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(54) Title: SYNTHESIS OF METABOLICALLY STABLE ANALGESICS, PAIN MEDICATIONS AND OTHER AGENTS

(57) **Abrégé/Abstract:**

Disclosed are analgesic-related compositions and methods of using the compositions for modulation of analgesic receptor activity. The compositions and methods are useful for reducing pain, as well as for therapeutic intervention of addictions or other diseases or disorders amenable to treatment or prophylaxis by modulation of analgesic receptor signaling.



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SYNTHESIS OF METABOLICALLY STABLE ANALGESICS, PAIN MEDICATIONS AND OTHER AGENTS

FIELD OF THE INVENTION

[0002] The present invention pertains to pharmaceutical agents that interact with analgesic receptors, methods of preparing these agents, and their use for analgesia, pain, addictions, and other conditions.

BACKGROUND OF THE INVENTION

[0003] Morphine and other opiates act as powerful analgesics [Foye, W.O. in "*Principles of Medicinal Chemistry*," Third Edition, Lea & Febiger, Philadelphia, 1989]. Considerable effort has been put forth to develop and understand the appropriate use of narcotic analgesics for terminal patients and for easing the pain of cancer, yet new medications are greatly needed. Morphine elicits a number of pharmacological activities mediated by mu opioid receptors, including analgesia, respiratory depression, and inhibition of gastrointestinal transit. [See O. Ray, "*Drugs, Society and Human Behavior*," Third Edition, The C.V. Mosby Co., St. Louis (1983)]. However, adverse side effects and the abuse potential have limited morphine availability and optimal use. Solubility and potency issues limit the amount of injectable morphine as well. There is a need for longer-lived agents for severe pain. There is a need for agents that do not need to be administered by expensive i.v. or epidural routes of administration. There is also a need for medications that do not cause respiratory depression, tolerance, urinary retention, constipation, physical dependence, and/or addiction. In addition, some of the existing pain conditions are resistant to the analgesic action of currently available opiates. There is also a need for effective analgesics that only work in the periphery and do not enter the brain.

[0004] Tolerance is defined as a reduced sensitivity to the effect of an opiate and generally indicates an attenuation in analgesic efficacy causing dependence revealed by the physical

manifestations of withdrawal. [See B. L. Kieffer *et al.*, *Cell*, **108**:87-90 (2002).] Tolerance is almost exclusively associated with analgesia. It has been long thought that tolerance is caused by a reduction in surface receptors and opioid receptor signaling. However, morphine does not promote efficient mu receptor internalization, [see J. L. Whistler *et al.*, *Neuron*, **23**:737-46 (1999)] whereas other opioids such as the mu-selective peptide DAMGO and the alkaloid fentanyl do promote such internalization. *In vitro* models show that DAMGO administered at concentrations below the threshold for inducing internalization can induce internalization of the mu receptor in the presence of morphine. [See L. He *et al.*, *Cell*, **108**:271-82 (2002).] Analgesia following continuous administration of morphine is markedly enhanced when a sub-internalizing dose of DAMGO is co-administered to rats. [See L. He *et al.*, *supra*.] This link between mu receptor internalization on the cellular level and tolerance *in vivo* suggests that receptor internalization may provide protection against tolerance. Determining which analogs of M6G effect receptor internalization may therefore be an important step to developing a non-addictive analgesic and furthering our understanding of the addiction process. Development of antagonists of the mu, delta, or kappa receptor also result in useful medications. Replacement of the *N*-17 methyl group in these M6G analogs with other alkyl, cycloalkyl and alkenyl groups could provide pharmacologically active antagonists at the opioid receptors. Such antagonists could be useful in treatment of diseases of the CNS including drug addiction, gambling addiction, and alcoholism. Elaboration of a derivative that is constantly charged and contains a quaternary amine or a guanadino group could also provide a new set of analgesics that only work in the periphery.

[0005] A major pathway for removing morphine and related opiates from the body is through the formation of water soluble glucuronide conjugates in the liver and subsequent excretion in the urine. In the case of morphine, three glucuronides are formed: morphine-6- β -D-glucuronide, morphine-3- β -D-glucuronide and morphine-3,6-di- β -D-glucuronide. Morphine-6- β -D-glucuronide (M6G) is an analgesic with a potency 100-fold greater than morphine itself. [See G. W. Pasternak, *Life Sci.*, **41**:2845-2849 (1987).] The low bioavailability (11%) of M6G due to hydrolysis in the gut by stomach acid is a significant limitation in the development of a drug from this compound. [See R. T. Penson *et al.*, *Br. J. Clin. Pharmacol.*, **53**:347-354 (2002).] Development of new medications based upon M6G is promising because of its analgesic potency, favorable side effect profile, and distinct pharmacological activity. [See M.H. Hanna *et al.*, *Anesthesiology*, **102**:815-821 (2005).]

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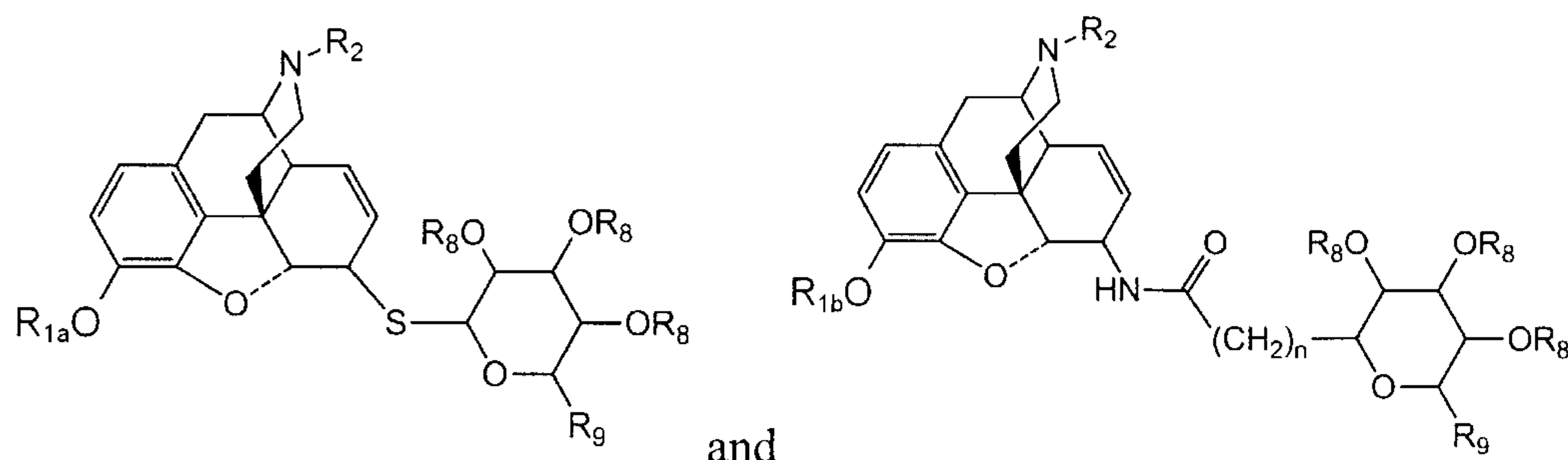
[0006] Glucuronides as a rule are thought to be highly polar metabolites and unable to cross the blood brain barrier (BBB). [See G. W. Pasternak, *Clin. Neuropharmacol.*, **16**:1-18 (1993).] However, M6G is apparently much more lipophilic than predicted. [See P. A. Carrupt *et al.*, *J. Med. Chem.*, **34**:1272-1275 (1991).] Polar surface area (PSA) calculations suggest molecules above $90 \text{ \AA}^2$ do not get into the brain. [See K. Palm *et al.*, *J. Pharm. Sci.*, **85**:32-39 (1996a).] For BBB penetration via the transcellular route a molecule should have a MW of <450 and a PSA $<90 \text{ \AA}^2$. Related calculations show that oral absorption is optimal with a PSA $<120 \text{ \AA}^2$. [See J. Kelder *et al.*, *Pharmaceutical Research*, **16**:1514-1519 (1999).] In rats, after oral administration, M6G was absorbed per se in the proximal intestine, showing that M6G is capable of membrane penetration. [See R. Stain-Textier *et al.*, *Drug Metab. Dispos.*, **26**:383-387, (1998).] But analogs of M6G with a molecular weight greater than 450 are predicted to not get into the brain, and because of the more polar nature compared to morphine, are predicted by others to not have more favorable CNS biodistribution and onset of action properties.

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BRIEF SUMMARY OF THE INVENTION

[0007] In one aspect, the present invention provides analgesic-related agents having pharmacological activity against analgesic receptors. In typical embodiments, the agents comprise an analgesic or derivative thereof linked to an optionally substituted aryl, optionally substituted heteroaryl, or a saccharide. In preferred embodiments, the analgesic or derivative thereof is an opiate or an opiate derivative. The analgesic-related agent can be an agonist or an antagonist of a corresponding analgesic receptor to which the agent specifically binds.

[0007a] In a particular embodiment, the present invention relates to a compound selected from the group consisting of:



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wherein R_{1a} is selected from the group consisting of H, (C₁-C₅)alkylC(O), (C₇-C₁₀)aralkylC(O), (C₆-C₁₂)arylC(O), and silyl; R_{1b} is selected from the group consisting of H, (C₁-C₅)alkyl, (C₁-C₅)alkylC(O), (C₇-C₁₀)aralkylC(O), (C₆-C₁₂)arylC(O), and silyl; R_2 is selected from the group consisting of (C₁-C₅)alkyl, C₃-C₆(cycloalkyl)alkyl, C₅-C₇(cycloalkenyl)alkyl, (C₆-C₁₂)aryl, (C₇-C₁₂)aralkyl, trans(C₄-C₅)alkenyl, allyl, and furan-2-ylalkyl; each R_8 is independently selected from the group consisting of H, (C₁-C₅)alkylC(O), (C₇-C₁₀)aralkylC(O), (C₇-C₁₀)aralkyl, and (C₁-C₅)alkyl; R_9 is selected from the group consisting of CH₂OH, CH₂O₂C(C₁-C₅)alkyl, CH₂O(C₇-C₁₀)aralkyl, CO₂H, CO₂(C₁-C₅)alkyl, and CO₂(C₇-C₁₀)aralkyl; n is an integer of from 0 to 5; and wherein alkyl is a straight chain, branched chain or cyclic saturated aliphatic group.

[0008] The agents of the present invention are useful, for example, for reducing pain in a subject, or for the treatment or prophylaxis of a disease or disorder amenable to such treatment or prevention by modulation (*e.g.*, inhibition or stimulation) of analgesic receptors. Accordingly, in another aspect, the present invention provides pharmaceutical compositions comprising an analgesic-related agent as set forth herein. Also provided are methods for reducing pain, or for treating or preventing a disease or disorder amenable to such treatment or prevention by modulation of analgesic receptor activity, by administration of an effective amount of an analgesic-related agent to a subject. Diseases or disorders amenable to therapeutic intervention in accordance with the compositions and methods provided herein include, for example, addictions or other disorders of the CNS that are mediated, at least in

part, directly or indirectly, by analgesic receptors. In certain variations of the pharmaceutical compositions or methods, such as, *e.g.*, for the treatment of pain, the analgesic-related agent is an analgesic receptor agonist. In other embodiments, such as, *e.g.*, for the treatment of drug addiction, gambling addiction, or alcoholism, the agent is typically an analgesic receptor antagonist.

[0009] For modulation of analgesic receptors in the periphery, without significant effect on such receptors in the brain, the agent is typically has a constant charge at physiological pH. Such agents can include, for example, quaternary amines, guanidines, and the like, and are particularly suitable for use as, *e.g.*, peripheral analgesics.

DEFINITIONS

[0010] Unless defined otherwise, 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. Although any methods and material similar to those described herein can be used in the practice or testing of the present invention, only exemplary methods and materials are described. For purposes of the present invention, the following terms are defined below.

[0011] The terms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0012] The term "alkyl" refers to saturated aliphatic groups including straight chain, branched chain, and cyclic groups, all of which may be optionally substituted. Suitable alkyl groups include methyl, ethyl and the like, and may be optionally substituted.

[0013] The term "alkenyl" refers to unsaturated groups which contain at least one carbon-carbon double bond and includes straight chain, branched chain, and cyclic groups, all of which may be optionally substituted.

[0014] The term "alkynyl" refers to unsaturated groups which contain at least one carbon-carbon triple bond and includes straight chain, branched chain, and cyclic groups, all of which may be optionally substituted. Suitable alkynyl groups include ethynyl, propynyl, butynyl and the like which may be optionally substituted.

[0015] The term "aryl" refers to aromatic groups which have at least one ring having conjugated "pi" electron system and includes carbocyclic aryl, biaryl, both of which may be optionally substituted.

[0016] The term "aralkyl" refers to an alkyl group substituted with an aryl group. Suitable aralkyl groups include benzyl, and the like, and may be optionally substituted.

[0017] The term "heteroaryl" refers to carbon containing 5-14 membered cyclic unsaturated radicals containing one, two, three, or four O, N, P, or S atoms and having 6, 10 or 14 π electrons delocalized in one or more than one rings.

[0018] The term "pharmaceutically acceptable derivative" refers to any derivative of a compound as described herein that is suitable for pharmacological use, including, *e.g.*, pharmaceutically acceptable esters, amides, or salts. Pharmaceutically acceptable esters, amides, or salts" refers to esters, amides, or salts derived from the combination of a compound of this invention and an organic or inorganic acid.

[0019] The term "analgesic" refers to a compound capable of producing analgesia, *i.e.*, reducing or inhibiting pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness. In preferred embodiments of the present invention, an analgesic is an opiate.

[0020] The terms "opiate" and refers to any agent, natural or synthetic, capable of specifically binding to an opioid receptor, including opium or any of its derivatives (*e.g.*, morphine), as well as synthetic or semi-synthetic narcotics.

[0021] The term "analgesic-related agent" refers to a metabolite, analog, or derivative of an analgesic. The term "opiate-related agent" refers to a metabolite, analog, or derivative of an opiate, such as further described herein. In accordance with the present invention, analgesic-related agents, including opiate-related agents, can have agonist or antagonist activity with respect to one or more analgesic receptors to which the agent specifically binds.

[0022] The term "inhibit" means to reduce by a measurable amount, or to prevent entirely.

[0023] The phrase "promote efficient receptor internalization" means that an agent is capable of promoting cellular internalization of a receptor to which the agent specifically binds such that, as compared to control cells not contacted with the agent, cells contacted with the agent display no more than 80%, typically no more than 70% or 60%, and more

typically no more than 50% or 40%, of surface staining for the corresponding receptor by FACS.

[0024] "Treating," "treatment," or "therapy" of a disease or disorder means slowing, stopping, or reversing progression of the disease or disorder, as evidenced by a reduction or elimination of either clinical or diagnostic symptoms, using the compositions and methods of the present invention as described herein.

[0025] "Preventing," "prophylaxis," or "prevention" of a disease or disorder means prevention of the occurrence or onset of a disease or disorder or some or all of its symptoms.

[0026] "Addiction" as used herein refers to a disease or disorder characterized by a habitual psychological and physiologic dependence on a substance or practice that is substantially beyond voluntary control. Addictions amenable to treatment using the compounds and methods described herein include substance addictions such as, *e.g.*, addictions to narcotics (*e.g.*, morphine, heroin), alcohol, and nicotine, as well as behavioral addictions such as, *e.g.*, addiction to gambling.

[0027] The term "subject" as used herein means any mammalian patient to which the compositions of the present invention may be administered according to the methods described herein. Subjects specifically intended for treatment or prophylaxis using the methods of the present invention include humans.

[0028] The term "therapeutically effective regime" means that a pharmaceutical composition or combination thereof is administered in sufficient amount and frequency and by an appropriate route to reduce pain, or to at least detectably prevent, delay, inhibit, or reverse development of at least one symptom or biochemical marker of a disease or disorder amenable to treatment by modulation of an analgesic receptor.

[0029] The term "therapeutically effective amount" refers to an amount of an agent of the present invention, or a combination of an agent of the present invention with other agent(s), that is present to achieve a desired result, *e.g.*, reducing pain, or preventing, delaying, inhibiting, or reversing a symptom or biochemical marker of a disease or disorder amenable to treatment by modulation of an analgesic receptor, when administered in an appropriate regime.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0030] Figure 1 depicts the synthesis of compounds represented by Formula IV.
- [0031] Figure 2 depicts the synthesis of thiosaccharides 2a and 2b.
- [0032] Figure 3 depicts the synthesis of compounds of Formula V.
- [0033] Figure 4 depicts the synthesis of compounds of Formula VI.
- [0034] Figure 5 depicts dose-dependent analgesia induced by administration of morphine. Data are mean %MPE ($\pm$ SEM). Asterisks represent significant differences from vehicle controls (Student Newman-Keuls, $p < 0.05$). Plus signs represent a significant difference from 3 mg/kg morphine (Student Newman-Keuls, $p < 0.05$).
- [0035] Figure 6 analgesic effects produced by two high doses 13e. Data are mean %MPE ($\pm$ SEM). Asterisks represent significant differences from vehicle controls (Student Newman-Keuls, $p < 0.05$). Plus signs represent a significant difference between 10 and 30 mg/kg 13e (Student Newman-Keuls, $p < 0.05$).
- [0036] Figure 7 depicts dose-dependent analgesia induced by administration of 3a. Data are mean %MPE ($\pm$ SEM). Asterisks represent significant differences from vehicle controls (Student Newman-Keuls, $p < 0.05$). Plus signs represent a significant difference from 3 mg/kg 3a (Student Newman-Keuls, $p < 0.05$).
- [0037] Figures 8A-C depict an effect of the opiate analog 13e on heroin intake in a heroin-dependent rat (Rat #96). Rats were injected in a within-subjects design with the opiate analog 13e (0, 0.04, and 0.2 mg/kg, s.c.) 15 mins prior (5:45 pm) to the active/dark phase (6pm-6am). Data are expressed as total heroin intake (60 μ g/kg/0.1 ml infusion) for each hour (Figure 8A), every 3 hours (Figure 8B), and all 12 hours (Figure 8C) in the dark phase.
- [0038] Figures 9A-C depict an effect of the opiate analog 3a on heroin intake in a heroin-dependent rat (Rat #99). Rats were injected in a within-subjects design with the opiate analog 3a (0, 0.04, and 0.2 mg/kg, s.c.) 15 mins prior (5:45 pm) to the active/dark phase (6pm-6am). Data are expressed as total heroin intake (60 μ g/kg/0.1 ml infusion) for each hour (Figure 9A), every 3 hours (Figure 9B), and all 12 hours (Figure 9C) in the dark phase.
- [0039] Figures 10A-C depict an effect of the opiate analog 13g on heroin intake in a heroin-dependent rat (Rat #100). Rats were injected in a within-subjects design with the opiate analog 13g (0, 0.04, and 0.2 mg/kg, s.c.) 15 mins prior (5:45 pm) to the active/dark

phase (6pm-6am). Data are expressed as total heroin intake (60 µg/kg/0.1 ml infusion) for each hour (Figure 10A), every 3 hours (Figure 10B), and all 12 hours (Figure 10C) in the dark phase.

[0040] Figures 11A-C depict an effect of M6G on heroin intake in a heroin-dependent rat (Rat #103). Rats were injected in a within-subjects design with M6G (0, 0.04, and 0.2 mg/kg, s.c.) 15 mins prior (5:45 pm) to the active/dark phase (6pm-6am). Data are expressed as total heroin intake (60 µg/kg/0.1 ml infusion) for each hour (Figure 11A), every 3 hours (Figure 11B), and all 12 hours (Figure 11C) in the dark phase.

[0041] Figures 12A-C depict an effect of the opiate analog 13h on heroin intake in heroin-dependent rats (n=4). Rats were injected in a between-subjects design with the opiate analog 13h (0 [Rat #96], 0.01 [Rat #99], 0.04 [Rat #100], and 0.2 mg/kg [Rat #103], s.c.) 15 mins prior (5:45 pm) to the active/dark phase (6pm-6am). Data are expressed as total heroin intake (60 µg/kg/0.1 ml infusion) for each hour (Figure 12A), every 3 hours (Figure 12B), and all 12 hours (Figure 12C) in the dark phase.

[0042] Figure 13 depicts chemical structures of MG6 (1) and two metabolically stable analogs (2 and 3) described in Example 33.

[0043] Figure 14 depicts the preparation of the C-glycosides of MG6 described in Example 33. (i) CH₃S(O)CH₃, Ac₂O; (ii) LiCH₂CO₂Et, THF then HCl, -78 °C to rt; (iii) Et₃SiH, BF₃·OEt₂, CH₃CN, 0 °C to rt; (iv) NaOH, H₂O, THF, reflux then HCl; (v) SOCl₂; (vi) 3-*O*-triisopropylsilyl-6-β-aminomorphine, Et₃N, CH₂Cl₂; (vii) B_u₄NF, THF, H₂O; (viii) H₂, 10% Pd-C, MeOH; (ix) H₂, 10% Pd-C, MeOH, HCl.

[0044] Figure 15 depicts chemical structures of norBNI and naltrindole (NTI).

[0045] Figure 16 depicts chemical structures of JD_Tic and guanidinenaltrindole (GNTI).

[0046] Figure 17 depicts the chemical structures of nalmeferene (1) and naltrexone (2).

[0047] Figure 18 depicts the general synthesis of opioid antagonists.

[0048] Figure 19 depicts the effect of compound 6d of Example 38 on somatic signs of withdrawal.

[0049] Figure 20 depicts the effect of compound 6a of Example 35 on somatic signs of withdrawal.

DETAILED DESCRIPTION

[0050] The present invention pertains to analgesics and analgesic derivatives, particularly opiate-related compounds. The structure, synthesis, and biological evaluation of these compounds are described herein, as well as pharmaceutical compositions comprising these compounds and their pharmacological use such as, *e.g.*, for treatment of pain and substance addiction. In certain embodiments, the compounds described herein are related to the morphine metabolite M6G. Unexpectedly, analogues unrelated to M6G possessed more favorable pharmacological properties than M6G in several functional *in vitro* and *in vivo* tests.

[0051] *In vitro* pharmacological and metabolic studies and animal models of different components of analgesic receptor signaling and substance addiction can predict medications development that will be effective in different components of a human model in the treatment of pain and substance addiction. Using a dynamic medicinal chemistry feedback from the *in vitro* and *in vivo* components, both of which streamline information to facilitate ultimate medications development, compounds useful for, *e.g.*, treatment of pain and/or addiction have been identified. Pharmacological activity of these compounds in one or more components of the addiction cycle provides, *inter alia*, a basis for combination therapies such that multiple components of the addiction cycle can be covered by a given pharmacological agent.

[0052] For purposes of setting forth embodiments of the present invention, it is understood that the chemical formulas described herein include pharmaceutically acceptable derivatives of the respective compounds, including salts, esters, and amides, as well as all possible stereochemical arrangements of substituents, including racemic or stereochemically pure compounds.

Compounds

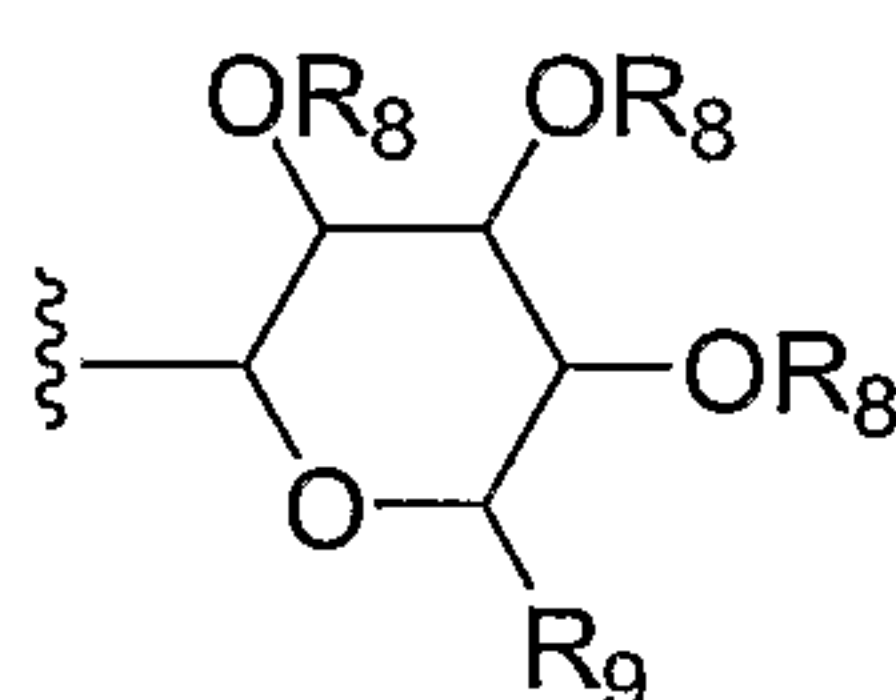
[0053] In one aspect of the present invention, compounds are provided having pharmacological activity against analgesic receptors and which are useful for, *e.g.*, the treatment of pain or diseases or disorders amenable to treatment via modulation of such receptors, including addictions. Compounds of the present invention generally have the following Formula I:

A-B-C

(I)

where A is an analgesic or derivative thereof, B is a linking group, and C is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, and a saccharide; and all pharmaceutically acceptable derivatives thereof. In preferred variations, the analgesic A is an opiate. Opiates particularly suitable for use in accordance with the invention described herein include, for example, naltrexones, phenyl piperidines, piperidinols, prodines, piperidyl propionanilides, isoprodines, prodilidines, benzomorphans, morphans, azabicyclanes, morphinans, prodines, diphenylaminoethylpropionates, methadones, isomethadones, propoxyphenes, dextromethorphans, benzazocin-8-ols, norbinaltrophines, naltrindoles, and guanidinenaltrindoles. The linking group B can be, for example, -S- or -NH(CO)(CH₂)_n-, where the subscript n is an integer of from 0 to 5.

