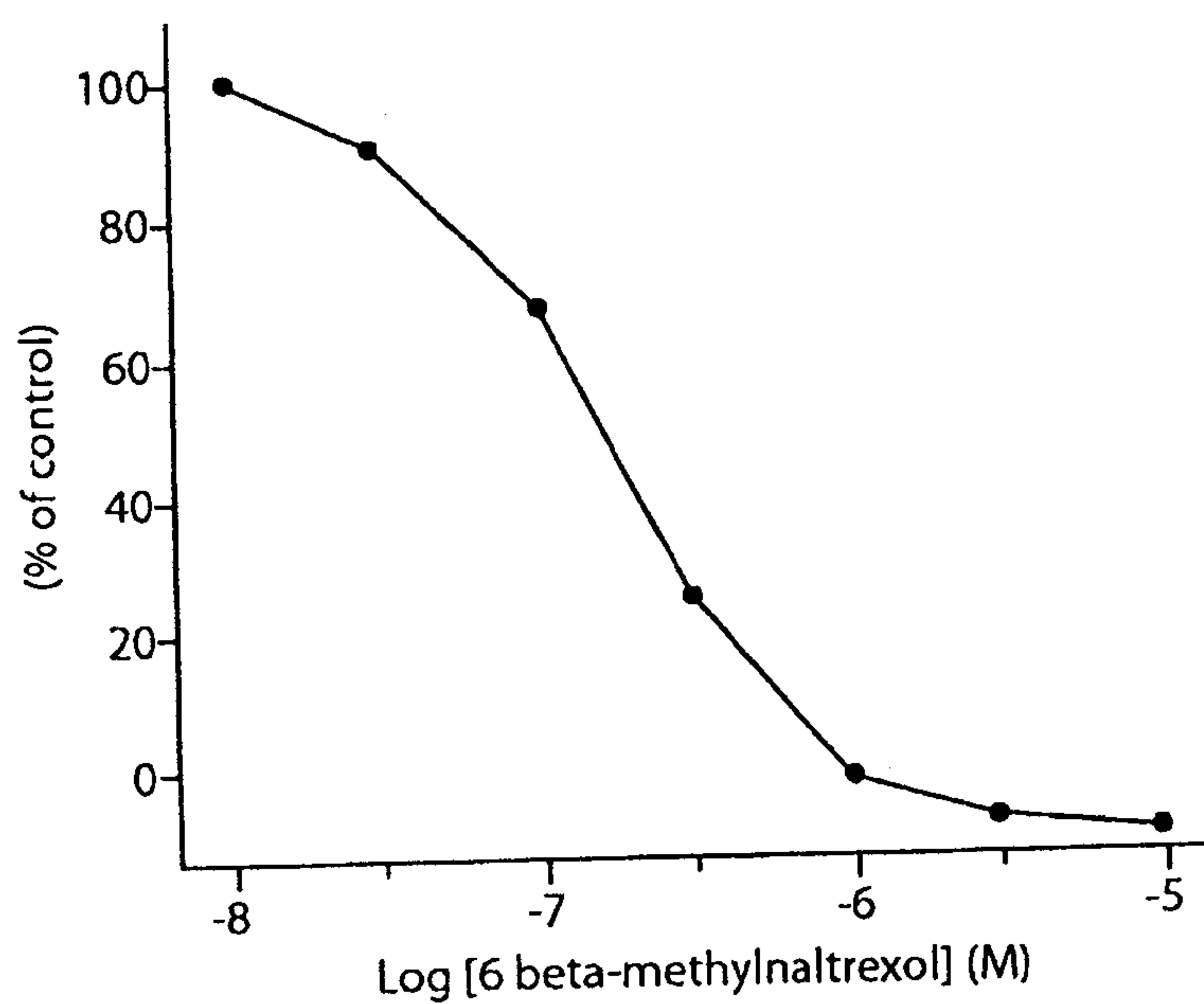


Fig. 5

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Concentration-response curve for the effects of 3 sulfo-methylnaltrexone on the DAMGO-induced decrease in twitch contraction amplitude in the guinea pig ileum