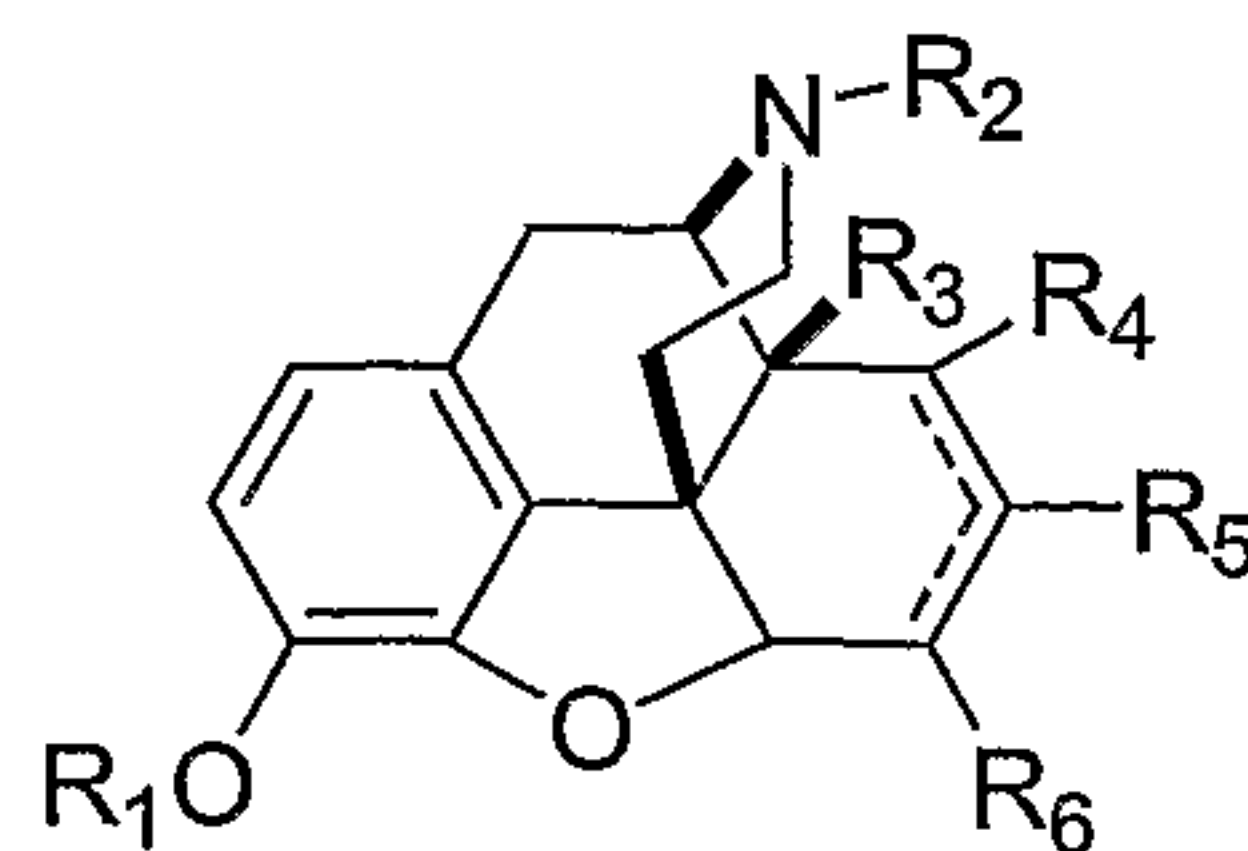
[0054] In certain embodiments, C is aryl or heteroaryl, optionally substituted with halogen, (C₁-C₅)alkoxy, nitro, or CO₂R, where R is H or (C₁-C₅)alkyl. In specific embodiments, C is, *e.g.*, phenyl, thiophene, or a saccharide. Particularly suitable saccharides are those having the following Formula II:



(II)

where each R₈ is independently H, (C₁-C₅)alkylC(O)-, (C₇-C₁₀)aralkylC(O)-, (C₇-C₁₀)aralkyl, (C₁-C₅)alkyl, (C₆-C₁₂)aryl, or (C₆-C₁₂)aryl(CO)-; R₉ is CH₂OH, CH₂O(C₁-C₅)alkyl, CH₂O₂C(C₁-C₅)alkyl, CH₂O(C₇-C₁₀)aralkyl, CH₂O(C₆-C₁₂)aryl, CO₂H, CO₂(C₁-C₅)alkyl, CO₂(C₆-C₁₂)aryl, or CO₂(C₇-C₁₀)aralkyl; and the wavy line indicates the point of attachment to the rest of the molecule.

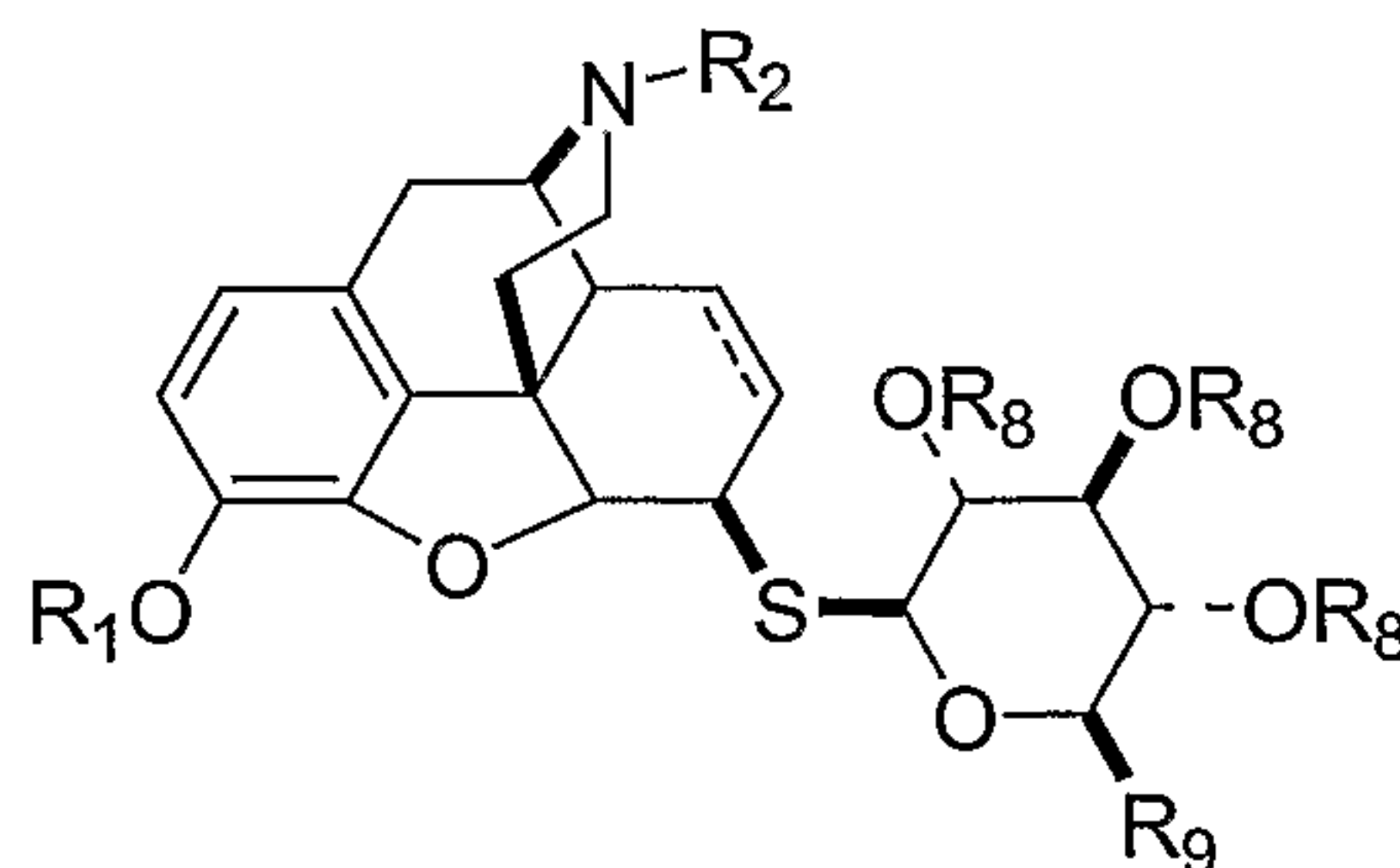
[0055] In one suitable variation, the compound has the following Formula III:



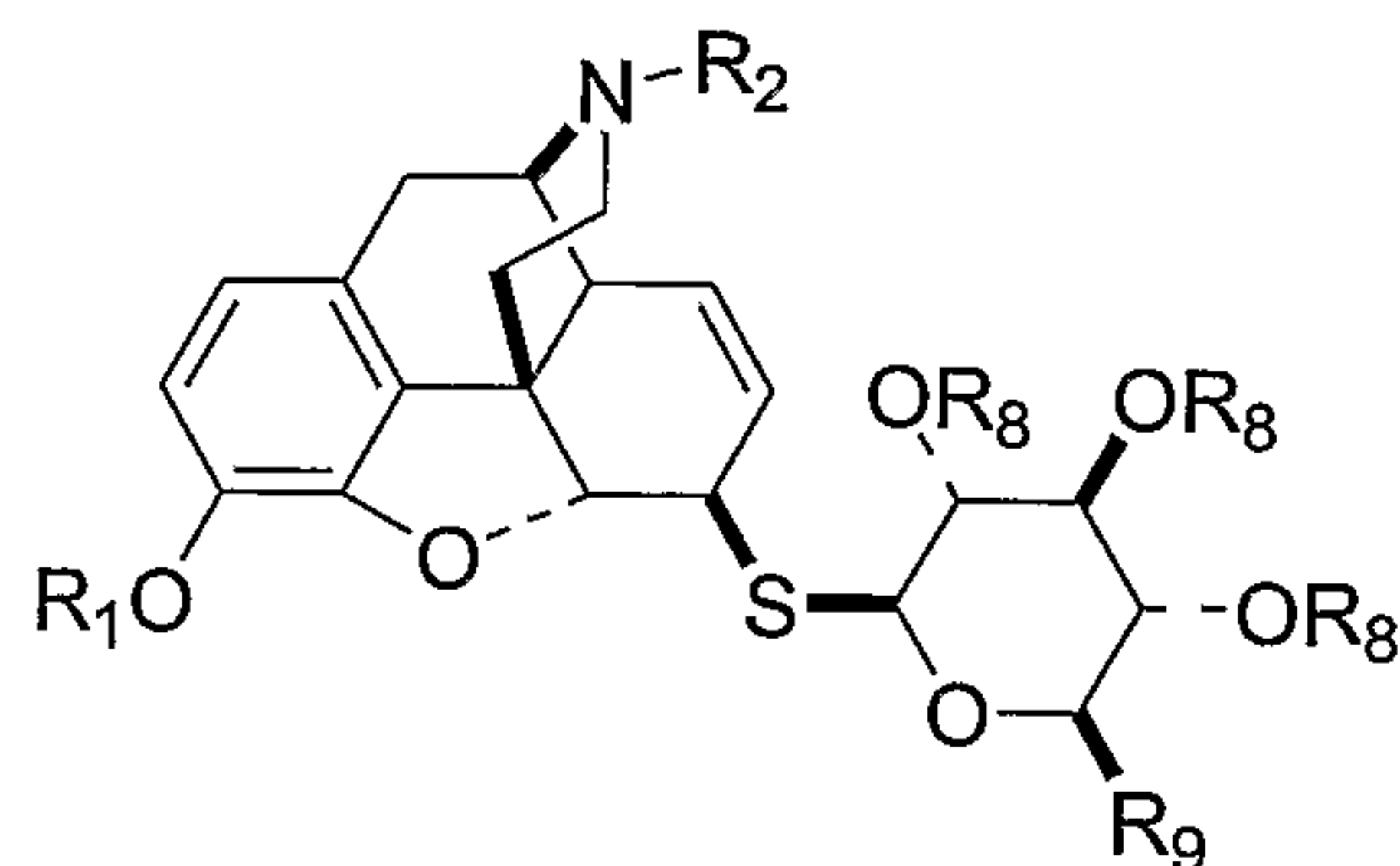
(III)

where the dashed line indicates a single, double, or normalized bond; R_1 is H, $(C_1-C_5)alkylC(O)-$, $(C_7-C_{10})aralkylC(O)-$, $(C_7-C_{10})aralkyl$, $(C_1-C_5)alkyl$, $(C_6-C_{12})aryl$, $(C_6-C_{12})aryl(CO)-$, or silyl; R_2 is $(C_1-C_5)alkyl$, $(C_3-C_6)cycloalkyl$, $(C_3-C_6)cycloalkyl-alkyl$, $(C_5-C_7)cycloalkenyl-alkyl$, $(C_6-C_{12})aryl$, $(C_7-C_{12})aralkyl$, $(C_6-C_{12})heteroaryl$, $(C_7-C_{12})heteroaralkyl$, $(C_2-C_5)alkenyl$, $(C_2-C_5)alkynyl$, optionally substituted with a substituent selected from the group consisting of halogen, $(C_1-C_5)alkoxy$, nitro, or CO_2R , where R is H or $(C_1-C_5)alkyl$; R_3 is H or OH; R_4 is H; R_5 is H or is combined with R_6 to form a heteroaryl group substituted with YR_7 ; R_6 is YR_7 or is combined with R_5 to form a heteroaryl group substituted with YR_7 ; Y is $-S-$ or $-NH(CO)(CH_2)_n-$, where the subscript n is an integer of from 0 to 5; and R_7 is an optionally substituted aryl, optionally substituted heteroaryl, or a saccharide, the saccharide having Formula II as set forth above. Particularly suitable R_2 groups include, for example, cyclopropylmethyl, cyclobutylmethyl, and allyl.

[0056] In some alternative embodiments, the compound has the following Formula IVa or IVb:



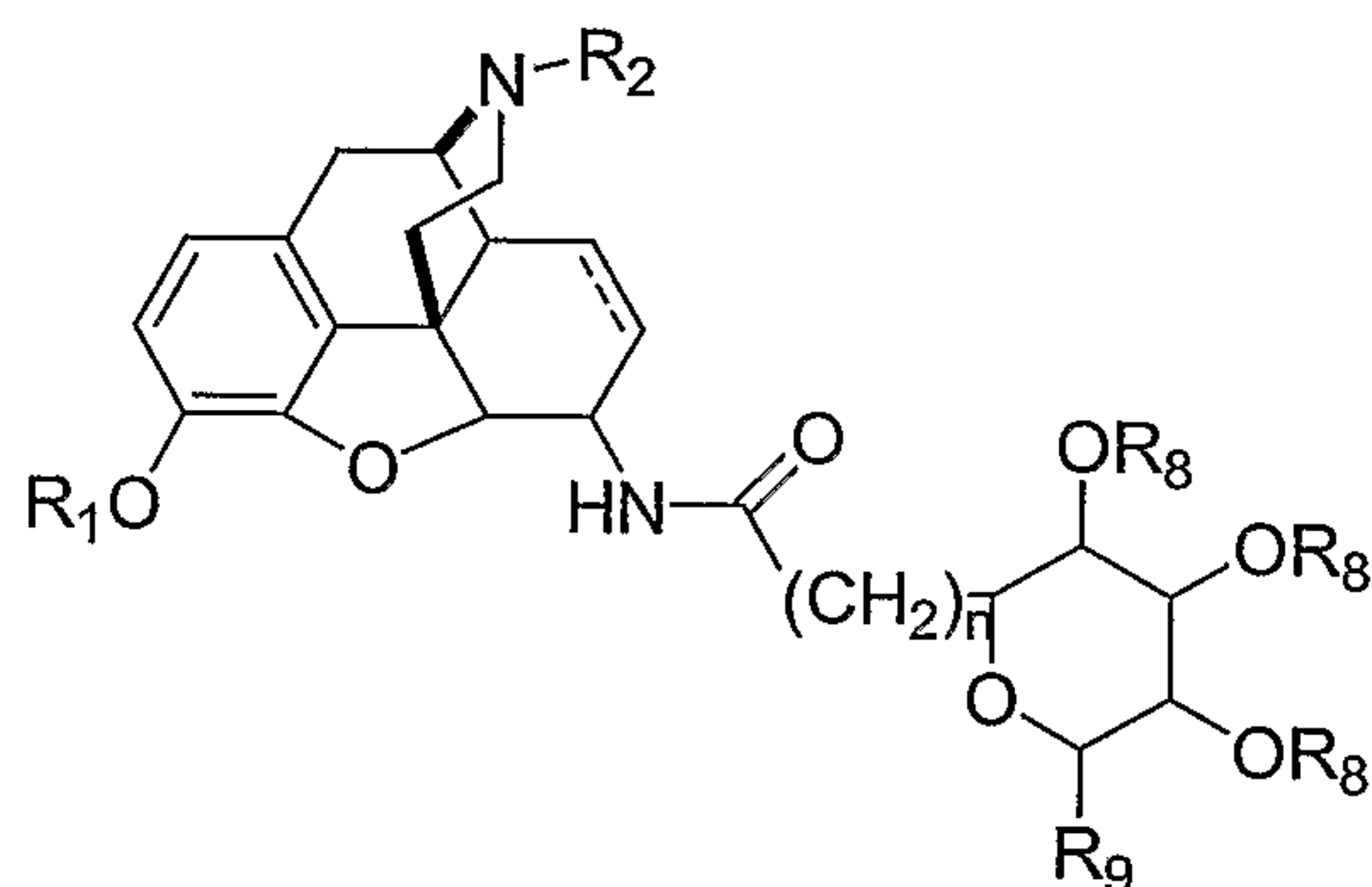
(IVa)



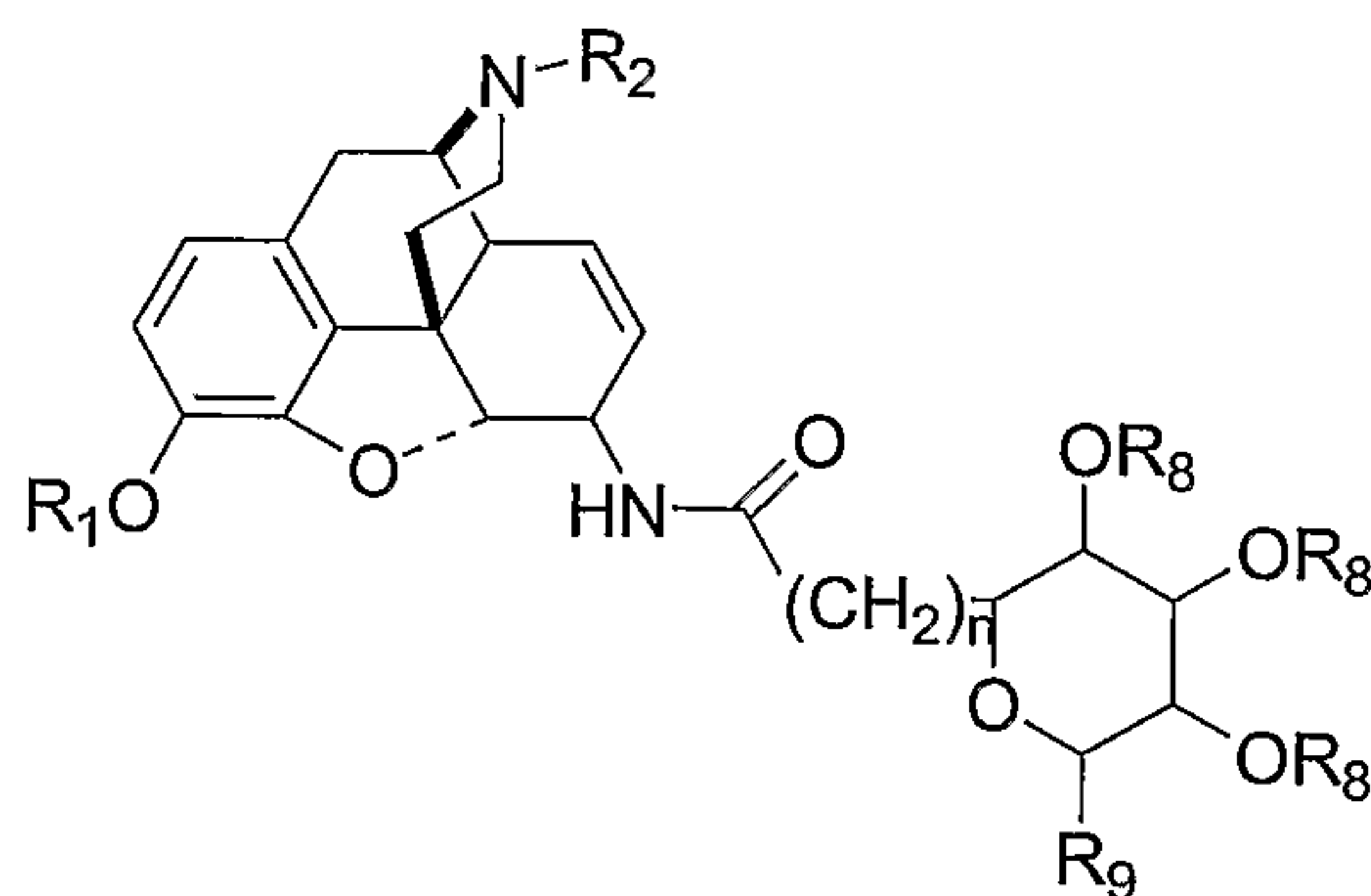
(IVb)

where R₁ is H, (C₁-C₅)alkylC(O)-, (C₇-C₁₀)araryl, or (C₁-C₅)alkyl; R₂ is (C₁-C₅)alkyl, C₃-C₆(cycloalkyl)alkyl, C₅-C₇(cycloalkenyl)alkyl, (C₆-C₁₂)aryl (C₇-C₁₂)aralkyl, trans(C₄-C₅)alkenyl, allyl, or furan-2-ylalkyl; each R₈ is independently H, (C₁-C₅)alkylC(O), (C₇-C₁₀)ararylC(O), (C₇-C₁₀)araryl, or (C₁-C₅)alkyl; and R₉ is CH₂OH, CH₂O₂C(C₁-C₅)alkyl, CH₂O(C₇-C₁₀)araryl, CO₂H, CO₂(C₁-C₅)alkyl, or CO₂(C₇-C₁₀)aralkyl.

[0057] In yet another variation, the compound has the following Formula Va or Vb:



(Va)

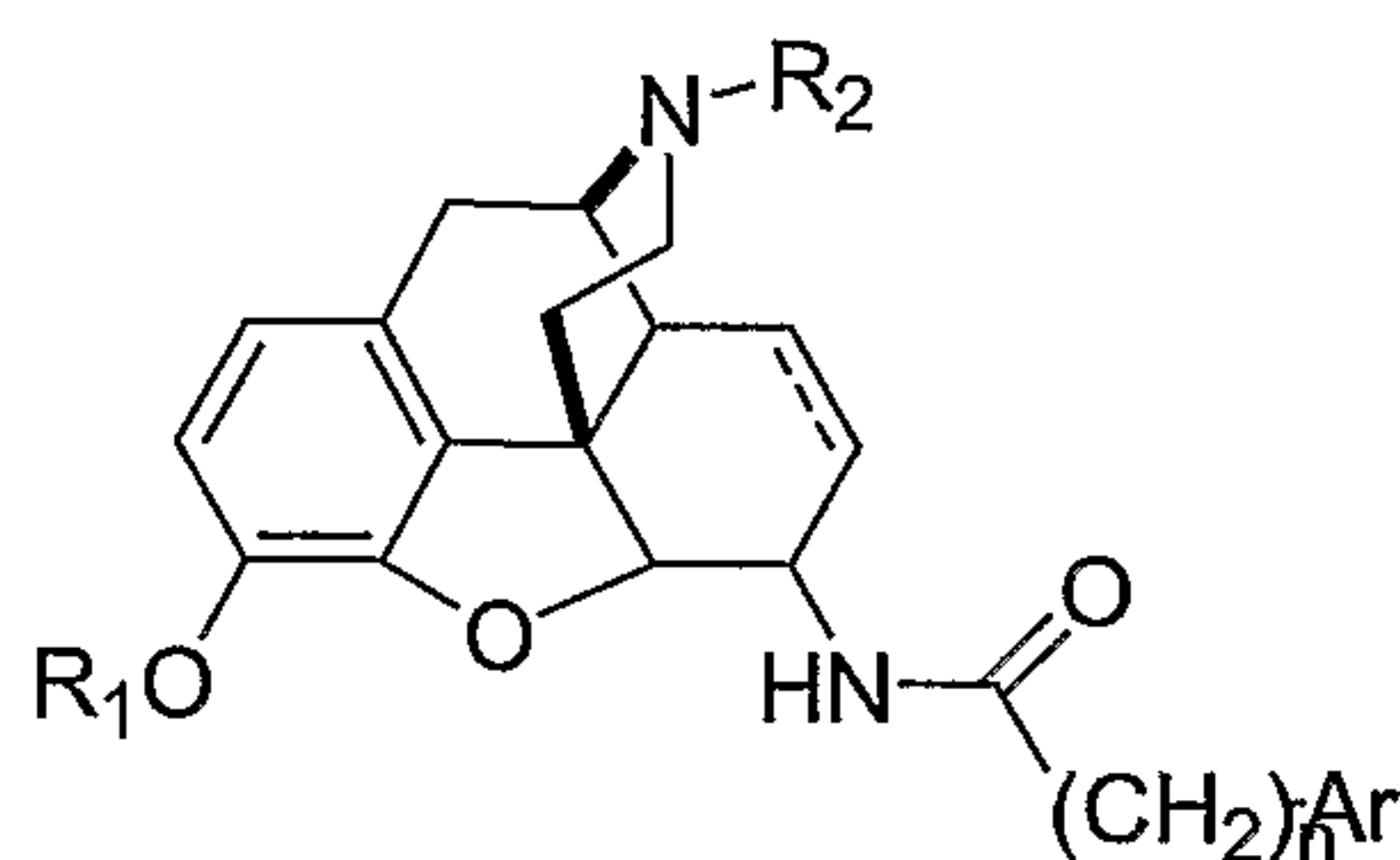


(Vb)

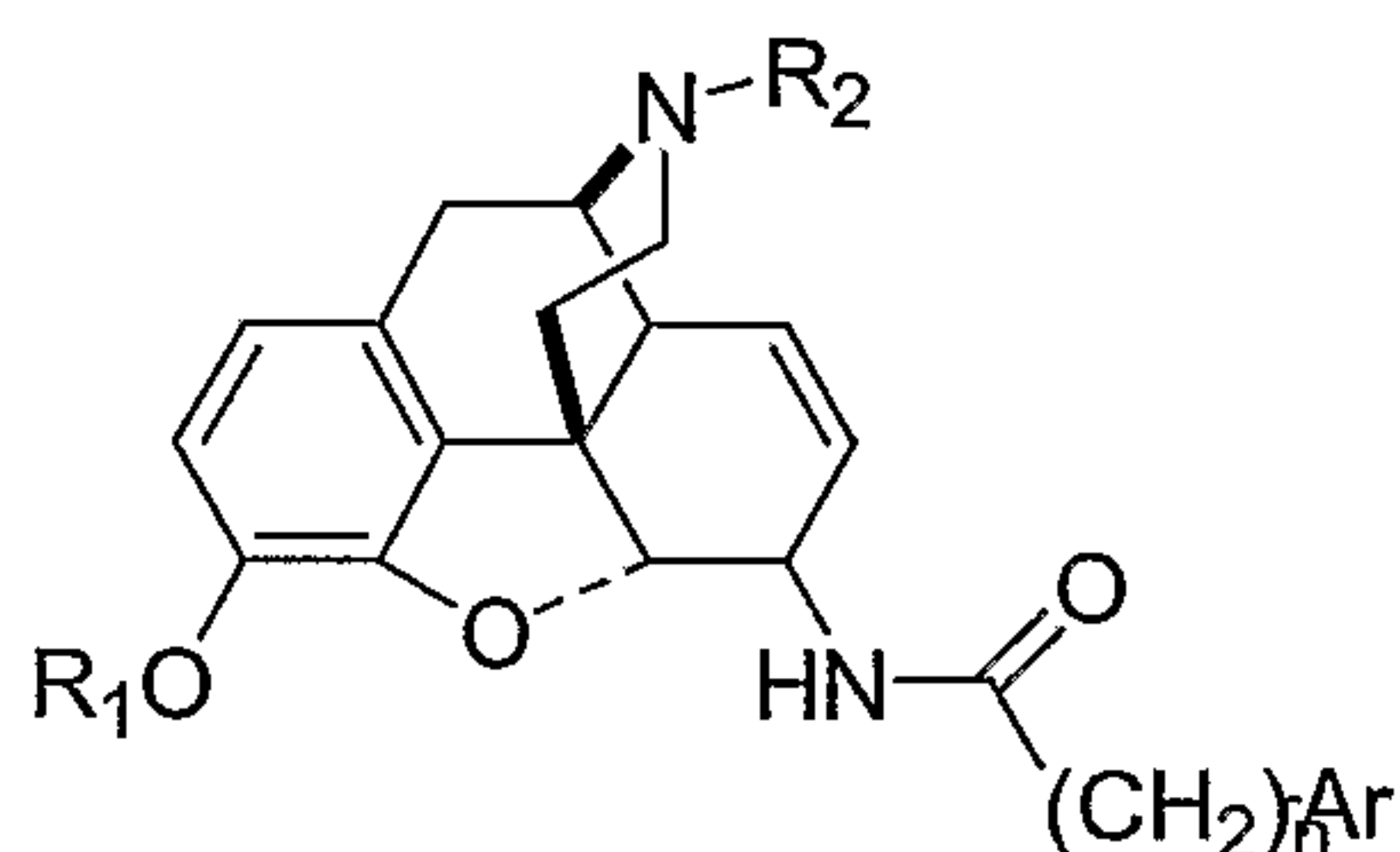
where R₁ is H, (C₁-C₅)alkylC(O)-, (C₇-C₁₀)araryl or (C₁-C₅)alkyl; R₂ is (C₁-C₅)alkyl, C₃-C₆(cycloalkyl)alkyl, C₅-C₇(cycloalkenyl)alkyl, (C₆-C₁₂)aryl (C₇-C₁₂)aralkyl, trans(C₄-

C₅)alkenyl, allyl or furan-2-ylalkyl; R₈ is independently H, (C₁-C₅)alkylC(O), (C₇-C₁₀)aralkylC(O), (C₇-C₁₀)aralkyl, or (C₁-C₅)alkyl, R₉ is CH₂OH, CH₂O₂C(C₁-C₅)alkyl, CH₂O(C₇-C₁₀)aralkyl, CO₂H, CO₂(C₁-C₅)alkyl or CO₂(C₇-C₁₀)aralkyl; and the subscript n is an integer of from 0 to 5.