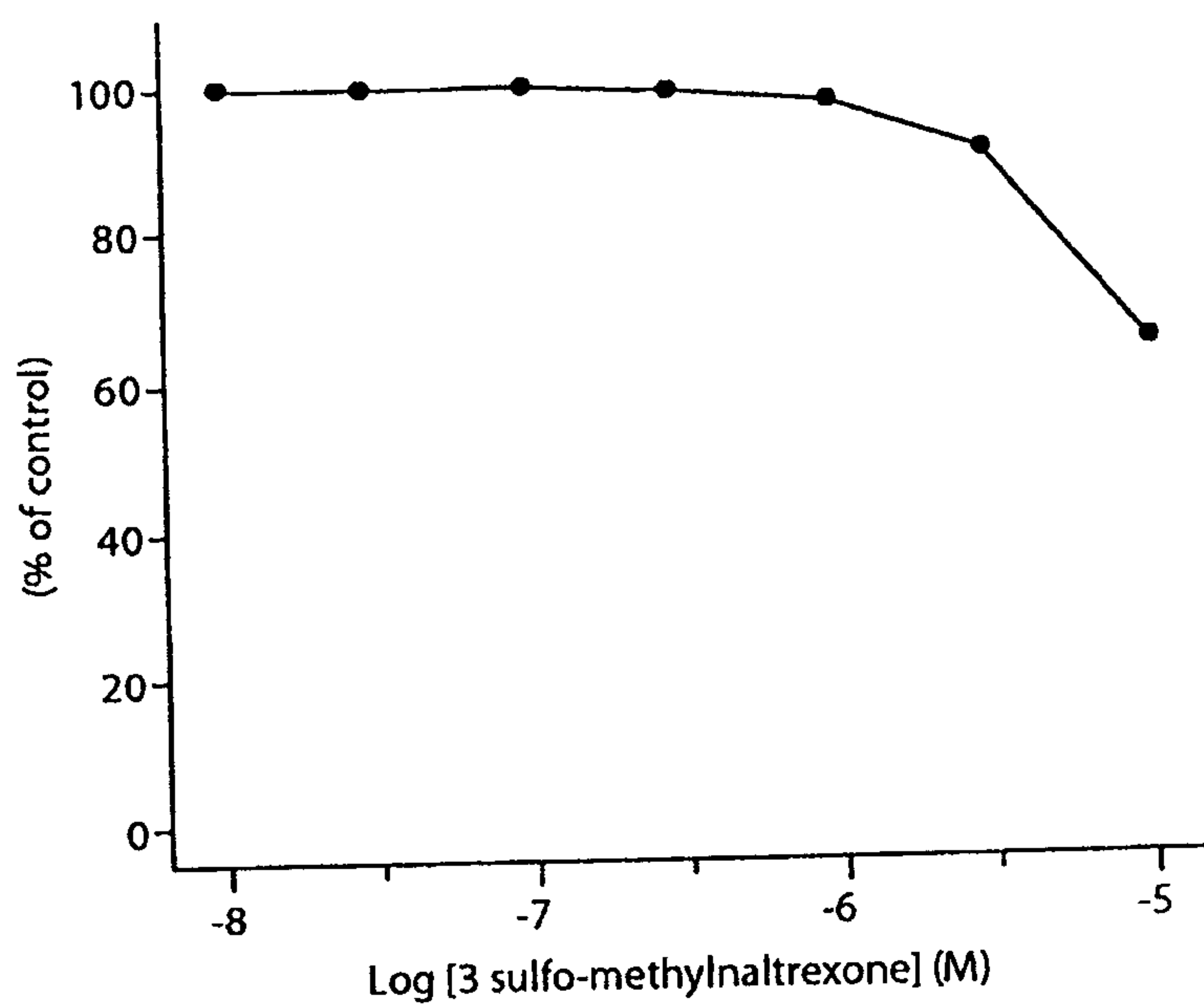
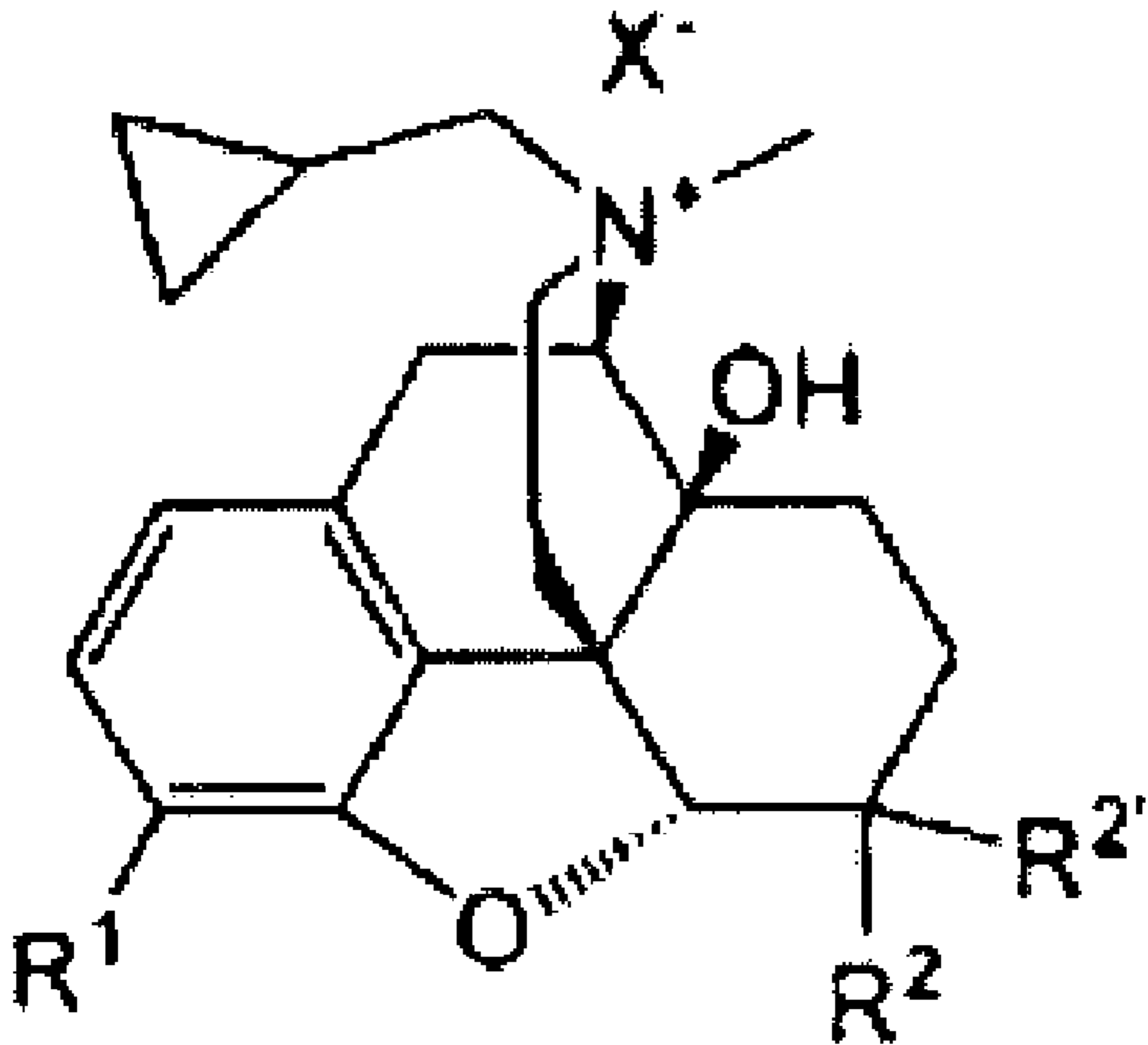


Fig. 6



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