[0058] In still other embodiments, the compound has the following Formulas VIa or VIb:



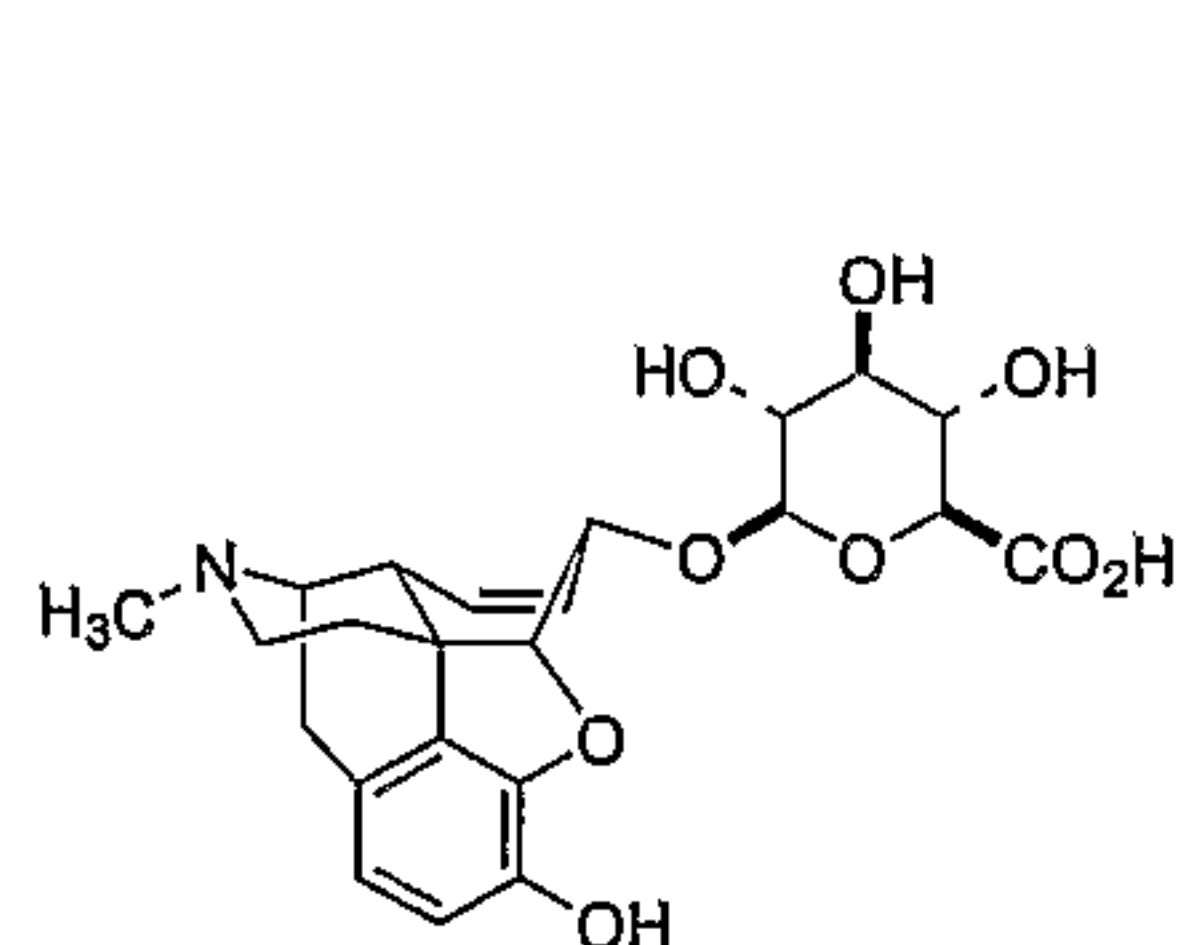
(VIa)



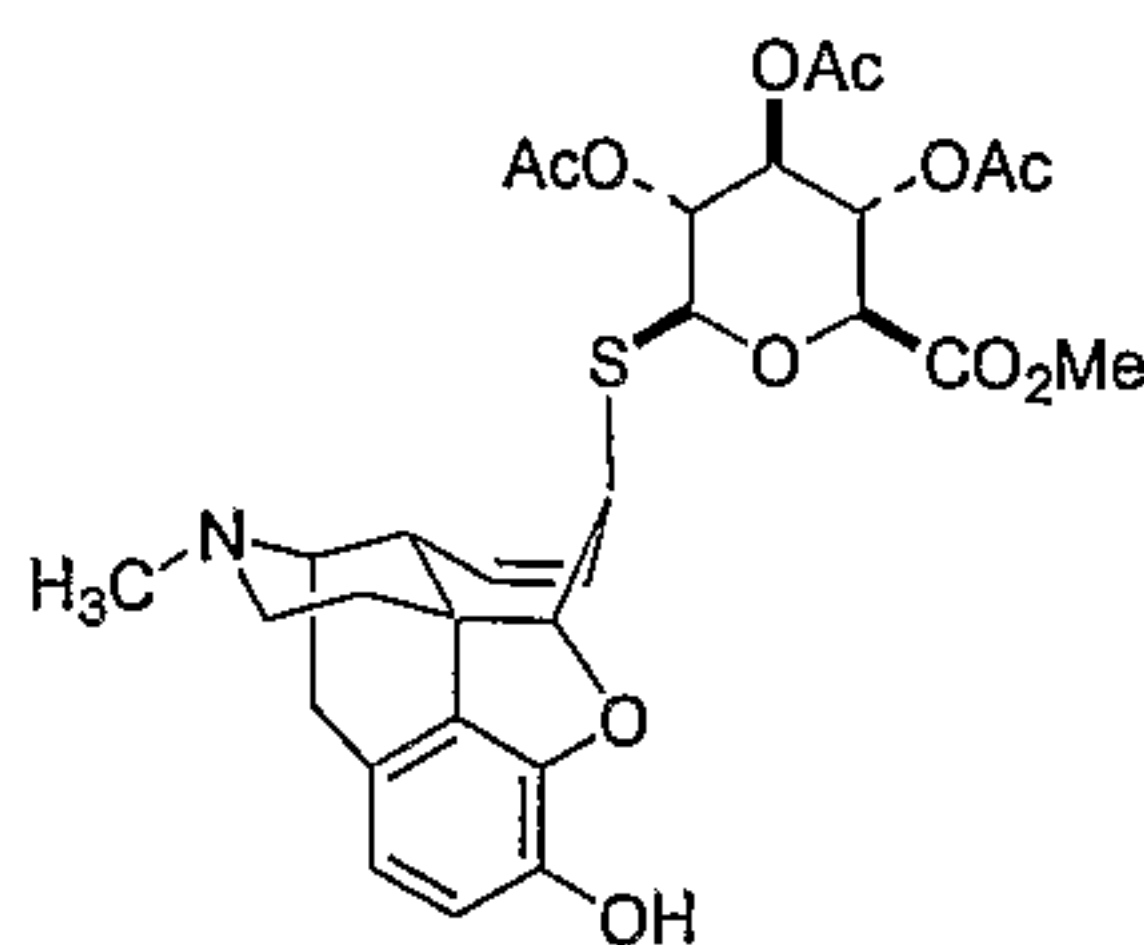
(VIb)

where R₁ is H, (C₁-C₅)alkylC(O)-, (C₇-C₁₀)aralkyl, or (C₁-C₅)alkyl; R₂ is (C₁-C₅)alkyl, C₃-C₆(cycloalkyl)alkyl, C₅-C₇(cycloalkenyl)alkyl, (C₆-C₁₂)aryl (C₇-C₁₂)aralkyl, trans(C₄-C₅)alkenyl, allyl, or furan-2-ylalkyl; and the subscript n is an integer of from 0 to 5.

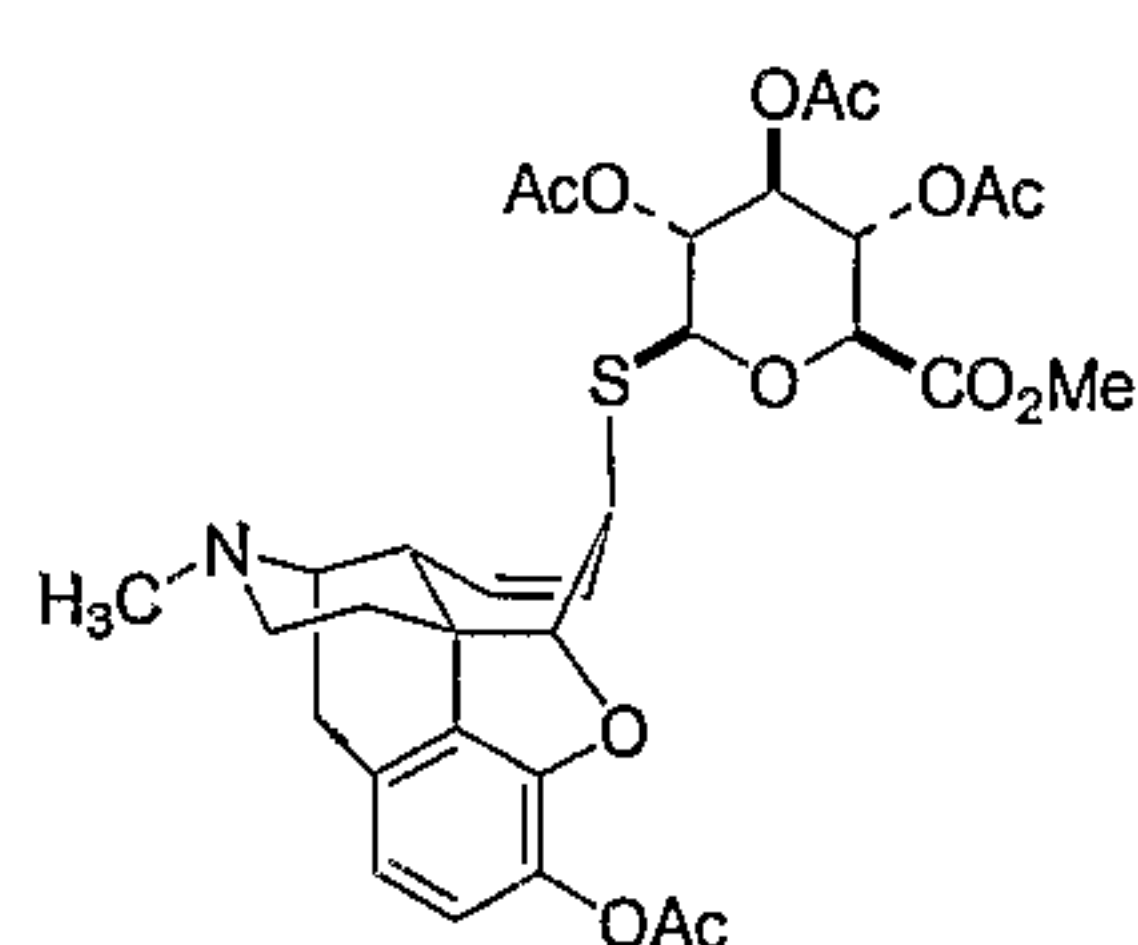
[0059] In specific embodiments, the compound of the present invention has any one of the following Formulas VII through XXX:



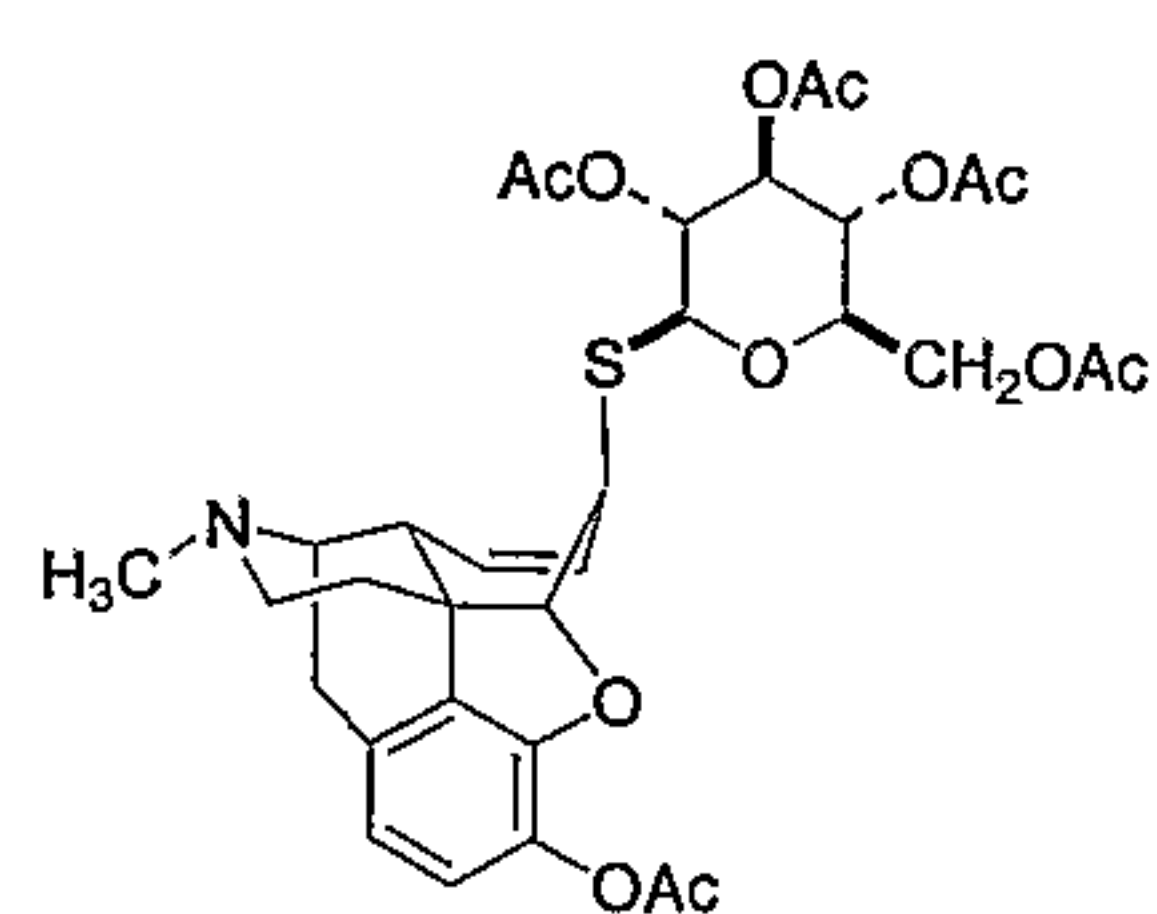
(VII)



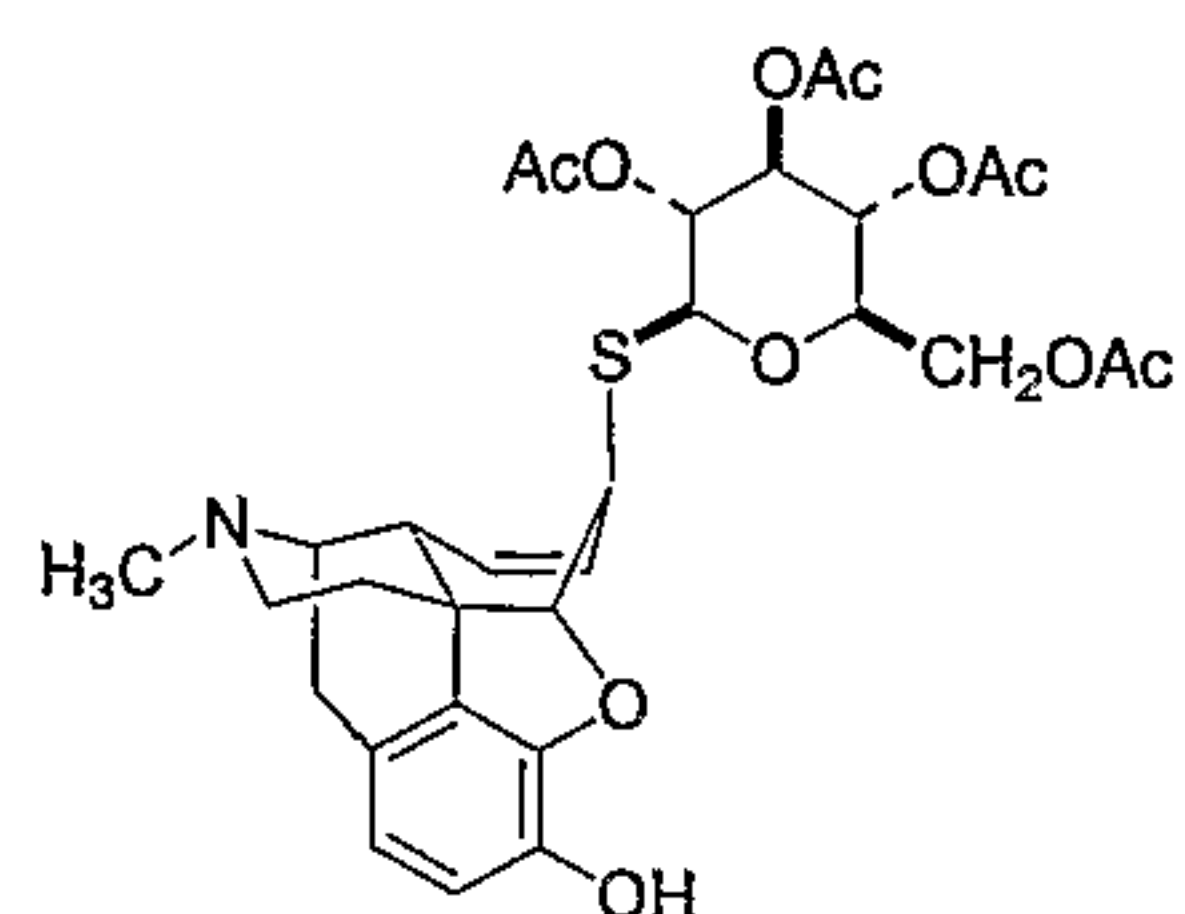
(VIII)



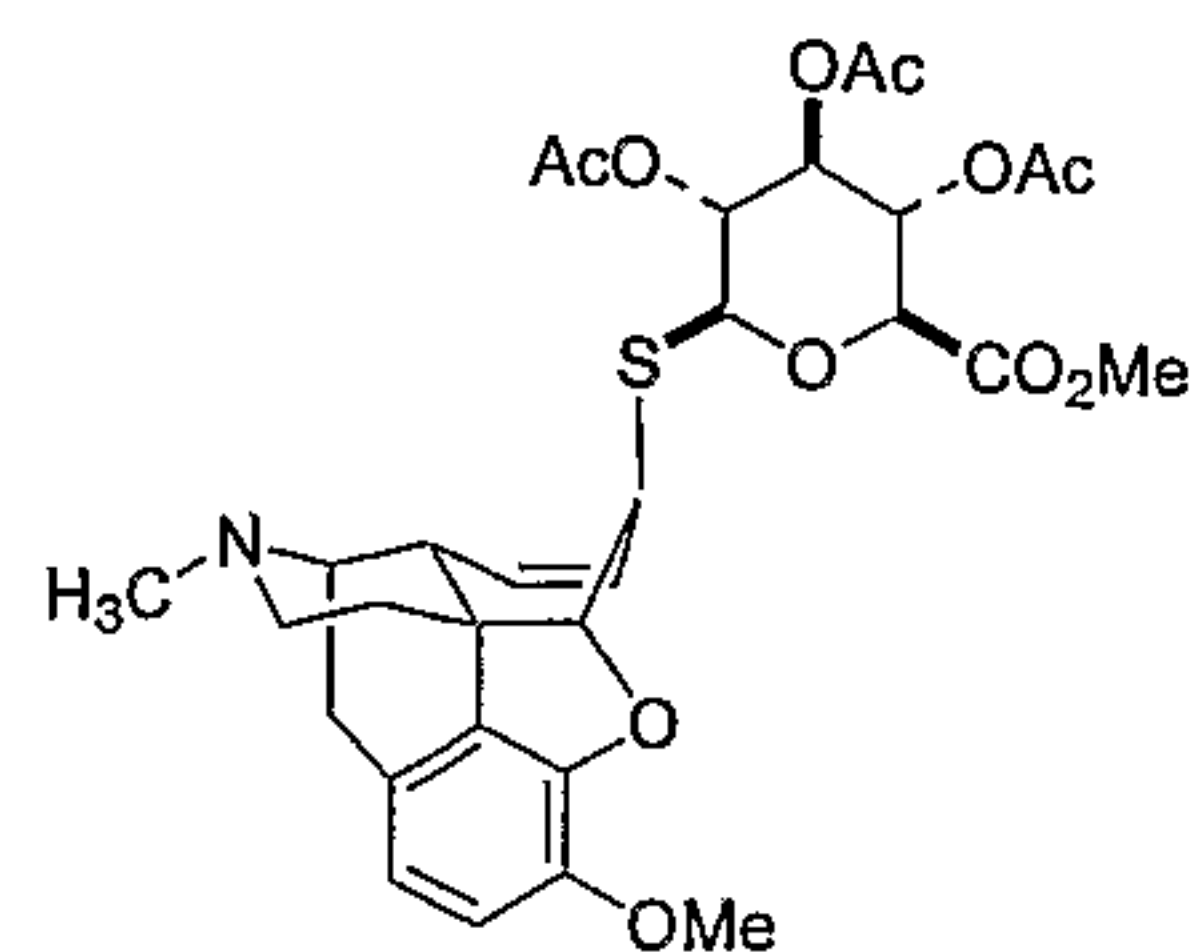
(VIX)



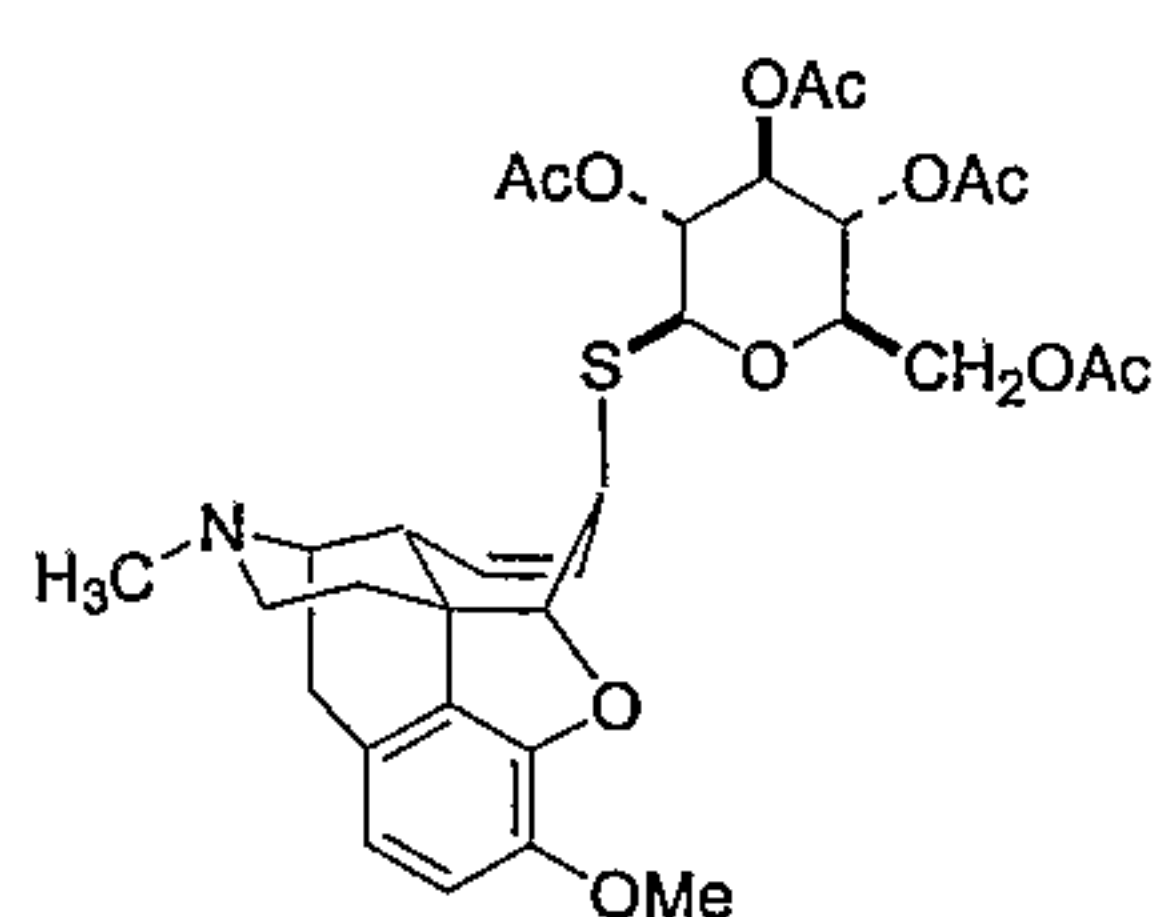
(X)



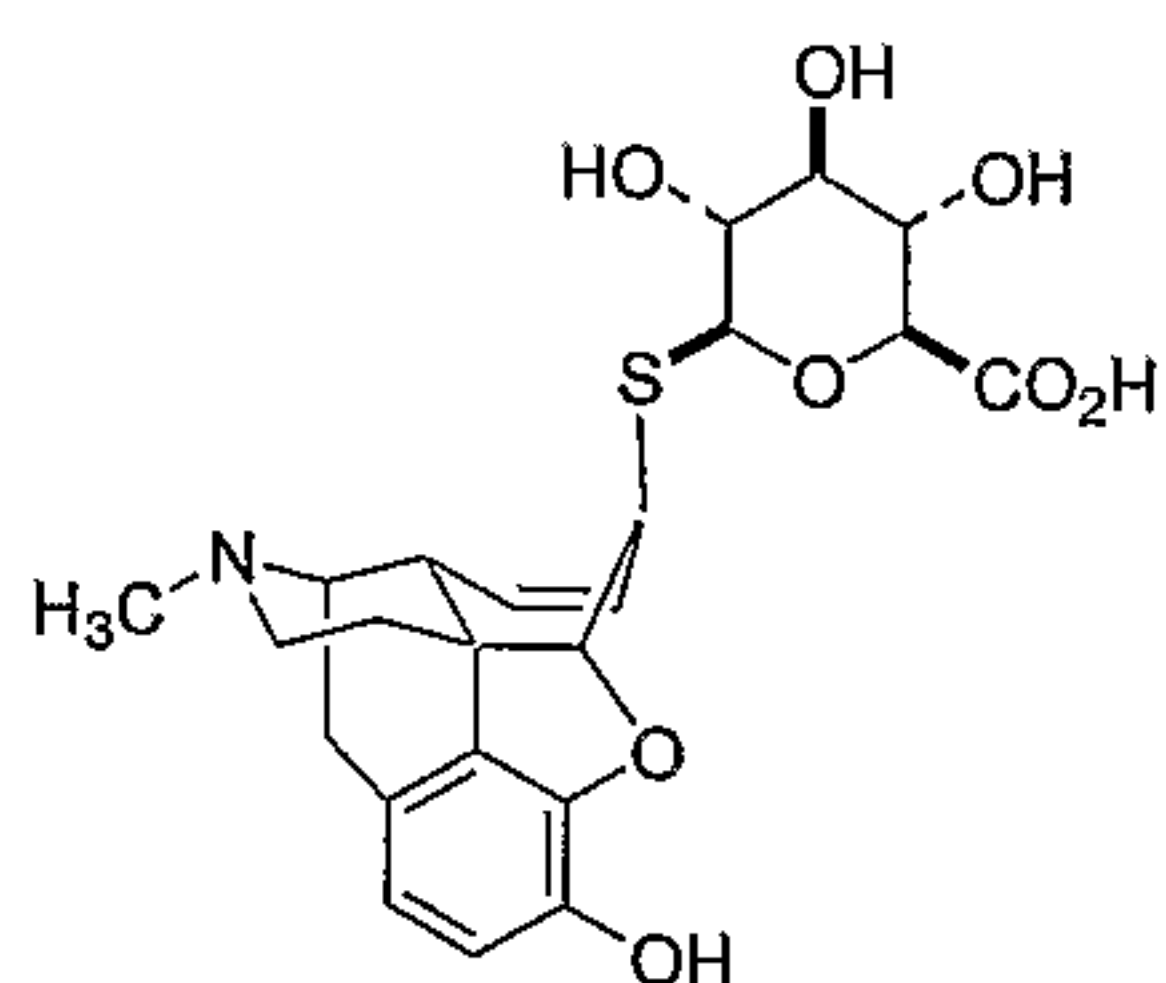
(XI)



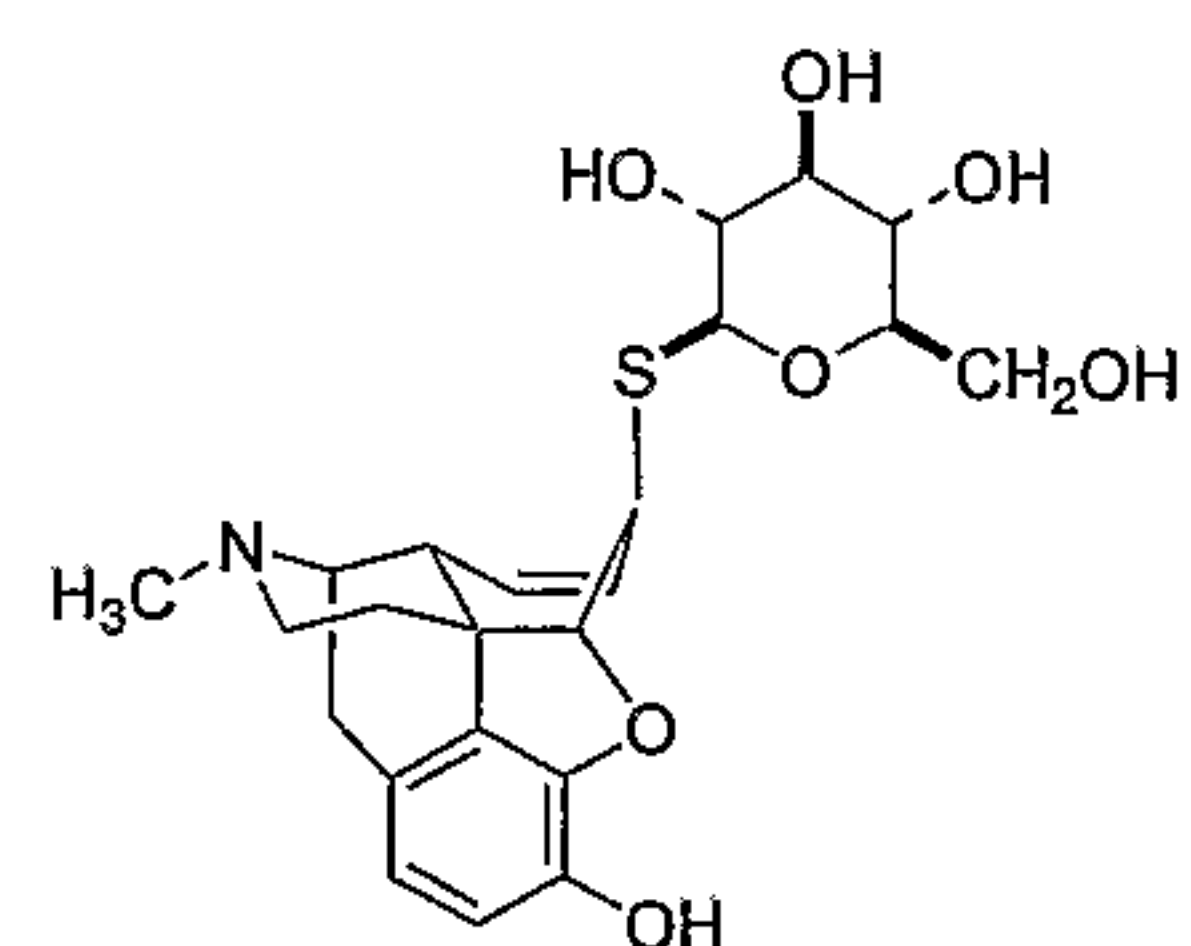
(XII)



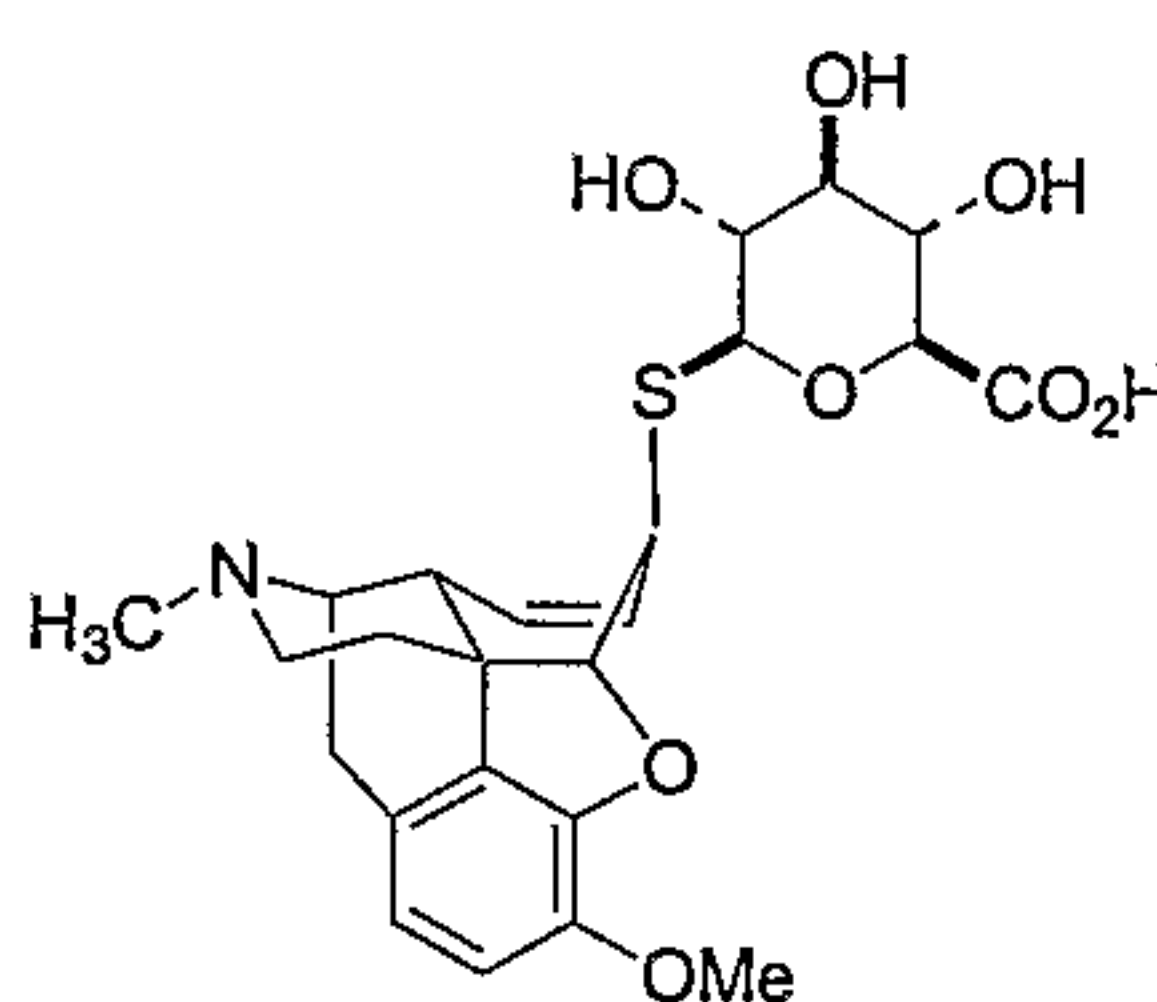
(XIII)



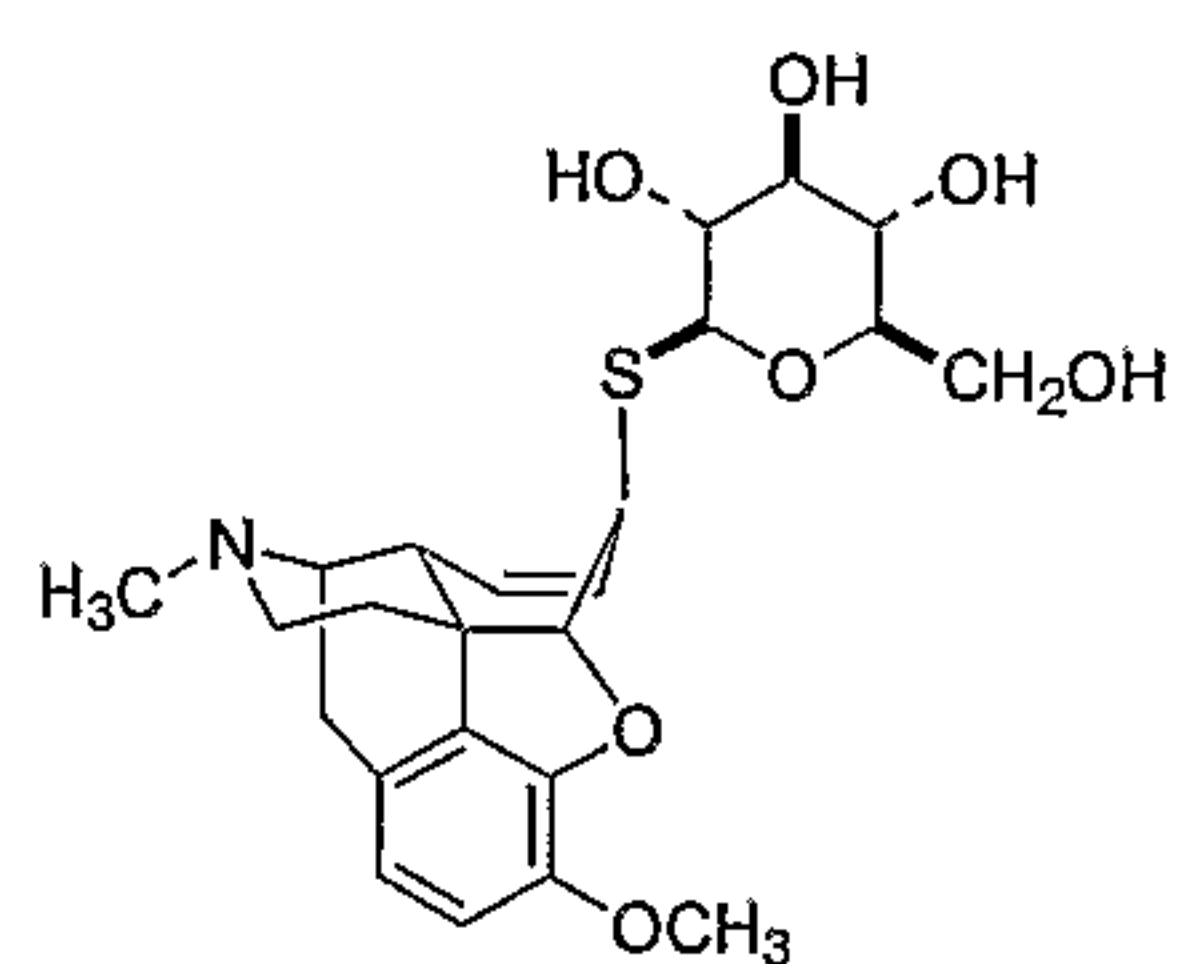
(XIV)



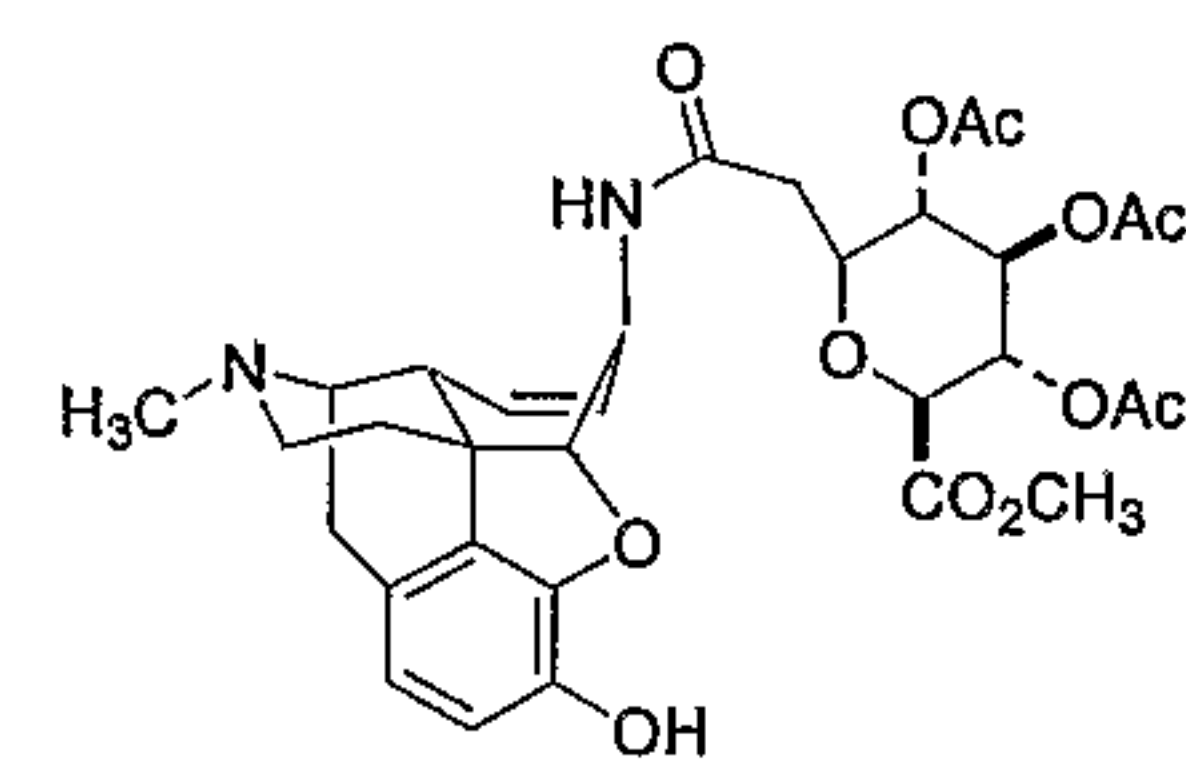
(XV)



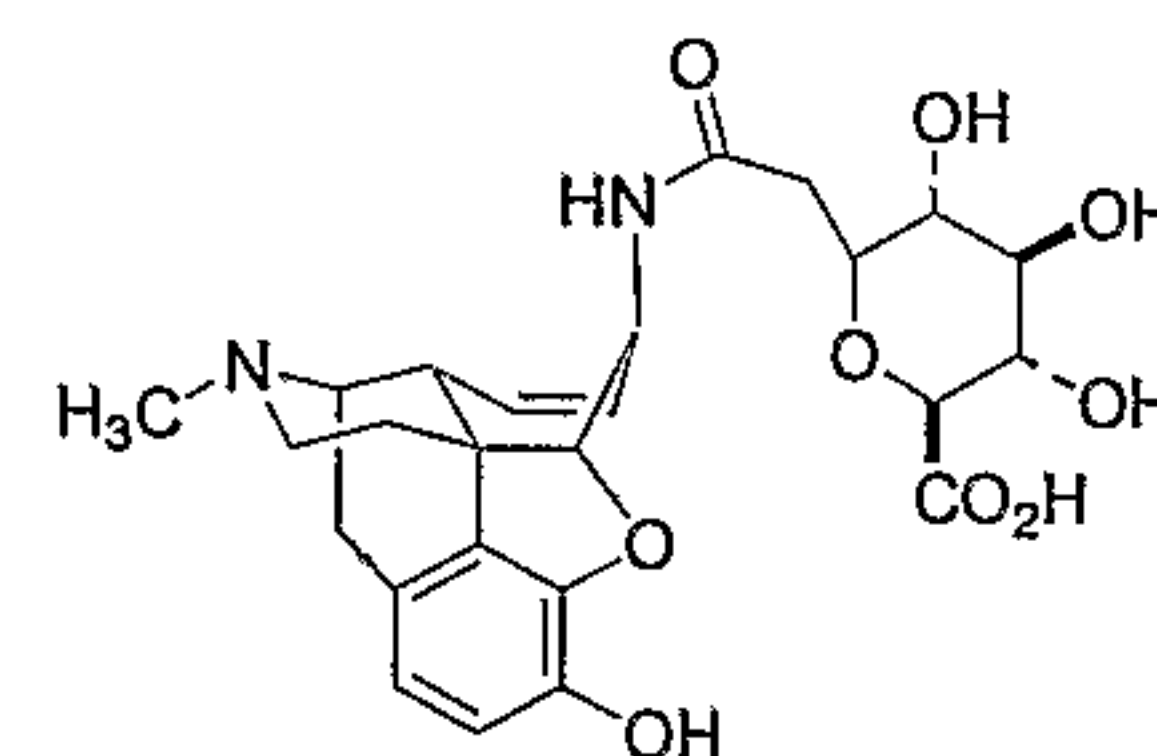
(XVI)



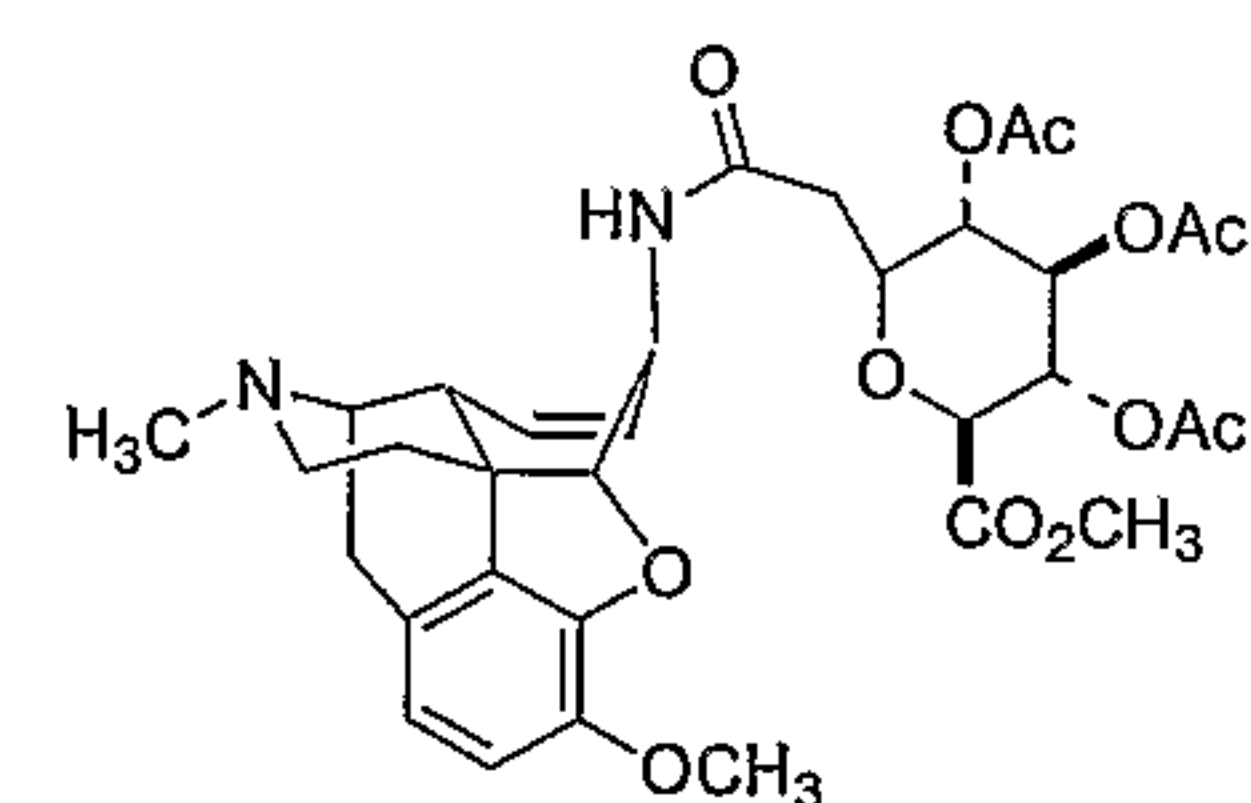
(XVII)



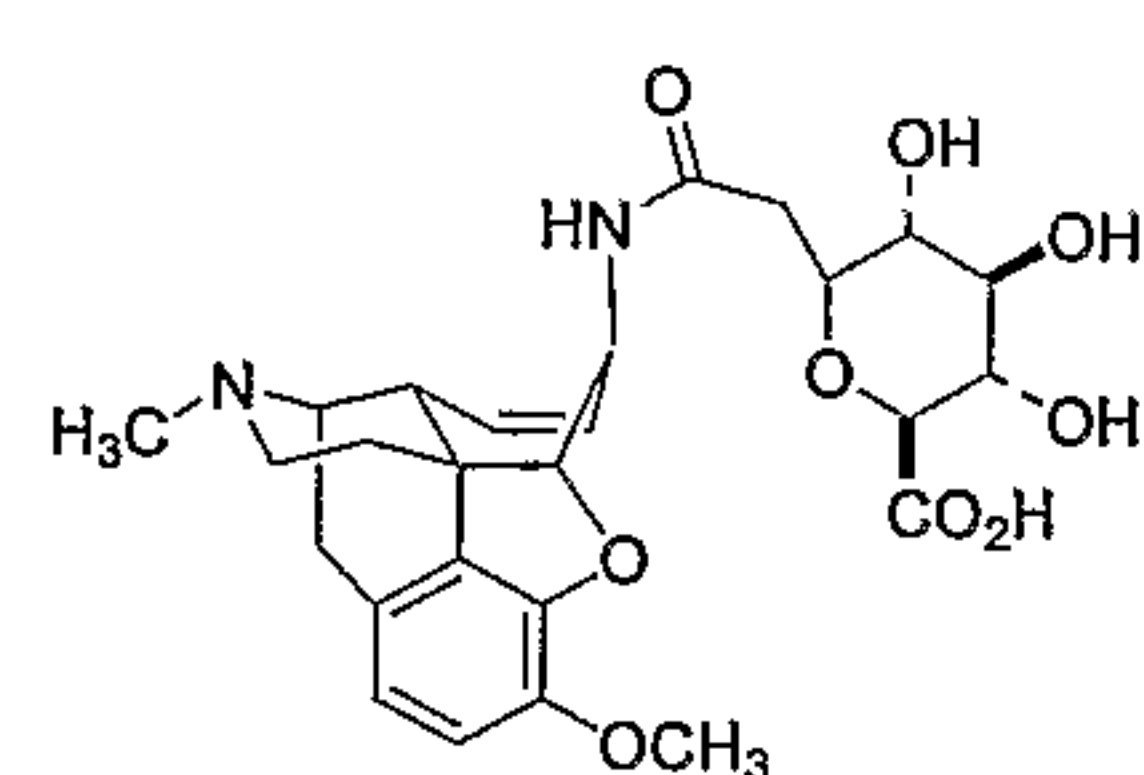
(XVIII)



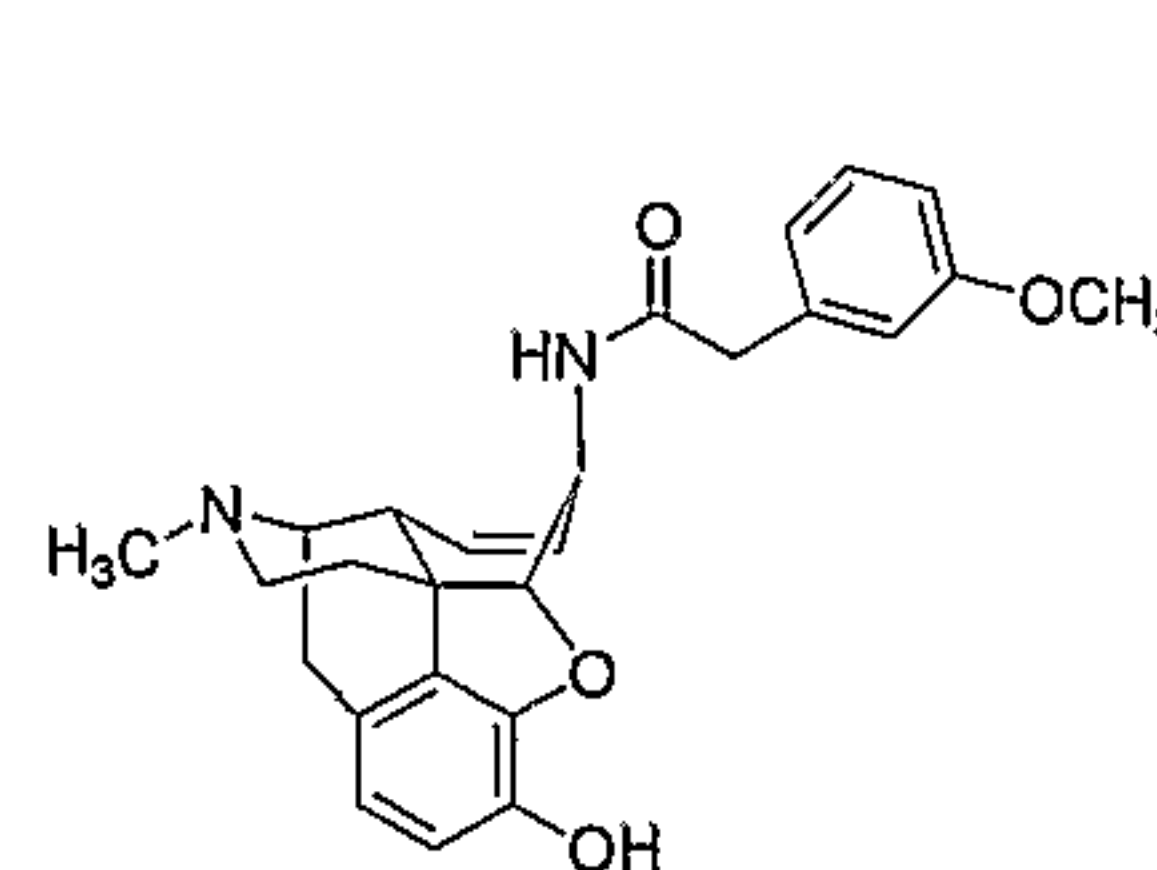
(XIX)



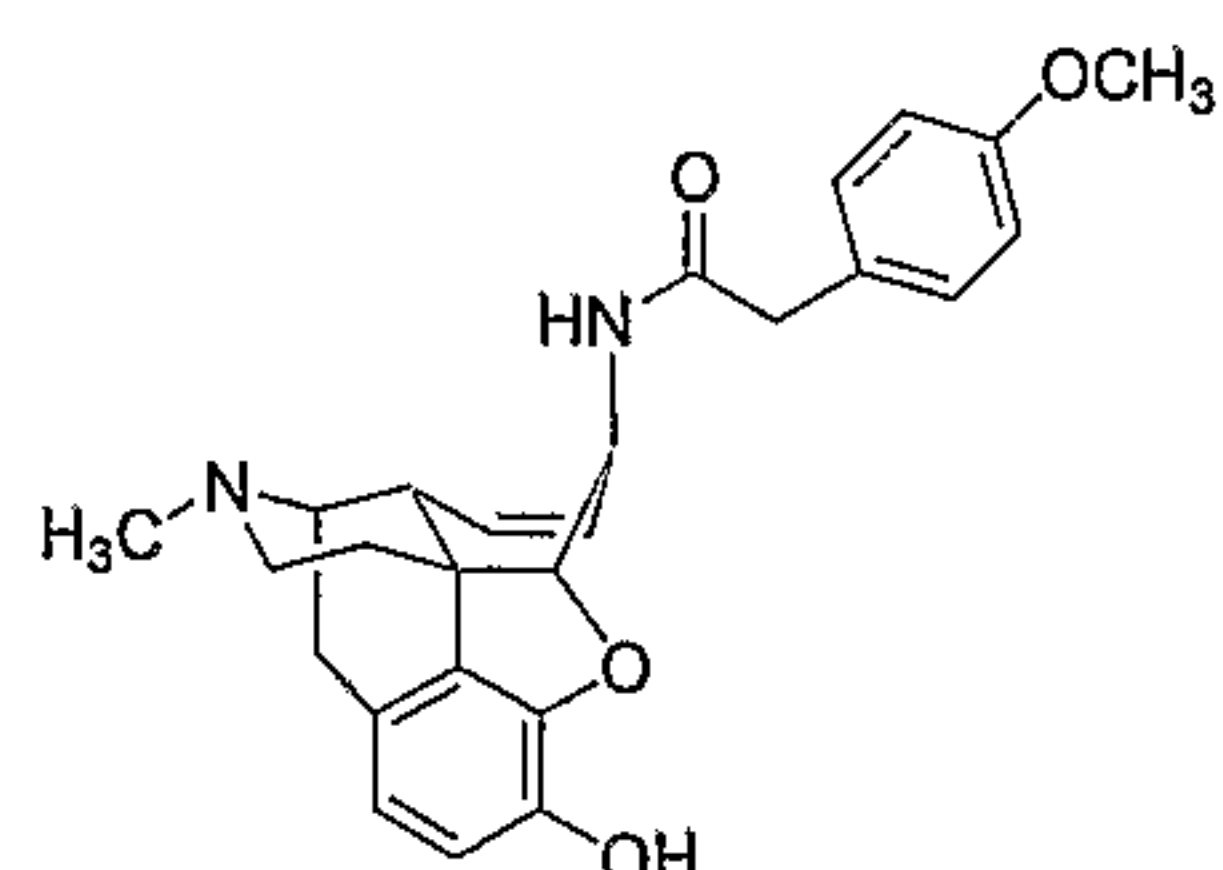
(XX)



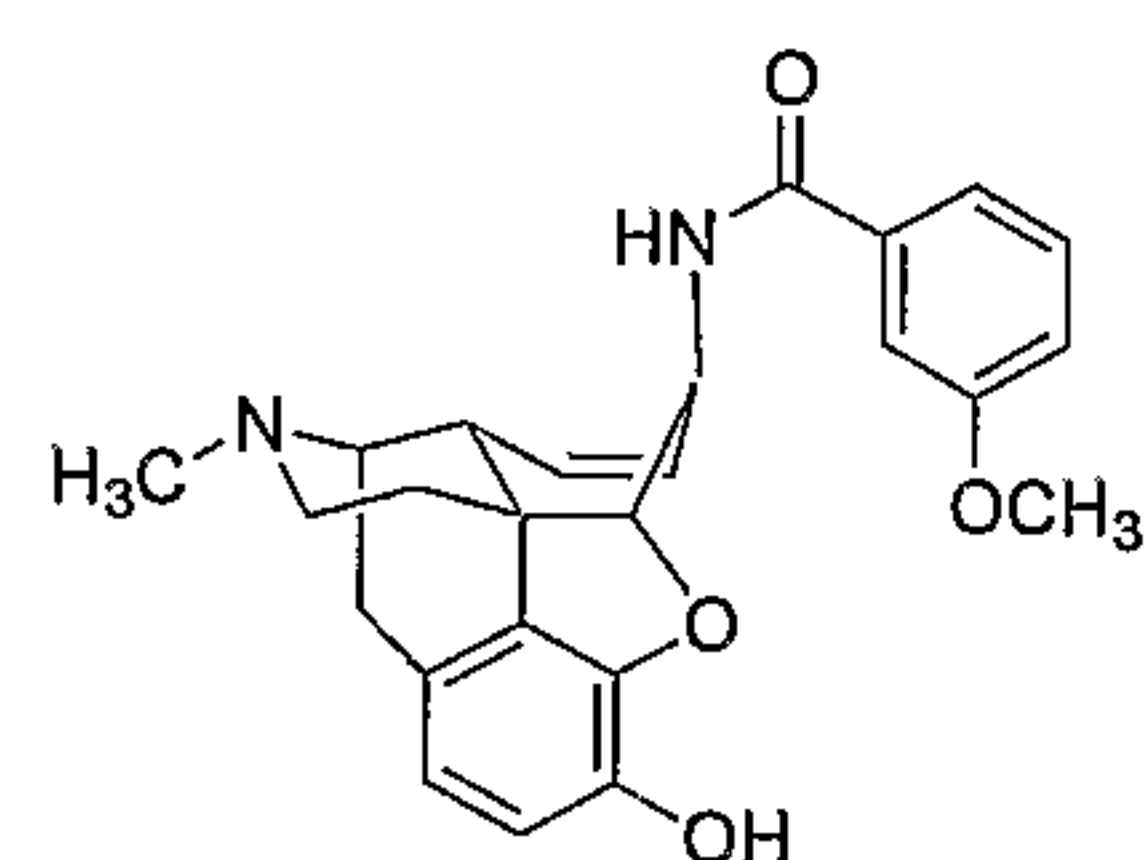
(XXI)



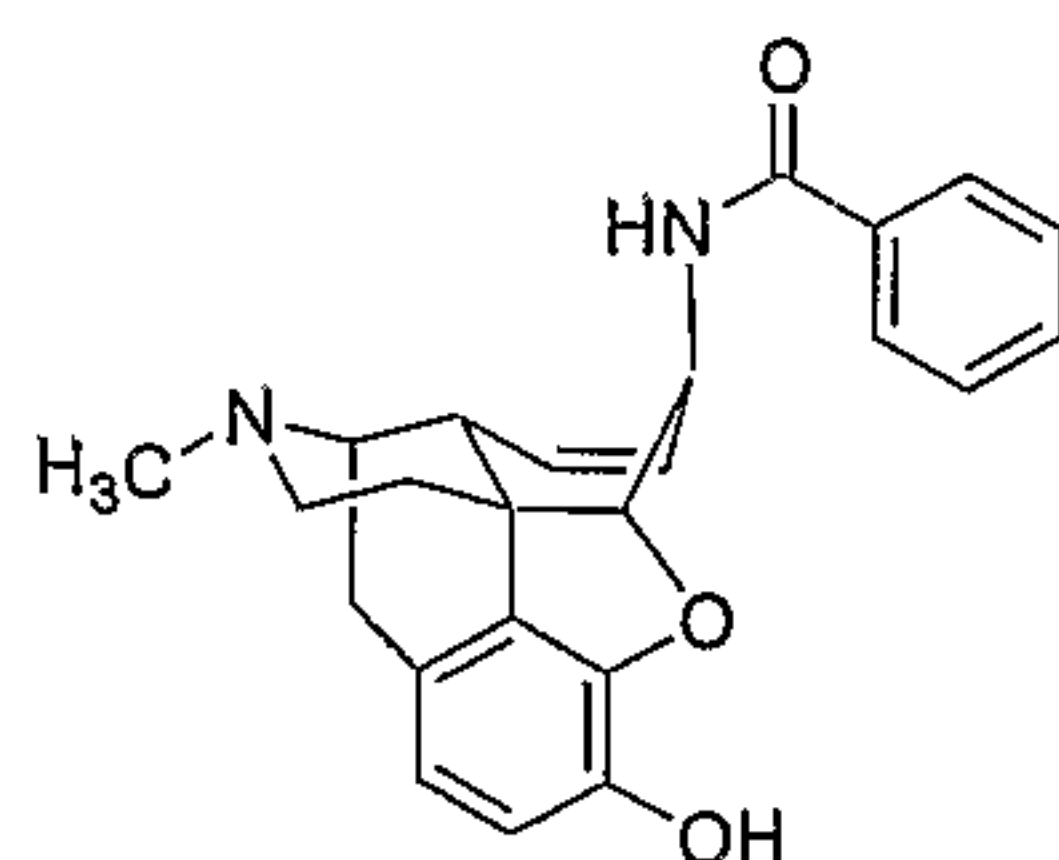
(XXII)



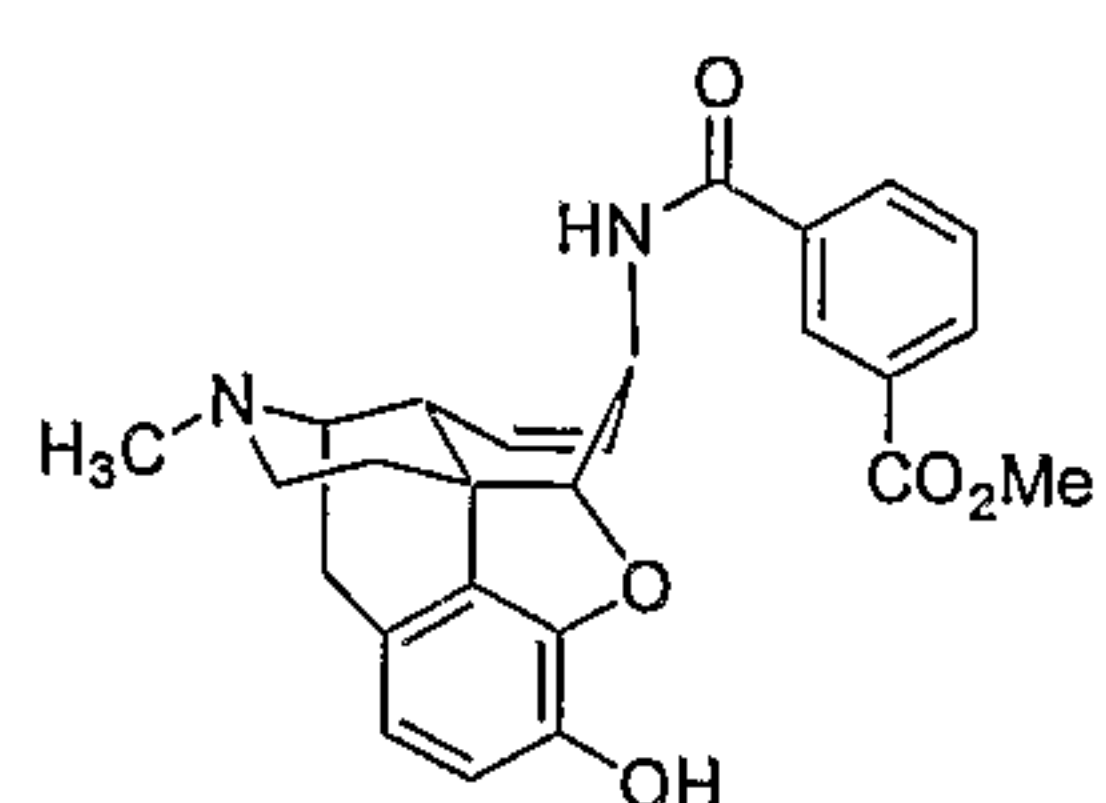
(XXIII)



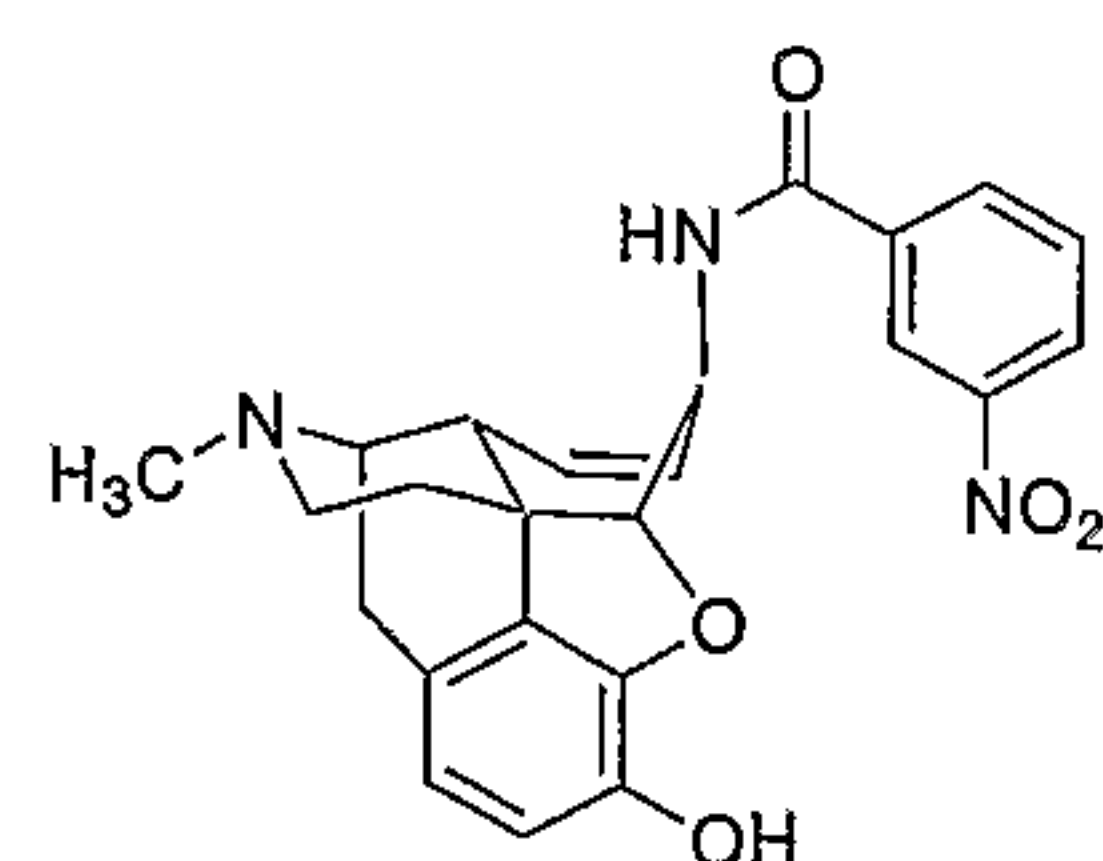
(XXIV)



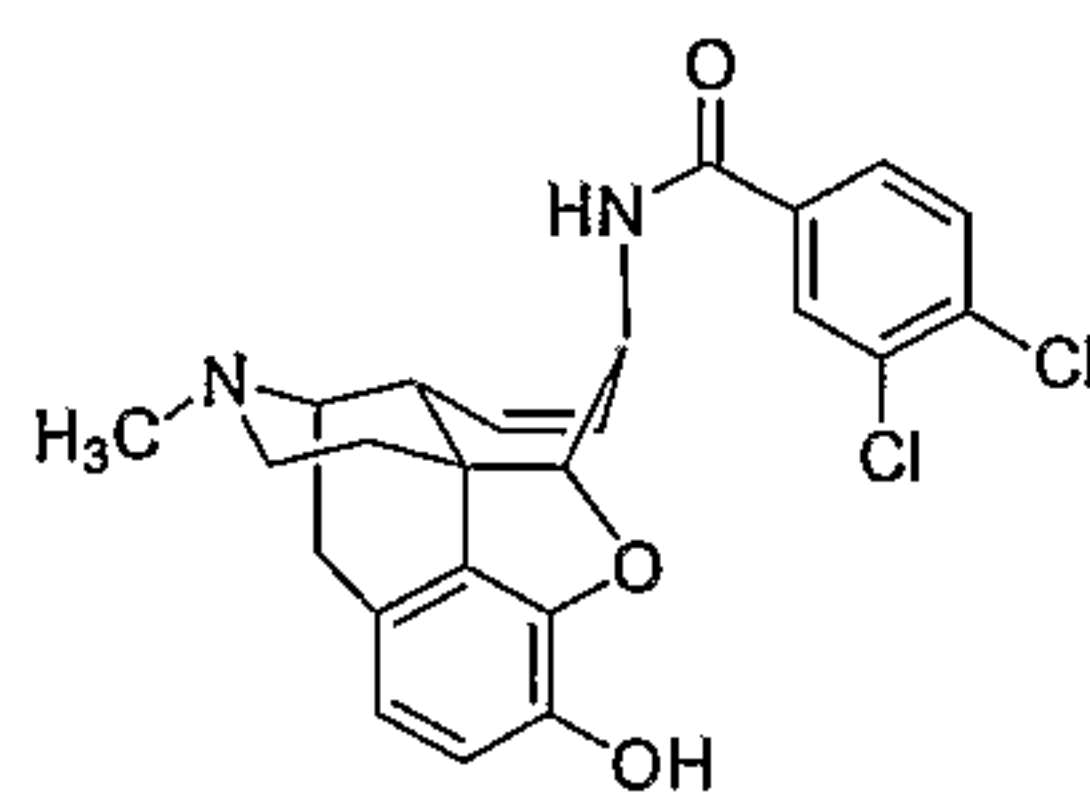
(XXV)



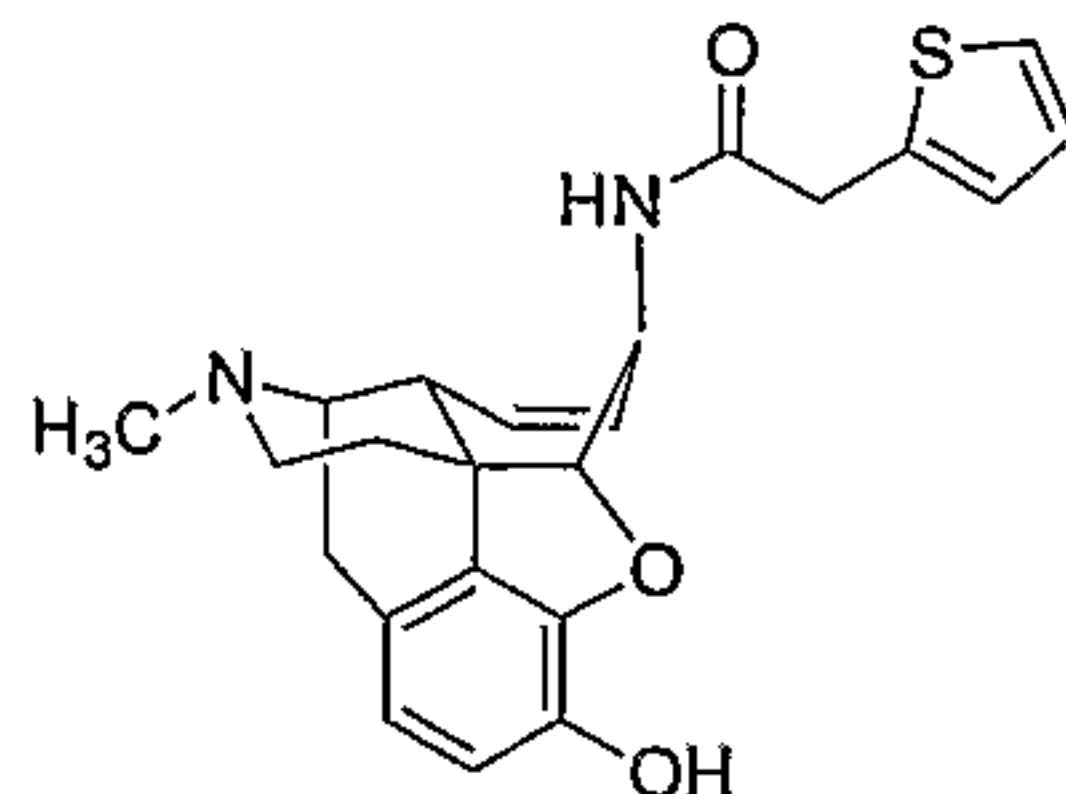
(XXVI)



(XXVII)

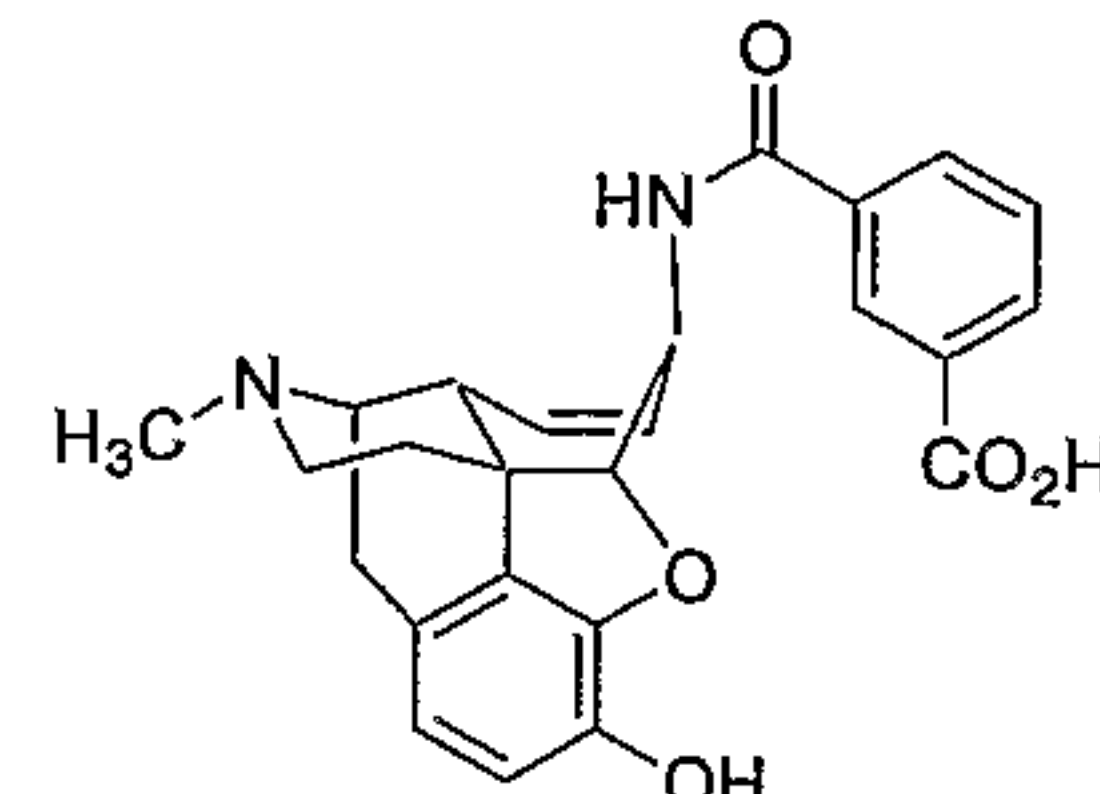


(XXVIII)



(XXIX)

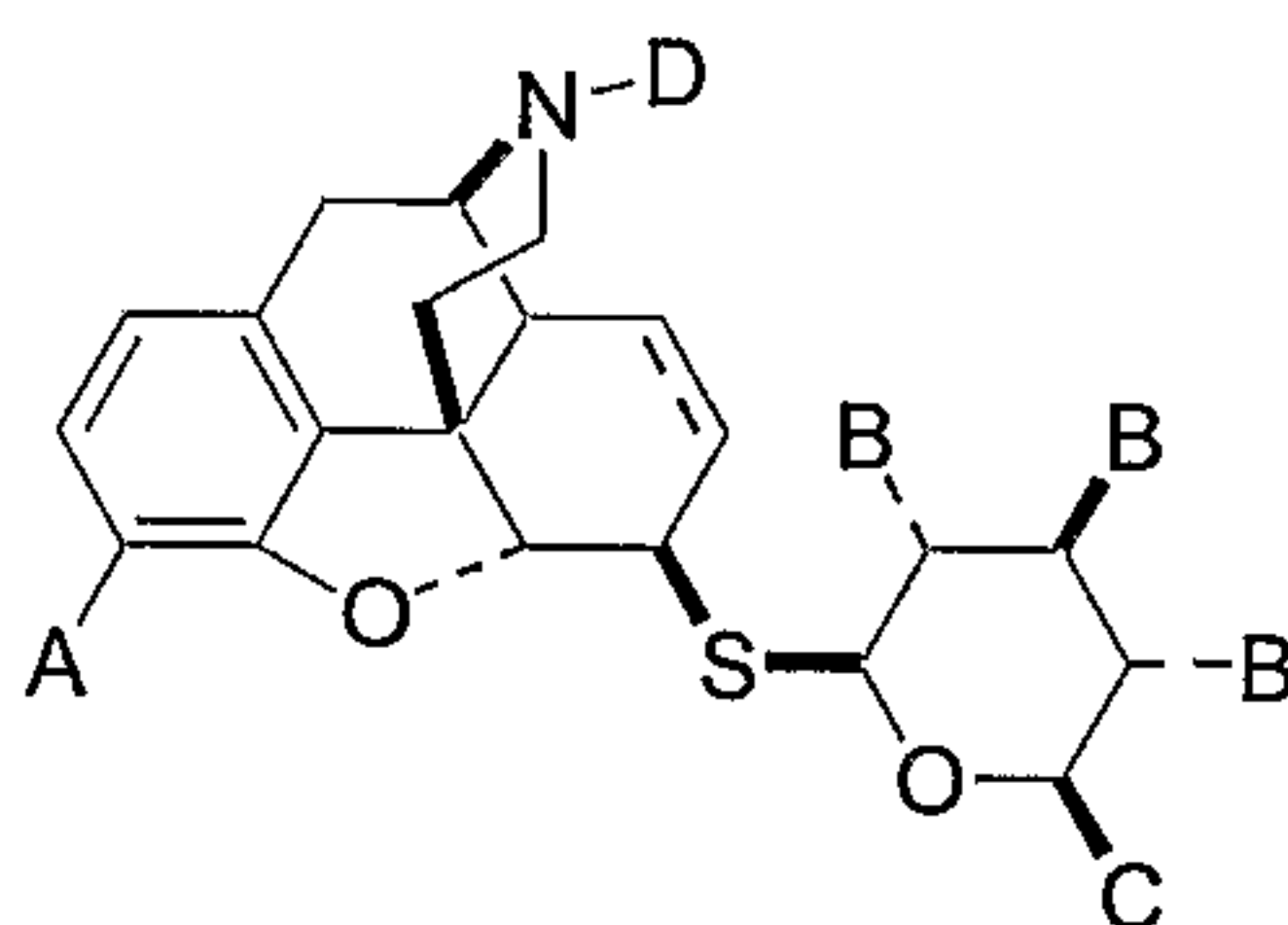
and



(XXX)

Other Embodiments

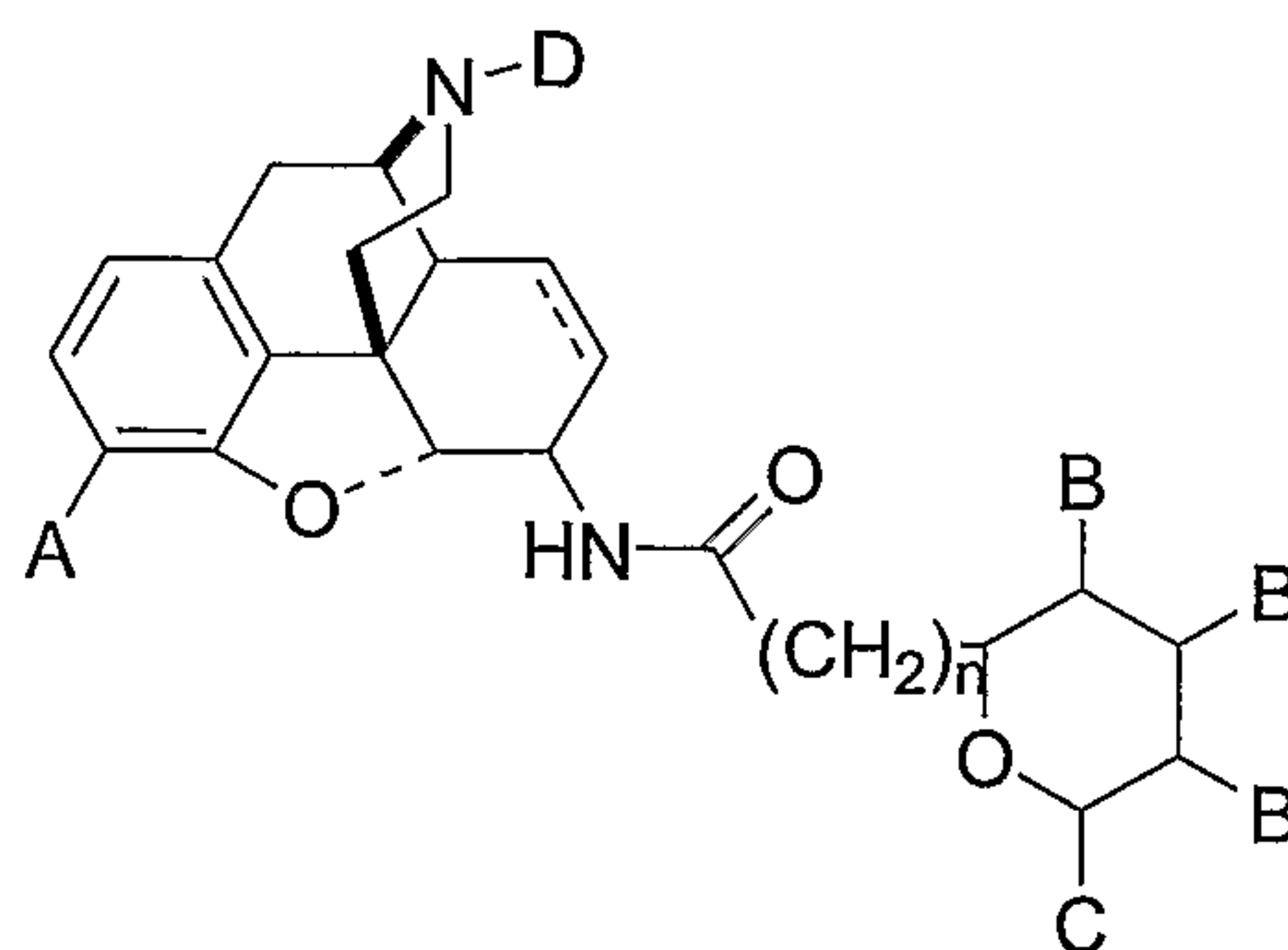
[0060] In certain embodiments, compounds of the present invention include morphine, dihydromorphine-6-glucuronide, codeine, and dihydrocodeine-6-glucuronide sulfur analogues having the following Formula IV:



(IV)

wherein A is OR, OH, or OC(O)R; B is OC(O)R, OH, or OR; C is CO₂R, CO₂H, CH₂OR, or CH₂OH; D is alkyl, cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, or optionally substituted aralkyl; and R in the substituents A, B, C, D is an alkyl or aryl group.

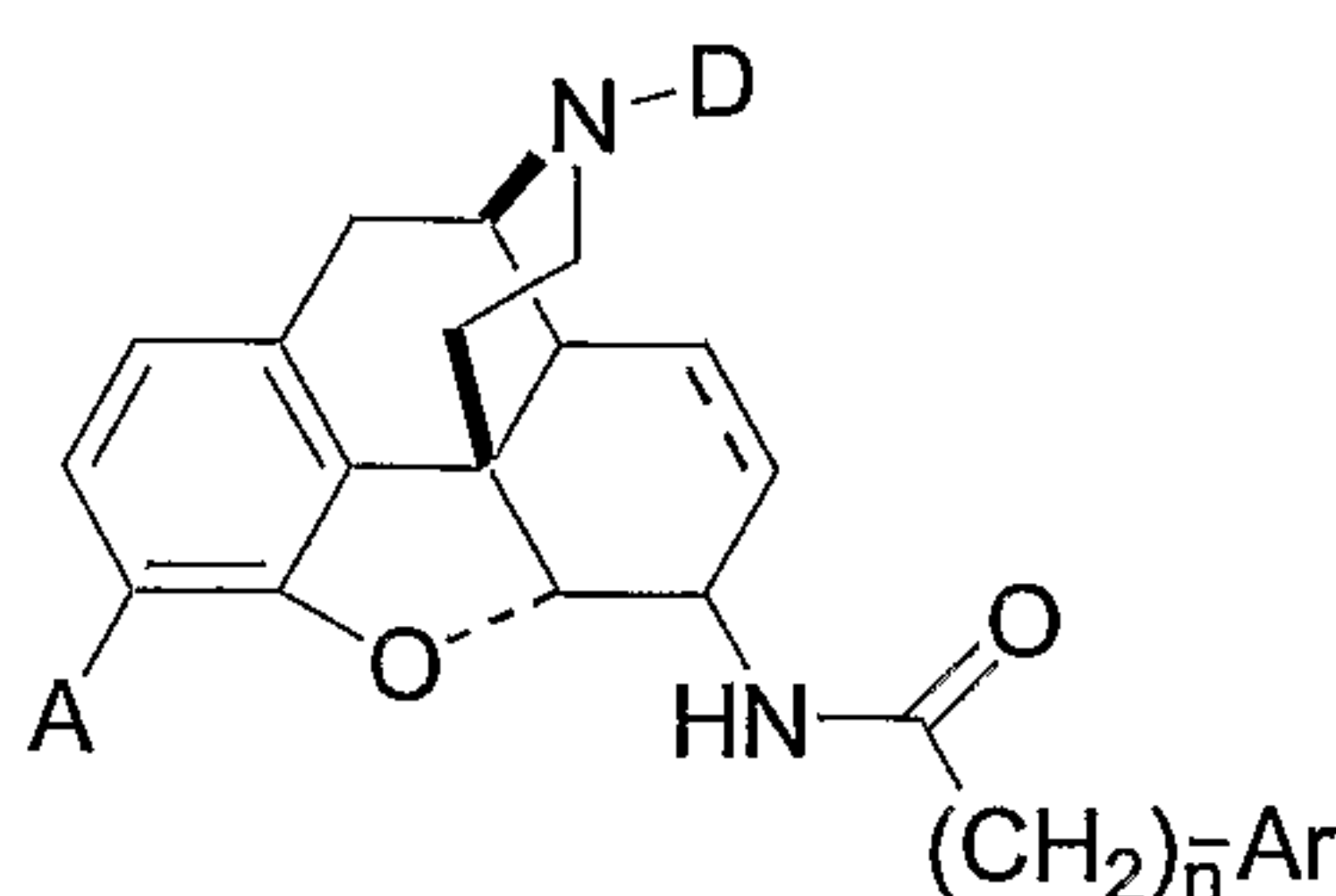
[0061] In other embodiments, compounds of the present invention include the codeine, dihydrocodeine, morphine, and dihydromorphine analogues having the following Formula V:



(V)

where A is RO, OH, or OC(O)R; B is OC(O)R, OH, or OR; C is CO₂R, CO₂H, CH₂OR, or CH₂OH; D is alkyl, cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, or optionally substituted aralkyl; and R in the substituents A, B, C, D is an alkyl or aryl group.

[0062] In yet other variations, compounds of the present invention include the morphine, dihydromorphine, codeine, and dihydrocodeine amides of the following Formula VI:



(VI)

where A is RO, OH, or OC(O)R, where n is an integer from 0-5; aryl is phenyl, 3,4-dichlorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-nitrophenyl, 3-carbomethoxyphenyl, 3-carboxyphenyl or thiophen-2-yl, or an optionally substituted aryl or heteroaryl derivative; D is alkyl, cycloalkyl, alkenyl, alkynyl, optionally substituted aryl, or optionally substituted aralkyl; and R in the substituents A and D is each independently an alkyl or aryl group.

[0063] The compounds of Formula IV can be synthesized by the S_N2 reaction of the 6β-tosylates of morphine, 3-O-acetylmorphine and codeine **1a-c** with the sodium salts of the thiosaccharides **2a-b** in dimethylformamide (see Figure 1) giving **3a-f**. For the preparation of the starting tosylates, [see L. H. Welsh, *J. Org. Chem.*, **19**:1409 (1954); G. Stork and F. Clarke, *J. Am. Chem. Soc.*, **78**:4619-4624 (1956)]. The ester protecting groups are subsequently removed by stirring overnight in aqueous sodium hydroxide to provide additional compounds which are the S-β-D-glucuronides or S-β-D-glucose conjugates of morphine, codeine and their congeners **4a-d**. The thiosaccharides **2a-b** used in these preparations were made by the reaction of the corresponding glycosyl bromides with potassium thioacetate followed by selective S-deacetylation with sodium thiomethoxide (see Figure 2). [See G. N. Bollenback *et al.*, *J. Org. Chem.*, **77**:3310-3315 (1955)] for the preparation of the starting glycosyl bromides. [See Wallace *et al.*, *Tetrahedron Lett.*, 2693-2694 (1998)] for a related S-deacetylation. This synthetic methodology constitutes a general synthetic route for the attachment of saccharides to morphine, codeine and their N-17 derivatives at the C-6 position via a sulfur atom and is applicable to the preparation of the dihydromorphine and dihydrocodeine derivatives of these compounds. In addition, utilizing

the 6 β -tosylates of morphine, codeine and derivatives allows for the preparation of the C-6 α derivatives of all compounds mentioned above.

[0064] The compounds of Formula V can be synthesized from the 6 β -phthalimides of morphine, dihydromorphine, codeine, dihydrocodeine and their *N*-alkyl and cycloalkyl derivatives **6** (see Figure 3). [See S. Makleit *et al.*, *Synthetic Commun.*, **21**:407-412 (1991).] For compounds in the morphine series the phenolic hydroxyl group is protected as a silyl ether by the reaction with *tert*-butyldimethylsilylchloride or triisopropylsilylchloride and imidazole in room temperature dimethylformamide. The phthalimide group is then removed by heating with hydrazine hydrate in EtOH to give the amines **7**. The amines **7** are reacted with the acid chloride of *C*-glycosides **8** giving the amides **9**. When the R1 in **9** is a silyl ether it can be removed by treatment with TBAF to give the phenols **10**. The sugar protecting groups in **9** or **10** are removed by treatment with aqueous NaOH or by hydrogenation giving compounds **11**. The *C*-glycosides **8** used in these syntheses were prepared by known methods [M. Lewis *et al.*, *J. Am. Chem. Soc.*, **104**:4976-4978 (1982)]. This synthetic sequence provides a general route for the attachment of saccharides to morphine and their *N*-17 derivatives at the C-6 position via an amide bridge and is applicable to the preparation of the dihydromorphine and dihydrocodeine derivatives of these compounds.

[0065] The compounds of Formula VI can be synthesized from the 6 β -aminomorphine **7c** (see Figure 4) used in the preparation of compounds of Formula V. The amine **7c** is treated with aryl and heteroaryl acid chlorides to give the amides **12a-h**. The treatment of **12a-h** with TBAF in aqueous THF provides the 6 β -amidomorphines **13a-h**. Treatment of the methyl ester **13e** with aqueous sodium hydroxide provide the carboxylic acids **14**. This synthetic sequence provides a general route for the attachment of aryl and heteroaryl substituents to morphine, codeine and their *N*-17 alkyl derivatives at the C-6 position via an amide bridge and is applicable to the preparation of the dihydromorphine and dihydrocodeine derivatives of these compounds. This synthetic methodology also provides for the preparation of the C-6 α derivatives of all of the above compounds by starting with the C-6 epimer of the amine **7c**. Replacement of the *N*-methyl substituent of the bridgehead N for the compounds described herein with cyclopropyl methyl or cyclobutyl methyl or similar substituents will typically afford antagonists of the receptors for the activity described below. Such antagonists are useful for antagonizing drug addiction, gambling addiction, alcoholism, or other diseases of the CNS. Further, application of the synthetic methodology described herein (attachment of metabolically stable saccharides or their chemical homologues or isosteric equivalents) to

other analgesics including naltrexone, phenyl piperidines, piperidinols, prodines, piperidyl propionanilides, isoprodines, prodilidines, benzomorphans, morphans, azabicyclanes, morphinans, prodines, diphenylaminoethylpropionates, methadones, isomethadones, propoxyphenes, dextromethorphans, benzazocin-8-ols, and all related stereoisomers and N-substituted derivatives (cyclopropyl methyl, cyclobutylmethyl, allyl, and the like) will lead to pharmacologically active CNS agents useful for reducing pain, as well as for the treatment of addiction and other diseases.

[0066] In yet other variations, the analgesic-related agent of the present invention has a constant charge (*i.e.*, is ionized 100% or substantially 100% of the time) at physiological pH. Such variations can be synthesized by, for example, putting a quaternary amine or guanidino moiety off the aromatic or saccharide group. Such modifications will typically yield derivatives that do not get into the brain and are therefore useful for peripheral indications (*e.g.*, as peripheral analgesics for reducing pain in the periphery without significant effect on brain receptors).

Pharmaceutical Compositions and Methods of Administration

[0067] The analgesic-related agents of the present invention are useful in a variety of applications relating to modulation of analgesic receptor signaling within the nervous system. For example, the agents of the present invention are useful as analgesics for the treatment of pain (*e.g.*, for easing pain associated with surgical procedures or terminal illnesses such as cancer). The agents are also useful for the treatment of diseases or disorders amenable to amelioration via modulation analgesic (*e.g.*, opioid) receptor signaling, particularly, for example, diseases or disorders of the CNS. Such diseases or disorders include, *e.g.*, various addictions. Addictions amenable to treatment using the agents described herein include, for example, addictions to drugs such as narcotics (*e.g.*, morphine, heroin, and other opiates), nicotine, and alcohol, as well as behavioral addictions (*e.g.*, gambling addiction).

[0068] Accordingly, the present invention further provides pharmaceutical compositions and methods for the treatment of pain as well as for the treatment of addictions and other CNS-related disorders. The analgesic-related agents of the present invention can be delivered or administered to a mammal, *e.g.*, human subject, alone, in the form of a pharmaceutically acceptable salt or hydrolysable precursor thereof, or in the form of a pharmaceutical composition wherein the compound is mixed with suitable carriers or excipient(s) in a therapeutically effective amount. In a preferred embodiment, for treating a drug addiction in

a subject and when administered in an appropriate therapeutically effective regime, a sufficient amount of the analgesic-related agent is present to inhibit analgesic receptors *in vivo* so as to predispose the subject to ingest lower amounts of a drug.

[0069] The analgesic-related agents that are used in the methods of the present invention can be administered as pharmaceutical compositions comprising the agent together with one or more other pharmaceutically acceptable components. Pharmaceutical compositions can be in the form of solids (such as, *e.g.*, powders, granules, dragees, tablets, or pills), semi-solids (such as, *e.g.*, gels, slurries, or ointments), liquids, or gases (such as, *e.g.*, aerosols or inhalants).

[0070] Suitable formulations for use in the present invention are found in, for example, [*Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed. (1985) and Langer, *Science*, **249**:1527-1533 (1990)]. The pharmaceutical compositions described herein can be manufactured in a conventional manner, *e.g.*, mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

[0071] In preparing the formulations of the present invention, pharmaceutically recognized equivalents of each of the compounds can be alternatively used. These pharmaceutically recognized equivalents can be pharmaceutically acceptable esters, amides, or salts or pharmaceutically acceptable acid addition salts.

[0072] A pharmaceutically acceptable salt is a non-toxic metal, alkaline earth metal, or an ammonium salt commonly used in the pharmaceutical industry including, for example, a sodium, potassium, lithium, calcium, magnesium, barium, ammonium, and protamine zinc salt, which is prepared by methods well-known in the art. The term also includes a non-toxic acid addition salt, which is generally prepared by reacting the compounds of the present invention with a suitable organic or inorganic acid. Representative salts include, *e.g.*, hydrochloride, hydrobromide, sulfate, bisulfate, acetate, oxalate, valerate, oleate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, and napsylate.

[0073] A pharmaceutically acceptable acid addition salt is a salt that retains the biological effectiveness and properties of the free bases and that is not biologically or otherwise undesirable, formed with inorganic acids such as, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, and organic acids such as, *e.g.*, acetic

acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, menthanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like [see, e.g., Bundgaard ed., *Design of Prodrugs*, Elsevier Science Publishers, Amsterdam (1985)].

[0074] The analgesic-related agents can be formulated with common excipients, diluents or carriers, and compressed into tablets, for formulated as elixirs or solutions for convenient oral administration. The agents can also be formulated as sustained release dosage forms and the like.

[0075] In order to exert the desired therapeutic effects associated with binding of analgesic receptors in the brain, the analgesic-related agents of the present invention must reach brain cells and brain tissue, requiring their passage from the blood to the brain by crossing the blood brain barrier, comprising the microcapillary membranes of the cerebrovascular endothelium. The present invention provides methods for administering a therapeutically effective dosage regime of the analgesic-related agent to a peripheral tissue in a patient (*i.e.*, tissues other than central nervous system tissues). This can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, transdermal, subcutaneous, intratracheal, and intramuscular administration. Moreover, the agents can be administered in a local rather than systemic manner, in a depot or sustained release formulation (*e.g.*, patient controlled analgesia). In addition, the agents can be administered in a vesicle, in particular a liposome [see, e.g., Langer, *supra*; Treat, In *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler eds., Liss, New York, pp. 353-365 (1989)].

[0076] For injection, the analgesic-related agents of the present invention can be formulated into preparations by dissolving, suspending, or emulsifying them in an aqueous or nonaqueous solvent such as, *e.g.*, vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids, or propylene glycol; and, if desired, with conventional additives such as, *e.g.*, solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers, and preservatives. Preferably, for injection, the compounds of the present invention can be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0077] For oral administration, the analgesic-related agent can be formulated readily by combining with pharmaceutically acceptable carriers that are well-known in the art. Such carriers enable the compounds to be formulated as tablets, pills, dragees, capsules, emulsions, lipophilic and hydrophilic suspensions, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained by mixing the compounds with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Particularly suitable excipients include fillers such as, for example, sugars (*e.g.*, lactose, sucrose, mannitol, or sorbitol), cellulose preparations (*e.g.*, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as, *e.g.*, sodium alginate.

[0078] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions, and/or suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0079] Pharmaceutical preparations that can be used orally include, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as, *e.g.*, glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as, for example, lactose, binders (*e.g.*, starches), and/or lubricants (*e.g.*, talc or magnesium stearate) and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as, *e.g.*, fatty oils, liquid paraffin, or liquid polyethylene glycol.

[0080] For buccal administration, the compositions can take the form of tablets or lozenges formulated in a conventional manner.

[0081] For administration by inhalation, the compounds for use in accordance with the present invention are conveniently delivered in the form of an aerosol spray preparation from

pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from propellant-free, dry-powder inhalers. In the case of a pressurized aerosol the dosage unit can be determined by, for example, providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as, for example, lactose or starch.

[0082] Analgesic-related agents of the present invention can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampules or in multidose containers, with an added preservative. The compositions can take such forms as, *e.g.*, suspensions, solutions, or emulsions in oil-based or aqueous vehicles, and can contain formulator agents such as, for example, suspending, stabilizing, and/or dispersing agents.

[0083] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Alternatively, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils (*e.g.*, sesame oil), synthetic fatty acid esters (*e.g.*, ethyl oleate or triglycerides), or liposomes. Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, such as, for example, sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0084] Analgesic-related agents can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as, for example, cocoa butter, carbowaxes, polyethylene glycols, or other glycerides, all of which melt at body temperature, yet are solidified at room temperature.

[0085] In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Accordingly, for example, the compounds can be formulated with suitable polymeric or

hydrophobic materials (*e.g.*, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives (*e.g.*, a sparingly soluble salt).

[0086] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds can be employed. Liposomes and emulsions are well-known examples of delivery vehicles or carriers for hydrophobic drugs. In some methods, long-circulating, *e.g.*, stealth, liposomes can be employed. Such liposomes are generally described in U.S. Patent No. 5,013,556 to Woodle *et al.*

[0087] The compounds of the present invention can also be administered by controlled release means and/or delivery devices. In certain variations, a pump is used [*see, e.g.*, Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.*, **14**:201 (1987); Buchwald *et al.*, *Surgery*, **88**:507 (1980); Saudek *et al.*, *N. Engl. J. Med.*, **321**:574 (1989)]. In other embodiments, polymeric materials are used [*see, e.g.*, *Medical Applications of Controlled Release*, Langer and Wise eds., CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Bull eds., Wiley, New York (1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.*, **23**:61 (1983); *see also* Levy *et al.*, *Science*, **228**:190 (1985); During *et al.*, *Ann. Neurol.*, **25**:351 (1989); Howard *et al.*, *J. Neurosurg.*, **71**:105 (1989)]. Controlled release means and delivery devices are also described in, *e.g.*, U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719.

[0088] Certain organic solvents such as, *e.g.*, dimethylsulfoxide (DMSO) also can be employed, although usually at the cost of greater toxicity. Additionally, the compounds can be delivered using a sustained-release system such as, for example, semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established. Sustained-release capsules can, depending on their chemical nature, release the compounds for a few hours up to over 100 days.

[0089] The pharmaceutical compositions can also comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as, *e.g.*, polyethylene glycols.

[0090] For treatment of drug addiction, compounds of the present invention may also be administered by incorporating the agent into a drug-containing product (for example, in the case of nicotine ingestion, a tobacco product such as, *e.g.*, a cigarette). For example, in

certain embodiments, a compound of the present invention is sprayed or otherwise applied onto the drug-containing product prior to ingestion.

[0091] Pharmaceutical compositions suitable for use in accordance with the present invention include compositions wherein the active ingredients are contained in a therapeutically effective amount. The therapeutically effective amounts for the methods of the present invention can depend on a variety of factors, including, *e.g.*, age, body weight, general health, sex, diet, time and manner of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the particular affliction being treated. The amount of active agent will also depend upon the specific activity of the opiate-related agent and whether that agent is co-administered with any other therapeutic or prophylactic ingredients.

[0092] Typically, a subject treated in accordance with the methods provided herein has been identified as suffering from pain; has been diagnosed with a disease or disorder amenable to treatment or prophylaxis via modulation of analgesic (*e.g.*, opioid) receptors; or has otherwise been identified as a subject that will obtain a physiological benefit using the compound. In certain variations, a subject, suffering from pain or diagnosed with a disease or disorder amenable to treatment or prophylaxis via modulation of analgesic receptors (*e.g.*, addiction), is not suffering from a second disease or disorder. Further, in some embodiments, the subject is monitored during treatment for a physiological and/or clinical effect. For example, for treatment of pain, a subject can be monitored for relative severity of pain over the course of treatment; or, for the treatment of a disease or disorder amenable to amelioration via modulation of analgesic receptor signaling, a subject can be monitored for one or more symptoms associated with the disease or disorder.

EXAMPLES

[0093] The following examples are offered to illustrate, but not to limit the claimed invention. Compound reference numbers for Examples 1-32 correspond to those used hereinabove. Different compound reference designations are used in each of Example 33 and, collectively, Examples 34-45.

[0094] The following general information applies with respect to the synthesis and analysis of compounds set forth in Examples 1-32: All reactions were conducted under a positive pressure of nitrogen with magnetic stirring at ambient temperature using oven-dried glassware unless otherwise indicated. Air- and moisture-sensitive liquids were transferred

via syringe through rubber septa. Silica gel (230-400 mesh) was used for column chromatography. DMF was dried by filtration through a column of neutral alumina and stored over activated 4 Å molecular sieves under nitrogen prior to use. All other solvents and reagents were used as received. ¹H NMR and ¹³C NMR spectra were recorded at 500 MHz and 125 MHz, respectively. Melting points are uncorrected. Where combustion analyses are not specified, analytical purities were determined by straight phase HPLC using a Hitachi L74 liquid chromatograph with a D7500 integrator and a Hamilton PRP-I stainless steel column (250 mm x 4.6 mm i.d.). HPLC mobile phases: A = 55:45:0.01 MeOH/isopropanol/HClO₄; B = 45/55/0.01 MeOH/isopropanol/HClO₄; C = 70:30 CH₃CN/MeOH; D = MeOH.

[0095] Further, "type I," "type II," and "type III" as used hereinbelow refer generally to compounds of Formulas IV, V, and VI, respectively, described *supra*.

Example 1: 6β-S-(Methyl-2',3',4'-tri-O-acetyl-β-D-glucopyranosyluronate)morphine 3a

[0096] A 60% dispersion of NaH (46 mg, 1.16 mmol) was added to a 0 °C DMF solution of **2a** (424 mg, 1.21 mmol) and the resulting red mixture was stirred for 10 min. To the mixture of the thiol thus formed was added a 0 °C DMF (8 mL) solution of **1b** (183 mg, 0.416 mmol) by syringe over 1 min. The resulting solution was stirred for 4 h while warming to rt. The reaction was poured into 0.5% aqueous HC (20 mL) and the pH was raised to 9 by the careful addition of solid NaHCO₃. The mixture was extracted with CH₂Cl₂ (3 X 50 mL) and the combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄, filtered and concentrated to a grey solid that was purified by flash chromatography (15 X 2.5 cm SiO₂, 60:1 to 20:1 CH₂Cl₂/EtOH) to provide **3a** as an off-white solid (144 mg, 56%). An analytical sample of **3a** was obtained as a white solid by recrystallization from absolute EtOH: R_f = 0.10 (20:1 CH₂Cl₂/MeOH); mp = 135 °C (decomposed); ¹H NMR δ 6.63 (d, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 5.81 (ddd, *J* = 9.1, 5.7, 3.0 Hz, 1H), 5.29-5.21 (m, 2H), 5.05 (d, *J* = 9.2 Hz, 1H), 5.03 (s, 1H), 4.70 (d, *J* = 9.6 Hz, 1H), 4.06 (d, *J* = 9.6 Hz, 1H), 3.74 (s, 3H), 3.31 (m, 1H), 3.03-2.99 (m, 2H), 2.58 (dd, *J* = 11.7, 4.0 Hz, 1H), 2.43 (s, 3H), 2.38-2.28 (m, 2H), 2.15-2.09 (m, 2H), 2.05 (s, 3H), 2.02 (s, 3H), 1.76 (dd, *J* = 12.2, 1.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 170.3, 169.6, 169.5, 167.0, 144.7, 138.5, 131.8, 130.4, 128.5, 126.7, 119.7, 116.8, 93.7, 84.6, 76.3, 73.4, 70.0, 69.4, 59.2, 53.1, 47.2, 45.0, 44.5, 43.1, 39.8, 35.6, 20.9, 20.8, 20.7; HRMS calcd for C₃₀H₃₆NO₁₁S [M + H⁺] 618.2009, found 618.2011; the average purity of **3a** was found to be ≥99% by analytical HPLC giving t_R = 3.47 min (mobile phase A) and t_R = 3.98 min (mobile phase B).

Example 2: 3-O-Acetyl-6 β -S-(methyl-2',3',4'-tri-O-acetyl- β -D-glucopyranosyluronate) morphine 3b

[0097] According to the procedure described for **3a**, NaH (53 mg, 1.33 mmol), **1a** (484 mg, 1.38 mmol) and **2a** (246 mg, 0.51 mmol) provided **3b** as an off-white powder (211 mg, 63%): $R_f = 0.33$ (20:1 CH₂Cl₂/EtOH); mp 194 °C (decomposed); ¹H NMR (CDCl₃) δ 6.74 (d, $J = 8.2$ Hz, 1H), 6.58 (d, $J = 8.2$ Hz, 1H), 5.83-5.80 (m, 1H), 5.53 (dd, $J = 1.5, 10.2$ Hz, 1H), 5.29-5.21 (m, 2H), 5.09 (s, 1H), 5.00 (t, 1H), 4.72 (d, $J = 10.3$ Hz, 1H), 4.06 (d, $J = 9.3$ Hz, 1H), 3.76-3.73 (4H), 3.33 (m, 1H), 3.07-3.03 (2H), 2.60-2.58 (m, 1H), 2.44 (s, 3H), 2.37-2.20 (s, 3H over m, 2H), 2.15 (dt, $J = 3.7, 11.8$ Hz, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.80 (d, $J = 11.6$ Hz, 1H); ¹³C NMR (CDCl₃) δ 170.3, 169.5, 169.4, 168.8, 167.0, 149.0, 133.0, 132.6, 132.0, 131.8, 128.0, 121.8, 119.5, 94.5, 85.1, 76.2, 73.3, 70.3, 69.4, 59.0, 53.0, 46.9, 45.6, 44.5, 43.2, 40.0, 35.7, 20.93, 20.90, 20.8, 20.7; MS (ESI) $m/z = 660$ [M + H⁺]; Anal. (C₃₂H₃₇NO₁₂S) calcd: C 58.26; H 5.65; N 2.12; S 4.86. Found C 57.94; H 5.75; N 2.07; S 4.97.

Example 3: 3-O-Acetyl-6 β -S-(2',3',4',5'-tetra-O-acetyl- β -D-glucopyranosyl)-6 β -thiomorphine 3c

[0098] According to the method described for **3a**, thiol **2b** (500 mg, 1.37 mmol), NaH (53 mg, 1.32 mmol) and tosylate **1b** (246 mg, 0.51 mmol) gave **3c** as an off-white foam (255 mg, 74%): $R_f = 0.20$ (20:1 CH₂Cl₂/MeOH); mp = 151.9 °C; ¹H NMR (CDCl₃) δ 6.73 (d, $J = 8.2$ Hz, 1H), 6.58 (d, $J = 8.2$ Hz, 1H), 5.83-5.79 (m, 1H), 5.50 (dd, $J = 1.8, 9.7$ Hz, 1H), 5.24-5.17 (m, 2H), 5.04 (t, $J = 9.9$ Hz, 1H), 4.96 (t, $J = 9.9$ Hz, 1H), 4.69 (d, $J = 10.2$ Hz, 1H), 4.19 (d, $J = 4.2$ Hz, 2H), 3.79-3.75 (m, 1H), 3.71 (d, $J = 6.0$ Hz, 1H), 3.30 (dd, $J = 3.3, 5.6$ Hz, 1H), 3.04 (d, $J = 18.8$ Hz, 1H), 2.57 (dd, $J = 4.0, 12.2$ Hz, 1H), 2.42 (s, 3H), 2.34-2.29 (m, 2H), 2.14-2.11 (m, 1H), 2.07 (s, 6H), 2.05 (s, 6H), 2.00 (s, 6H), 1.80-1.77 (m, 1H); ¹³C NMR (CDCl₃) δ 170.8, 170.1, 169.5, 169.3, 169.5, 148.8, 132.8, 132.1, 131.7, 131.6, 127.9, 121.6, 119.3, 94.4, 85.1, 75.9, 73.8, 70.3, 68.5, 62.4, 58.8, 46.7, 45.8, 44.3, 43.0, 39.7, 35.6, 20.7, 20.6, 20.5; MS $m/z = 674$ [M + H]⁺; HRMS m/z calcd for 674.2271, found 674.2238; the average purity of **3c** was found to be 97.3% by analytical HPLC giving $t_R = 4.86$ min (mobile phase A) and $t_R = 5.66$ min (mobile phase B).

Example 4: 6- β -S-(2',3',4',5'-Tetra-O-acetyl- β -D-glucopyranosyl)-6 β -thiomorphine 3d

[0099] This compound was isolated as a side product in the preparation of **3c** (47 mg, 14.6%): $R_f = 0.08$ (20:1 CH₂Cl₂/MeOH); mp 165.4 °C; ¹H NMR δ 6.63 (d, $J = 8.2$ Hz, 1H), 6.51 (d, $J = 8.2$ Hz, 1H), 5.79 (ddd, $J = 3.6, 5.8, 9.6$ Hz, 1H), 5.50 (dd, $J = 1.7, 9.6$ Hz, 1H),

5.22 (t, $J = 9.3$ Hz, 1H), 5.09-4.99 (m, 3H), 4.69 (d, $J = 10.2$ Hz, 1H), 4.27-4.19 (m, 2H), 3.78-3.74 (m, 1H), 3.67 (d, $J = 5.8$ Hz, 1H), 3.32 (m, 1H), 3.01 (d, $J = 18.9$ Hz, 1H) over bs (1H), 2.61-2.58 (m, 1H), 2.44 (s, 3H), 2.39-2.27 (m, 2H), 2.16-2.11 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.78-1.75 (m, 1H); ^{13}C NMR δ 171.1, 170.4, 169.69, 169.66, 144.6, 130.3, 131.8, 130.6, 128.3, 126.9, 119.7, 116.7, 94.2, 84.9, 76.1, 74.0, 70.4, 68.7, 62.5, 59.2, 47.2, 45.8, 44.5, 43.2, 39.8, 35.8, 21.0, 20.83, 20.80, 20.6; MS $m/z = 632$ [$M + H$] $^+$; HRMS m/z calcd for $\text{C}_{31}\text{H}_{38}\text{NO}_{11}\text{S}$ 632.2166, found 632.2136; the average purity of **3d** was found to be $\geq 98\%$ by analytical HPLC giving $t_R = 3.98$ min (mobile phase A) and $t_R = 4.40$ min (mobile phase B).

Example 5: 6 β -S-(Methyl-2',3',4'-tri-*O*-acetyl- β -D-glucopyranosyluronate)codeine 3e

[0100] According to the general procedure described for **3a**, **1c** (231 mg, 0.51 mmol), **2a** (483 mg, 1.38 mmol) and NaH (1.33 mmol) gave **3e** as an off-white solid (249 mg, 77%): $R_f = 0.30$, 20:1 $\text{CH}_2\text{Cl}_2/\text{EtOH}$; mp = 172 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 6.64 (d, $J = 8.1$ Hz, 1H), 6.54 (d, $J = 8.1$ Hz, 1H), 5.82 (ddd, $J = 3.0, 6.0, 9.2$ Hz, 1H), 5.53 (dd, $J = 1.8, 9.4$ Hz, 1H), 5.27-5.22 (m, 2H), 5.14 (s, 1H), 4.99 (t, $J = 2.1$ Hz, 1H), 4.71 (d, $J = 10.3$ Hz, 1H), 4.02 (d, $J = 7.3$ Hz, 1H), 3.83 (s, 3H), 3.79 (d, $J = 6.0$ Hz, 1H), 3.73 (s, 3H), 3.29 (dd, $J = 3.3, 5.8$ Hz, 1H), 3.05-3.00 (d, $J = 19.0$ Hz, ^1H over m, 1H), 2.55 (dd, $J = 4.3, 12.2$ Hz, 1H), 2.42 (s, 3H), 2.35 (td, $J = 3.4, 12.4$ Hz, 1H), 2.29 (dd, $J = 6.0, 19.0$ Hz, 1H), 2.15 (td, $J = 5.0, 12.4$ Hz, 1H), 2.02 (s, 3H), 2.016 (s, 3H), 2.00 (s, 3H), 1.77 (dd, $J = 1.5, 12.3$ Hz, 1H); ^{13}C NMR δ 170.2, 169.5, 169.4, 166.9, 146.3, 142.2, 133.1, 130.7, 127.9, 127.7, 119.1, 112.8, 93.6, 85.2, 76.1, 73.4, 70.3, 69.3, 59.1, 56.4, 53.0, 47.0, 45.5, 44.7, 43.3, 40.0, 36.2, 20.9, 20.8, 20.7, 20.6; MS (ESI) 632 [$M + H$] $^+$; Anal. ($\text{C}_{31}\text{H}_{37}\text{NO}_{11}\text{S}$) C, H, N, S.

Example 6: 6-S-(2',3',4',5'-Tetra-*O*-acetyl- β -D-glucopyranosyl)6 β -thiocodeine, 3f

[0101] According to the procedure described for **3a**, the thiol **2b** (440 mg, 1.21 mmol), NaH (47 mg, 1.16 mmol) and **1c** (203 mg, 0.448 mmol) provided **3f** as an off-white foam (237 mg, 82%). An analytical sample was obtained by recrystallization from boiling hexanes: $R_f = 0.26$ (20:1 $\text{CH}_2\text{Cl}_2/\text{EtOH}$); mp = 142.5 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 6.65 (d, $J = 8.2$ Hz, 1H), 6.55 (d, $J = 8.2$ Hz, 1H), 5.85-5.81 (m, 1H), 5.52 (dd, $J = 1.9, 9.6$ Hz, 1H), 5.22-5.19 (m, 2H), 5.06 (t, $J = 9.8$ Hz, 1H), 4.97 (dd, $J = 9.5, 10.1$ Hz, 1H), 4.69 (d, $J = 10.1$ Hz, 1H), 4.23-4.16 (m, 2H), 3.83 (s, 3H), 3.76 (d, $J = 6.0$ Hz, 1H), 3.76-3.71 (m, 1), 3.29 (dd, $J = 3.3, 5.8$ Hz, 1H), 3.06-3.01 (m, 2H), 2.56 (dd, $J = 4.0, 12.2$ Hz, 1H), 2.42 (s, 3H), 2.38-2.30 (m, 2H), 2.18-2.15 (m, 1H), 2.12 (s, 3H), 2.09 (s, 6H), 2.00 (s, 3H), 1.99-1.80 (m, 1H); ^{13}C NMR (CDCl_3) δ 171.0, 170.4, 169.6, 169.5, 146.3, 142.2, 132.9, 130.7, 127.9, 127.6, 119.1,

112.7, 93.8, 85.5, 76.1, 74.0, 70.5, 68.5, 62.5, 59.1, 56.4, 47.0, 46.1, 43.3, 40.0, 20.93, 20.92, 20.8, 20.5; MS $m/z = 646 [M + H]^+$; HRMS calcd for $C_{32}H_{40}NO_{11}S$ 646.2322, found 646.2304; the average purity of **3f** was found to be $\geq 99\%$ by analytical HPLC giving $t_R = 5.00$ min (mobile phase A) and $t_R = 5.71$ min (mobile phase B).

Example 7: Morphine-6 β -S-D-glucuronide 4a

[0102] To a solution of **3b** (50.0 mg, 0.076 mmol) in 1.6 mL of MeOH was added 5% aqueous NaOH (0.12 mL). The resulting golden solution was stirred at rt for 18.5 h, acidified to a pH of 5 with ten drops of glacial AcOH and concentrated. The resulting white, amorphous solid was purified by flash chromatography on silica gel (16 x 1 cm, 5:1 to 1:1 $CH_3CN/MeOH$), followed by drying for 4 h at 100 °C (0.25 mm Hg) to provide a white powder (19.4 mg, 54%): $R_f = 0.26$ (1:1 $CH_3CN/MeOH$ with 0.2% AcOH); mp = >300 °C (decomposed); ^1H NMR (D_2O) δ 6.65 (d, $J = 8.1$ Hz, 1H), 6.61 (d, $J = 8.1$ Hz, 1H), 5.92 (m, 1H), 5.61 (d, $J = 9.6$ Hz, 1H), 5.19 (s, 1H), 4.69 (d, $J = 9.9$ Hz, 1H), 3.87 (d, $J = 5.9$ Hz, 1H), 3.77 (d, $J = 9.0$ Hz, 1H), 3.64 (m, 1H), 3.57-3.51 (m, 2H), 3.38 (t, $J = 9.2$ Hz, 1H), 3.13-3.09 (m, 2H), 2.83 (dd, $J = 3.7, 12.3$ Hz, 1H), 2.59-2.54 (s, 3H over m, 2H), 2.19 (dt, $J = 8.5, 13.2$ Hz, 1H), 1.87 (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (D_2O) δ 174.6, 144.3, 139.6, 129.8, 128.8, 127.7, 123.3, 119.0, 116.9, 91.7, 85.0, 79.3, 76.1, 71.3, 70.7, 58.0, 45.6, 43.3, 42.6, 40.3, 37.2, 33.0, 19.7; MS (ESI) $m/z = 478 [M + H]^+$; Anal ($C_{23}H_{27}NO_8S$) calcd: C 57.85; H 5.70; N 2.93; S 6.71. Found C 57.75; H 5.95; N 2.73; S 6.58.

Example 8: 6 β -Thiomorphine-6 β -S-D-glucopyranoside, 4b

[0103] To an amber solution of **3c** (50 mg, 0.0742 mmol) in MeOH (6 mL) was added 5% aqueous NaOH (0.4 mL). A white precipitate formed within 5 min. The mixture was stirred for 18 h and then the pH was reduced to 7 by the addition of 1.5 N AcOH (15 drops). The solution was stirred 5 min and then the pH was reduced to 8.5 by the addition of saturated $NaHCO_3$ (15 drops). The mixture was concentrated and the residue was dissolved in 0.5 mL of water with 3 drops of 13% NH_4OH and purified by preparative TLC (SiO_2 , 200:40:5:0.05 $CH_2Cl_2/MeOH/H_2O/13\% NH_4OH$). The single uv active band was removed from the SiO_2 and the SiO_2 was washed with 4:1 $CHCl_3/MeOH$ (100 mL). The filtrate was concentrated and the residue was refiltered through a cotton plug using 9:1 $CHCl_3/MeOH$ (10 mL). The filtrate was concentrated and the resulting solid was dried for 4 h at 100 °C (0.25 mm Hg) giving the title compound as a white powder (20 mg, 59%): $R_f = 0.21$; mp = >300 °C (dec) ^1H NMR (CD_3OD) δ 6.55 (d, $J = 8.0$ Hz, 1H), 6.46 (d, $J = 8.0$ Hz, 1H), 5.90 (ddd, $J = 2.9, 5.8, 9.0$ Hz, 1H), 5.52 (dd, $J = 1.6, 9.7$ Hz, 1H), 5.22 (s, 1H), 4.54 (d, $J = 9.8$ Hz, 1H), 3.90 (d, $J =$

11.2 Hz, 1H), 3.77 (d, $J = 6.0$ Hz, 1H), 3.70 (dd, $J = 5.2, 11.9$ Hz, 1H), 3.42 (dd, $J = 3.2, 5.6$ Hz, 1H), 3.42-3.41 (m, 3H), 3.24 (dd, $J = 8.4, 9.6$ Hz, 1H), 3.07 (bs, 1H), 3.05 (d, $J = 18.7$ Hz, 1H), 2.68 (dd, $J = 4.0, 12.3$ Hz, 1H), 2.49 (s, 3H), 2.49-2.39 (m, 2H), 2.18 (dt, $J = 7.9, 12.8$ Hz, 1H), 1.81-1.79 (m, 1H); ^{13}C NMR δ 146.3, 140.4, 131.5, 131.4, 130.3, 126.7, 120.4, 117.9, 95.3, 88.4, 82.3, 79.9, 74.8, 71.6, 63.2, 60.7, 48.2, 46.3, 45.3, 43.0, 40.4, 36.7, 30.9, 24.2; MS $m/z = 464$ $[\text{M} + \text{H}]^+$; HRMS m/z calcd for $\text{C}_{23}\text{H}_{30}\text{NO}_7\text{S}$ 464.1743, found 464.1727; the average purity of **4b** was found to be 97.0% by analytical HPLC giving $t_R = 3.94$ min (mobile phase A) and $t_R = 4.42$ min (mobile phase B).

Example 9: Codeine 6 β -S-glucuronide, 4c

[0104] According to the procedure described for the preparation of **4a**, **3e** (60.4 mg, 0.095 mmol), MeOH (2 mL) and 5% aqueous NaOH (0.28 mL) provided **4c** (38 mg, 79%) as a white solid: $R_f = 0.08$ (1:1 MeCN/MeOH with 0.2% AcOH); mp = >300 °C (decomposed); ^1H NMR (D_2O) 6.82 (d, $J = 8.2$ Hz, 1H), 6.69 (d, $J = 8.2$ Hz, 1H), 5.83 (ddd, $J = 2.8, 6.0, 9.5$ Hz, 1H), 5.22 (s, 1H), 4.66 (d, $J = 9.9$ Hz, 1H), 3.84 (d, $J = 6.0$ Hz, 1H), 3.81 (s, 3H), 3.76 (d, $J = 6.0$ Hz, 1H), 3.57-3.50 (m, 2H), 3.42 (dd, $J = 3.3, 5.7$ Hz, 1H), 3.40-3.34 (m, 1H), 3.08 (d, $J = 19.0$ Hz, 1H), 3.01 (m, 1H), 2.60 (dd, $J = 4.0, 12.4$ Hz, 1H), 2.43-2.37 (s, 3H over m, 1H), 2.30 (td, $J = 3.4, 12.6$ Hz, 1H), 2.12 (td, $J = 4.8$ Hz, 13.0, 1H), 1.75 (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (D_2O) δ 174.5, 144.4, 140.5, 131.0, 129.5, 127.3, 127.1, 119.0, 112.9, 92.8, 85.1, 79.3, 76.1, 71.3, 70.8, 57.1, 55.7, 45.1, 43.2, 43.0, 40.5, 37.7, 33.8, 19.3; HRMS calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_8\text{S}$ $[\text{M} - \text{H}]$ 490.1536, found 490.1525; the average purity of **4c** was found to be 96% by analytical HPLC giving $t_R = 1.62$ min (mobile phase C) and $t_R = 1.46$ min (mobile phase D).

Example 10: 6 β -Thiocodeine-6 β -S-D-glucose, 4d

[0105] The ester **3f** (120mg, 0.186 mmol) was dissolved in MeOH (4 mL) and 5% aqueous NaOH (0.6 mL) was added. The mixture was stirred at rt for 18 h and then treated with saturated aqueous NH_4Cl (1 mL). The mixture was concentrated and the residue was purified by preparative TLC (SiO_2) using $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{water}/13\%$ concentrated NH_4OH (200:40:5:0.050) as the eluant. A single uv active band was removed from the SiO_2 with a razor blade and this SiO_2 was washed with 4:1 $\text{CHCl}_3/\text{MeOH}$ (100 mL). The filtrate was concentrated and the residue was refiltered through a cotton plug using 9:1 $\text{CHCl}_3/\text{MeOH}$ (10 mL) as the eluant. The filtrate was concentrated and the resulting solid was dried for 4 h at 100 °C (0.25 mm Hg) giving the **4d** as a white powder (23 mg, 26%): $R_f = 0.17$; mp = 201.6 °C; ^1H NMR (CD_3OD) δ 6.79 (d, $J = 8.3$ Hz, 1H), 6.68 (d, $J = 8.3$ Hz, 1H), 6.02 (ddd, $J = 3.0,$

5.9, 9.1 Hz, 1H), 5.55 (dd, $J = 1.8, 9.8$ Hz, 1H), 5.36 (s, 1H), 4.57 (d, $J = 9.8$ Hz, 1H), 4.10 (dd, $J = 3.0, 6.2$ Hz, 1H), 3.91 (dd, $J = 1.6, 12.1$ Hz, 1H), 3.83 (d, $J = 6.1$ Hz, 1H), 3.81 (s, 3H), 3.70 (dd, $J = 5.1, 12.0$ Hz, 1H), 3.39-3.23 (complex m, 6H), 3.01-3.00 (m, 1H), 2.98 (s, 3H), 2.90 (dd, $J = 6.6, 19.8$ Hz, 1H), 2.41 (dt, $J = 4.8, 13.8$ Hz, 1H), 2.04 (dd, $J = 2.7, 14.0$ Hz, 1H); ^{13}C NMR (CD₃OD) δ 147.8, 144.5, 131.7, 130.1, 128.9, 125.3, 121.1, 116.2, 94.5, 88.3, 82.3, 79.9, 79.6, 74.8, 71.6, 63.1, 62.3, 57.3, 45.7, 44.3, 41.9, 38.8, 34.8, 23.0.; MS $m/z = 478$ $[\text{M} + \text{H}]^+$; HRMS m/z calcd for C₂₄H₃₂NO₇S 478.1899, found 478.1886; the average purity of **4d** was found to be 96.5% by analytical HPLC giving $t_R = 4.79$ min (mobile phase A) and $t_R = 5.64$ min (mobile phase B).

Example 11: 6 β Methyl 2',3',4'-tri-O-acetyl- β -D-glucopyranosyluronate)acetamido-codeine 9b

[0106] Thionyl chloride (0.2 mL, 2.74 mmol) was added to carboxylic acid **8a** (20.0 mg, 0.053 mmol) and the resulting colorless solution was stirred for 4 h under nitrogen. Toluene (1 mL) was added and the solution was concentrated by distillation under high vacuum with the aid of a 45 °C water bath. The resulting residue was cooled in a 0 °C ice bath. A 0 °C CH₂Cl₂ (2 mL) solution of amine **9b** (32 mg, 0.106 mmol) containing 3 drops of NEt₃ was added by syringe. The resulting solution was stirred 20 h without replenishing the ice bath, diluted with CH₂Cl₂ (15 mL), washed with saturated aqueous NaHCO₃ (2 X 2 mL) and brine (2 mL). The organic layer was dried, filtered and concentrated to a thick yellow oil.

Purification by flash chromatography (10 X 1 cm SiO₂, 10:1 CH₂Cl₂/MeOH) provided the title compound as a white solid (10 mg, 29%): $R_f = 0.17$ (10:1 CH₂Cl₂/MeOH); ^1H NMR (CDCl₃) δ 7.06 (d, $J = 6.8$ Hz, 1H), 6.666 (d, $J = 8.2$ Hz, 1H), 6.54 (d, $J = 8.2$ Hz, 1H), 5.888 (ddd, $J = 3.0, 5.8, 9.4$ Hz, 1H), 5.60 (dd, $J = 1.5, 9.4$ Hz, 1H), 5.30 (s, 1H), 5.08 (t, $J = 3.0$ Hz, 1H), 4.78 (s, 1H), 4.68-4.66 (m, 2H), 4.57 (d, $J = 10.4$ Hz, 1H), 4.51 (t, $J = 6.2$ Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.30 (m, 1H), 3.03 (d, $J = 18.5$ Hz, 1H), 2.97 (m, 1H), 2.73 (dd, $J = 11.1, 17.0$ Hz, 1H), 2.55 (dd, $J = 3.9, 11.6$ Hz, 1H), 2.43 (s, 3H), 2.37-2.29 (m, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 2.04 (s, 3H), 2.03-1.99 (m, 1H), 1.81-1.79 (m, 1H); MS (ESI) $m/z = 657$ $[\text{M} + \text{H}]^+$.

Example 12: 6 α -(Methyl 2',3',4'-tri-O-acetyl- β -D-glucopyranosyluronate)acetamido-morphine, 10a

[0107] According to the procedure described for compound **9b**, carboxylic acid **8a** (38.5 mg, 0.102 mmol), thionyl chloride (0.6 mL) and amine **7a** (30 mg, 0.075 mmol) provided **10a** as a white solid (29 mg, 51%): $R_f = 0.11$ (20:1 CH₂Cl₂/MeOH); ^1H NMR (CDCl₃) δ 7.01 (d, J

= 6.7 Hz, 1H), 6.59 (d, $J = 7.7$ Hz, 1H), 6.45 (d, $J = 7.7$ Hz, 1H), 5.88-5.84 (m, 1H), 5.59 (dd, $J = 1.6, 9.6$ Hz, 1H), 5.08 (t, $J = 3.0$ Hz, 1H), 4.72-4.66 (m, 2H), 4.58 (d, $J = 16.4$ Hz, 1H), 4.49 (t, $J = 6.3$ Hz, 1H), 3.82 (s, 3H), 3.84-3.72 (m, 2H), 3.29 (m, 1H), 3.01 (d, $J = 18.5$ Hz, 1H), 2.94 (m, 1H), 2.75-2.69 (dd, $J = 11.0, 17.1$ Hz, 1H), 2.53 (m, 1H), 2.43 (s, 3H), 2.42-2.29 (m, 2H), 2.19-1.99 (m, 2H), 2.163 (s, 3H), 2.157 (s, 3H) 2.06 s, 3H), 1.78-1.75 (m, 1H), 0.98 (s, 9H), 0.194 (s, 3H), 0.174 (s, 3H); MS (ESI) 757 [100, (M+H)⁺]. The intermediate silyl ether (20 mg, 0.026 mmol) was dissolved in THF (1 mL). TBAF (0.030 mL, 0.030 mmol) and water (0.020 mL) were added and the purple solution was stirred at rt for 50 min, diluted with CH₂Cl₂ (20 mL) and washed with NH₄Cl (4 mL), brine (2 mL) and water (2 mL). The organic layer was dried (Na₂SO₄) filtered and concentrated to a pink foam (22 mg): $R_f = 0.22$ (10:1 CH₂Cl₂/MeOH); MS $m/z = 643$ [M + H]⁺

Example 13: 6 β -(α -Glucuronosyl)acetamidomorphine 11a

[0108] Prepared by the procedure described for Example 7 from **10a** (20 mg, 0.031 mmol), 5% aqueous NaOH (0.4 mL) and MeOH (2 mL) to give **11a** as a white solid (2.1 mg, 18%): $R_f = 0.19$ (SiO₂/ MeOH with 0.2% AcOH); MS $m/z = 501$ [M-H]⁻.

Example 14: 6 β -(α -D-glucuronosyl)acetamidocodeine 11b

[0109] The title compound was obtained by the procedure described for Example 7 as a white solid (13.5 mg, 86%): $R_f = 0.14$ (MeOH with 0.2% AcOH); ¹H NMR (D₂O) δ 6.97 (d, $J = 8.4$ Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 5.89-5.85 (m, 1H), 5.71 (d, $J = 12.2$ Hz, 1H), 4.94 (s, 1H), 4.62-4.59 (m, 1H), 4.36 (d, $J = 5.7$ Hz, 1H), 4.22 (m, 1H), 4.03 (d, $J = 6.2$ Hz, 1H), 3.88 (s, 3H), 3.80-3.73 (m, 2H), 3.35-3.30 (m, 2H), 3.03-2.94 (s, 3H overlapping m, 1H), 2.77-2.71 (m, 1H), 2.59 (dd, $J = 3.6, 16.1$ Hz, 1H), 2.31 (td, $J = 4.7, 13.5$ Hz, 1H), 2.06 (m, 1H); MS $m/z = 515$ [M- H]⁻.

Example 15: 6 β -(2',3',4',5'-Tetra-O-benzyl- β -D-glucopyranosyl)-3-O-Triisopropylsilyl-acetamidomorphine 9c

[0110] Reference JMM-VI-113-2. SOCl₂ (1.5 mL) was added to the carboxylic acid **8b** (115 mg, 0.20 mmol) and the solution was stirred at rt for 16 h. The excess SOCl₂ was removed by distillation and the colorless oil that resulted was dissolved in CH₂Cl₂ (2.5 mL) and added to the amine **7c** (43.5 mg, 0.10 mmol) and NEt₃ (0.035 mL, 0.25 mmol) in CH₂Cl₂ (1 mL). The solution was stirred at rt for 1 h, concentrated and purified by flash chromatography (SiO₂, 30:1 to 10:1 EtOAc/MeOH), providing **9c** as a white solid (70 mg, 70%): $R_f = 0.46$ (10:1 CH₂Cl₂/MeOH); ¹H NMR (CDCl₃) δ 7.35-7.10 (20H), 6.59 (d, $J = 8.0$

Hz, 1H), 6.40 (d, $J = 8.0$ Hz, 1H), 6.22 (d, $J = 6.9$ Hz, 1H), 5.71 (ddd, $J = 3.0, 6.0, 9.5$ Hz, 1H), 5.41 (dd, $J = 1.9, 9.5$ Hz, 1H), 4.89-4.48 (9H), 4.36 (t, $J = 6.3$ Hz, 1H), 3.72-3.46 (5H), 3.29 (t, $J = 9.0$ Hz, 1H), 3.17 (dd, $J = 3.0, 5.2$ Hz, 1H), 2.96 (d, $J = 18.7$ Hz, 1H), 2.88 (bs, 1H), 2.72 (dd, 2.7, 15.2 Hz, 1H), 2.50-1.72 (10H), 1.30-1.05 (21H).

Example 16: 6 β -(2',3',4',5'-Tetra-*O*-benzyl- β -D-glucopyranosyl)acetamidomorphine 10b

[0111] JMM-VI-114-2. The silyl ether **9c** (60 mg, 59.7 mmol) was dissolved in THF (2 mL) and water (0.050 mL) was added and then TBAF (0.090 mL, 0.090 mmol, 1.0 M solution in THF). After 2.5 h, 1% concentrated HCl (4 mL) was added and the mixture was stirred for 2 min, diluted with water (10 mL) and made basic with solid NaHCO₃. The mixture was extracted with CH₂Cl₂ (5 x 30 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (24:1 to 12:1 EtOAc/MeOH) provided **10b** as a white solid (42 mg, 83%): $R_f = 0.15$ (12:1 EtOAc/MeOH); ¹H NMR (CDCl₃) δ 7.34-7.10 (20H), 6.64 (d, $J = 8.2$ Hz, 1H), 6.46 (d, $J = 8.2$ Hz, 1H), 6.34 (d, $J = 6.3$ Hz, 1H), 5.68 (ddd, $J = 2.5, 5.8, 9.5$ Hz, 1H), 5.39 (d, $J = 9.5$ Hz, 1H), 4.89-4.46 (10H), 4.34 (t, $J = 6.3$ Hz, 1H), 3.72-3.46 (6H), 3.30 (t, $J = 9.1$ Hz, 1H), 3.18 (bs, 1H), 2.97 (d, $J = 18.1$ Hz, 1H), 2.94 (bs, 1H), 2.74 (dd, $J = 2.5, 15.7$ Hz, 1H), 2.55-2.16 (7H), 1.95 (dt, $J = 8.0, 12.6$ Hz, 1H), 1.76 (d, $J = 11.3$ Hz, 1H).

Example 17: 6 β -(β -D-Glucopyranosyl)acetamidodihydromorphine 11c

[0112] JMM-VI-116-2. The tetrabenzyl derivative **10b** (16 mg, 0.018 mmol) was dissolved in MeOH (2 mL) and concentrated HCl (3 drops) and then 10% Pd-C (16 mg) were added. The mixture was stirred under a balloon of hydrogen for 24 h and then filtered through Celite, washing the Celite with MeOH (10 mL). The filtrate was concentrated and the residue was purified by preparative TLC (SiO₂, 5:4:0.5:0.5 CHCl₃/MeOH/H₂O/concentrated NH₄OH), providing **11c** as a white film (2.3 mg, 26%): $R_f = 0.40$; MS $m/z = 491$ (MH⁺).

Example 18: 6 β -(3-Methoxyphenyl)acetamidomorphine, 13a

[0113] **7c** (80 mg, 0.182 mmol) was dissolved in CH₂Cl₂ (4 mL) and NEt₃ (72 μ L, 0.517 mmol) and 3-methoxyphenylacetyl chloride (80 μ L, 0.513 mmol) were added by syringe. The resulting pale yellow solution was stirred at rt under an atmosphere of dry nitrogen in a closed vial. After 2 h, the solution was concentrated and the residue was purified by flash chromatography (20:1 CHCl₃/MeOH) to provide **12a** as a white foam (78 mg, 73%): $R_f = 0.18$ (20:1 CH₂Cl₂/MeOH); MS m/z : 589 (M + H)⁺. **12a** (64 mg, 0.109 mmol) was

dissolved in 5% aqueous THF (2.2 mL). TBAF (0.18 mL, 1.0 M solution in THF) was added by syringe and the pale yellow solution was stirred at rt under an atmosphere of dry nitrogen for 2 h. The solution was concentrated and 1% HCl (2 mL) was added. The mixture was stirred for 2 min and then transferred to a separatory funnel with the aid of water (20 mL). The mixture was alkalized (pH 8.5) with solid NaHCO₃ and extracted with CHCl₃ (5 x 10 mL). The combined CHCl₃ extract was washed with brine (4 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (20:1 CHCl₃/MeOH) provided **13a** as a white solid (38 mg, 81%): mp 144 °C; R_f = 0.14 (20:1 CHCl₃/MeOH); ¹H NMR δ 7.24 (*J* = 7.9 Hz, 1H), 6.82-6.79 (m, 3H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 5.67 (ddd, *J* = 3.6, 6.1, 9.1 Hz, 1H), 5.58-5.53 (m, 2H), 4.65 (s, 1H), 4.37 (t, *J* = 6.4 Hz, 1H), 3.79 (s, 3H), 3.54 (s, 2H), 3.34 (m, 1H), 3.00 (d, *J* = 18.6 Hz, 1H), 2.89 (s, 1H), 2.61 (dd, *J* = 4.0, 12.2 Hz, 1H), 2.43 (s, 3H), 2.38-2.29 (m, 2H), 1.99 (dt, *J* = 9.6, 12.2 Hz, 1H), 1.76 (dd, 1.9, 12.6 Hz, 1H); ¹³C NMR δ 171.1, 160.2, 144.5, 138.9, 136.2, 132.8, 130.3, 129.9, 128.6, 125.8, 121.7, 119.6, 117.1, 115.1, 113.1, 93.0, 59.3, 55.4, 50.5, 47.3, 44.1, 43.9, 43.0, 39.8, 35.5, 20.5; MS *m/z* = 433 [M+H]⁺, 455 [M + Na]⁺; HRMS *m/z* 433.2115 [M + H]⁺; the average purity of **15a** was found to be ≥99% by analytical HPLC giving *t_R* = 4.38 min (mobile phase A) and *t_R* = 5.09 min (mobile phase B).

Example 19: 6β-(4-Methoxyphenyl)acetamidomorphine 13b

[0114] According to the general procedure described for **12a**, **7c** (78.4 mg, 0.178 mmol), NEt₃ (72 uL, 0.517 mmol) and 4-methoxyphenylacetyl chloride (80 uL, 0.523 mmol) gave **12b** as a white foam (70 mg, 67%): R_f = 0.11 (20:1 CHCl₃/MeOH); MS *m/z*: 589 (M + H)⁺, 611 (M + Na)⁺. Reference V-99. According to the procedure described for **13a**, **12b** (65 mg, 0.110 mmol) and TBAF (0.18 mL, 0.18 mmol) gave **13b** (29 mg, 61%) as a white solid: mp 247 (dec); R_f = 0.14 (20:1 CHCl₃/MeOH); ¹H NMR δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 8.1 Hz, 1H), 5.67 (ddd, *J* = 3.0, 5.6, 9.5 Hz, 1H), 5.56 (dd, *J* = 1.5, 9.5 Hz, 1H), 5.45 (d, *J* = 6.4 Hz, 1H), 4.65 (s, 1H), 4.36 (t, *J* = 6.3 Hz, 1H), 3.79 (s, 3H), 3.50 (s, 2H), 3.34 (m, 1H), 3.00 (d, *J* = 18.6 Hz, 1H), 2.87 (s, 1H), 2.61 (dd, *J* = 3.8, 11.9 Hz, 1H), 2.44 (s, 3H), 2.38-2.28 (m, 2H), 1.98 (dt, 4.9, 12.5 Hz, 1H), 1.77 (d, *J* = 10.7 Hz, 1H); ¹³C δ 171.5, 158.8, 144.4, 138.7, 132.6, 130.4, 129.7, 128.3, 126.5, 125.6, 119.3, 117.0, 114.5, 92.8, 59.1, 55.3, 50.3, 47.0, 43.9, 42.9, 42.7, 39.6, 35.4, 20.2; MS *m/z* = 433 (M + H)⁺, 456 (M + Na)⁺; HRMS *m/z* 433.2136 [M + H]⁺; the average purity of **13b** was found to be >99% by analytical HPLC giving *t_R* = 4.44 min (mobile phase A) and *t_R* = 5.24 min (mobile phase B).

Example 20: 6 β -(3-Methoxy)benzamidomorphine 13c

[0115] According to the general procedure described for **12a**, **7c** (82 mg, 0.185 mmol), NEt₃ (76 μ L, 0.545 mmol) and anisoyl chloride (71 μ L, 0.521 mmol) gave **12c** as a white foam (88 mg, 82%); R_f = 0.28 (10:1 CH₂Cl₂/MeOH); MS m/z: 575 (M + H)⁺. According to the general procedure described for **13a**, **12c** (73 mg, 0.174 mmol) and TBAF (0.210 mL, 0.210 mmol) gave **13c** as a white solid (42.5 mg, 58%): R_f = 0.15 (15:1 dcm/MeOH); mp = 212.9 °C (dec); ¹H NMR δ 7.34-7.33 (m, 1H), 7.27-7.23 (m, 2H), 7.02-7.00 (m, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 6.27 (d, *J* = 6.8 Hz, 1H), 5.84 (ddd, *J* = 3.0, 5.8, 9.2 Hz, 1H), 5.68 (dd, *J* = 1.2 Hz, 9.9 Hz, 1H), 4.85 (s, 1H), 4.59 (t, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 3.47 (dd, *J* = 3.0, 5.0 Hz, 1H), 3.19-3.16 (m, 1H), 3.04 (d, *J* = 18.5 Hz, 1H), 2.68 (dd, *J* = 4.0, 12.0 Hz, 1H), 2.49 (s, 3H), 2.43-2.38 (m, 1H), 2.11 (dt, *J* = 4.8, 12.6 Hz, 1H), 1.80 (d, *J* = 10.9 Hz, 1H); ¹³C NMR δ 167.5, 160.0, 144.7, 139.1, 135.6, 132.7, 129.9, 129.8, 128.9, 125.5, 119.7, 119.0, 118.2, 117.4, 112.6, 93.0, 59.5, 55.7, 50.9, 47.4, 44.1, 43.0, 39.9, 35.4, 20.6; MS m/z 419 (M + H)⁺, 441 (M + Na)⁺; HRMS m/z = 419.1984 [M + H]⁺; the average purity of **13c** was found to be 99% by analytical HPLC giving t_R = 4.41 min (mobile phase A) and t_R = 5.05 min (mobile phase B).

Example 21: 6 β -Benzamidomorphine, 13d

[0116] According to the general procedure described for **12a**, **7c** (82 mg, 0.232 mmol), NEt₃ (76 μ L, 0.55 mmol) and benzoyl chloride (61 μ L, 0.521 mmol) gave **12d** as a white foam (79 mg, 78%); R_f = 0.23 (20:1 CHCl₃/MeOH); MS m/z: 545 (M + H)⁺. According to the general procedure described for **13a**, **12d** (65 mg, 0.110 mmol) and TBAF (0.18 mL, 0.18 mmol) gave **13d** as a white solid (29 mg, 61%): R_f = 0.15 (15:1 CH₂Cl₂/MeOH); mp = 184.4 °C (dec); ¹H NMR δ 7.78 (m, 2H), 7.53-7.50 (m, 1H), 7.42-7.41 (m, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 6.18 (d, *J* = 6.2 Hz, 1H), 5.89 (ddd, *J* = 3.0, 5.3, 9.5 Hz, 1H), 5.69 (dd, *J* = 1.5, 9.5 Hz, 1H), 4.86 (s, 1H), 4.64 (t, *J* = 6.3 Hz, 1H), 3.54 (s, 1H), 3.31 (s, 1H), 3.06 (d, *J* = 18.7 Hz, 1H), 2.77 (m, 1H), 2.57 (s, 3H), 2.50-2.48 (m, 3H), 2.23-2.19 (m, 1H), 1.86 (dd, *J* = 2.2, 12.9 Hz, 1H); ¹³C NMR δ 167.4, 144.5, 138.8, 133.9, 132.9, 131.7, 129.8, 128.6, 128.6, 127.0, 125.7, 119.4, 117.1, 92.8, 59.1, 50.6, 47.0, 44.0, 42.9, 39.9, 35.5, 20.5; MS m/z = 389 [M + H]⁺, 411 (M + Na)⁺; HRMS m/z = 389.1867 [M + H]⁺; the average purity of **13d** was found to be 99% by analytical HPLC giving t_R = 4.43 min (mobile phase A) and t_R = 5.16 min (mobile phase B).

Example 22: 6 β -(3'-Carbomethoxy)benzamidomorphine 13e

[0117] According to the general procedure described for **12a**, **7c** (159 mg, 0.362 mmol), NEt₃ (151 uL, 1.09 mmol) and monomethylphthaloyl chloride (217 mg, 1.01 mmol) **12e** as a white foam (122 mg, 56%); R_f = 0.22 (20:1 CHCl₃/MeOH); MS m/z: 603 (M + H)⁺.

According to the general procedure described for **13a**, **12e** (102 mg, 0.170 mmol) and TBAF (0.47 mL, 0.470 mmol) gave **13e** as a white solid: R_f = 0.14 (30:1 dcm/MeOH); mp = 166.0 °C (dec); ¹H NMR δ 8.32 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 6.33 (d, *J* = 7.0 Hz, 1H), 5.85 (ddd, *J* = 9.4, 5.6, 3.1 Hz, 1H), 5.73 (d, *J* = 9.9, 1H), 4.85 (s, 1H), 4.62 (t, *J* = 6.2 Hz, 1H), 3.93 (s, 3H), 3.42 (dd, *J* = 3.2, 5.2, 1H), 3.10 (bs, 1H), 3.05 (d, *J* = 18.5 Hz, 1H), 2.63 (dd, *J* = 12.1, 4.2 Hz, 1H), 2.46 (s, 3H), 2.40-2.34 (m, 2H), 2.08 (dt, *J* = 12.5, 4.9 Hz, 1H), 1.81 (d, *J* = 10.8 Hz, 1H); ¹³C δ 166.4, 166.2, 144.3, 138.7, 134.2, 133.0, 132.7, 131.9, 130.5, 129.8, 128.9, 128.3, 127.6, 125.7, 119.5, 117.0, 92.9, 59.1, 52.4, 50.9, 47.1, 44.0, 42.9, 39.9, 35.4, 20.2; MS m/z = 447 [M + H]⁺; HRMS m/z = 447.1930 [M + H]⁺; the average purity of **13e** was found to be ≥99% by analytical HPLC giving t_R = 4.39 min (mobile phase A) and t_R = 5.06 min (mobile phase B).

Example 23: 6β-(3'-Nitro)benzamidomorphine 13f

[0118] According to the general procedure described for **12a**, **7c** (80 mg, 0.182 mmol), NEt₃ (76 uL, 0.55 mmol) and 3-nitrobenzoyl chloride (95 mg, 0.51 mmol) gave **12f** as a white foam (87 mg, 81%); R_f = 0.17 (20:1 CHCl₃/MeOH); MS m/z: 590 (M + H)⁺.

According to the general procedure described for **13a**, **12f** (73 mg, 0.168 mmol) and TBAF (0.200 mL, 0.200 mmol) gave **13f** as a light yellow solid (36 mg, 49%); R_f = 0.11 (20:1 CHCl₃/MeOH); mp 208.3 °C (dec); ¹H NMR δ 8.54 (t, *J* = 1.4 Hz, 1H), 8.26 (dd, *J* = 1.4, 8.2 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 6.4 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 5.84 (ddd, *J* = 3.0, 5.5, 9.2 Hz, 1H), 5.71 (d, *J* = 10.3 Hz, 1H), 4.88, s, 1H), 4.63 (t, *J* = 6.3 Hz, 1H), 3.45 (t, *J* = 3.2 Hz, 1H), 3.18 (s, 1H), 3.04 (d, *J* = 18.6 Hz, 1H), 2.68 (dd, *J* = 3.8, 11.8 Hz, 1H), 2.47 (s, 3H), 2.41-2.34 (m, 2H), 2.15 (dt, *J* = 7.6, 12.4 Hz, 1H), 1.78 (d, *J* = 11.5 Hz, 1H); ¹³C δ 165.2, 148.0, 144.4, 138.9, 135.5, 133.3, 132.7, 129.8, 129.7, 128.2, 126.1, 125.4, 122.0, 119.5, 117.3, 92.5, 59.2, 51.1, 47.1, 43.9, 42.8, 39.6, 35.1, 20.3; MS m/z = 434 [M + H]⁺; HRMS m/z = 434.1719 [M + H]⁺; the average purity of **13f** was found to be >99% by analytical HPLC giving t_R = 4.11 min (mobile phase A) and t_R = 4.78 min (mobile phase B).

Example 24: 6β-(3',4'-Dichloro)benzamidomorphine, 13g

[0119] According to the general procedure described for **12a**, **7c** (81 mg, 0.184 mmol), NEt₃ (77 μ L, 0.55 mmol) and 3,4-dichlorobenzoyl chloride (108 mg, 0.518 mmol) gave **12g** as a white foam (96 mg, 85%); R_f = 0.20 (20:1 CH₂Cl₂/MeOH); MS m/z: 614 (M + H)⁺, 616 (M + 2 + H)⁺; 618 (M + 4 + H). According to the general procedure described for **13a**, **12g** (81 mg, 0.177 mmol) and TBAF (0.22 mL, 0.22 mmol) gave **13g** as a white solid (48 mg, 49%); R_f = 0.17 (15:1 CH₂Cl₂/MeOH); mp 228.5 °C (dec); ¹H NMR δ 7.82 (d, *J* = 2.1 Hz, 1H), 7.54 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 6.2 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.82 (ddd, *J* = 2.9, 5.3, 9.5 Hz, 1H), 5.68 (dd, *J* = 1.2, 9.5 Hz, 1H), 4.83 (s, 1H), 4.58 (t, *J* = 6.3 Hz, 1H), 3.47 (dd, *J* = 3.0, 5.3 Hz, 1H), 3.19 (m, 1H), 3.05 (d, *J* = 18.6 Hz, 1H), 2.70 (dd, *J* = 3.8, 11.9 Hz, 1H), 2.50 (s, 3H), 2.43-2.37 (m, 2H), 1.77 (d, *J* = 11.0 Hz, 1H), ¹³C NMR δ 165.4, 144.4, 138.9, 136.1, 133.7, 133.0, 132.5, 130.5, 129.6, 129.3, 128.4, 126.3, 125.2, 119.5, 117.4, 92.5, 59.2, 52.4, 50.8, 47.2, 43.8, 42.7, 39.5, 35.1, 29.7, 25.8, 20.3, 20.5, 13.6; MS m/z 457 (M + H)⁺; HRMS m/z = 457.1087 [M + H]⁺; the average purity of **13g** was found to be >99% by analytical HPLC giving t_R = 3.93 min (mobile phase A) and t_R = 4.43 min (mobile phase B).

Example 25: 6 β -(Thiophen-2'-yl)acetamidomorphine 13h

[0120] According to the general procedure described for **12a**, **7c** (86 mg, 0.196 mmol), 2-thiopheneacetyl chloride (0.068 mL, 0.552 mmol) and NEt₃ (0.082 mL, 0.588 mmol) gave **12h** as a white foam (66 mg, 60%); R_f = 0.23 (20:1 CHCl₃/MeOH); MS m/z = 565 [M + H]⁺. According to the general procedure described for **13a**, **12h** (56 mg, 0.099 mmol) and TBAF (0.120 mL, 0.120 mmol) gave **13h** as a white solid (32 mg, 79%); R_f = 0.10 (20:1 CHCl₃/MeOH); mp 154.4 °C; ¹H NMR δ 7.18 (d, *J* = 4.5 Hz, 1H), 6.94-6.91 (m, 2H), 6.64 (d, *J* = 8.1 Hz, 1H), 5.82 (d, *J* = 7.1 Hz, 1H), 5.69 (ddd, *J* = 3.5, 5.5, 9.4 Hz, 1H), 5.59 (dd, *J* = 1.2, 9.9 Hz, 1H), 4.65 (s, 1H), 4.39 (t, *J* = 6.4 Hz, 1H), 3.77 (s, 2H), 3.37 (dd, *J* = 3.3, 5.8 Hz, 1H), 3.01 (d, *J* = 18.5 Hz, 1H), 2.93 (m, 1H), 2.64 (dd, *J* = 4.1, 12.1 Hz, 1H), 2.45 (s, 3H), 2.39-2.31 (m, 2H), 2.02 (dt, *J* = 7.6, 12.6 Hz, 1H), 1.77 (dd, *J* = 10.8, 1.7 Hz, 1H); ¹³C NMR δ 170.2, 144.6, 139.0, 136.0, 132.9, 129.9, 128.4, 127.6, 125.9, 125.6, 119.6, 117.3, 92.9, 59.2, 50.4, 47.3, 44.1, 43.0, 39.7, 37.7, 35.5, 20.5; MS m/z = 409 [M + H]⁺, 431 (M + Na)⁺; HRMS m/z = 409.1572 [M + H]⁺; the average purity of **13h** was found to be >99% by analytical HPLC giving t_R = 4.31 min (mobile phase A) and t_R = 5.02 min (mobile phase B).

Example 26: 6 β -(3'-Carboxy)benzamidomorphine 14

[0121] Reference V-110. **13e** (31 mg, 0.067 mmol) was dissolved in 4 mL of 1:1 THF/water and LiOH-H₂O (27 mg, 0.643 mmol) was added. The colorless solution was

stirred at rt for 3.75 h, glacial acetic acid was added (15 drops) and the solution was concentrated. The residue was purified by flash chromatography on SiO₂ (5:1 to 1:1 CHCl₃/MeOH). The appropriate fractions were concentrated and the residue was stirred with 10 mL of 10:1 CHCl₃/MeOH and filtered through paper. The filtrate was concentrated to provide the title compound as a white solid, 20 mg (69%): R_f = 0.17 (1:1 CHCl₃/MeOH with 0.2% AcOH), mp = 217.1 °C (dec); ¹H NMR δ 8.41-8.40 (m, 1H), 8.13-8.12 (m, 1H), 7.90-7.88 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 5.81-5.78 (m, 1H), 5.69 (d, *J* = 9.9 Hz, 1H), 4.82 (s, 1H), 4.51-4.50 (m, 1H), 3.65 (dd, *J* = 3.2, 5.4 Hz, 1H), 3.27 (bs, 1H), 3.12 (d, *J* = 18.9 Hz, 1H), 2.87 (dd, *J* = 4.0, 12.9 Hz, 1H), 2.64-2.57 (m, 2H), 2.20 (dt, *J* = 4.8, 12.9 Hz, 1H), 1.81 (dd, *J* = 2.4, 12.9 Hz, 1H); ¹³C NMR δ 180.5, 170.2, 145.6, 141.2, 139.4, 135.5, 133.6, 131.0, 130.9, 130.5, 130.3, 129.5, 129.2, 125.6, 120.7, 118.5, 93.8, 61.3, 52.8, 42.6, 39.9, 35.1, 30.9, 22.1 MS *m/z* 431 (*M* - H)⁻; HRMS *m/z* calcd for C₂₅H₂₅N₂O₅ 433.1758, found 433.1749; the average purity of 14 was found to be 99% by analytical HPLC giving *t_R* = 3.93 min (mobile phase A) and *t_R* = 4.43 min (mobile phase B).

Example 27: *In vitro* Binding Assays

[0122] A. Methods. Binding to cell membranes was conducted in a 96-well format. [See, N. Zaveri *et al.*, *Eur. J. Pharmacol.*, **428**:29-36 (2001)]. Cells were removed from the plates by scraping with a rubber policeman, homogenized in Tris buffer using a Polytron homogenizer, then centrifuged once and washed by an additional centrifugation at 27,000 x *g* for 15 min. The pellet was resuspended in 50 mM Tris, pH 7.5, and the suspension incubated with [³H]DAMGO, [³H]DPDPE, or [³H]U69593, for binding to *u*, *d* or *k* opioid receptors, respectively. The total volume of incubation was 1.0 mL and samples were incubated for 60-120 min at 25 °C. The amount of protein in the binding reaction varied from approximately 15 µg to 30 µg. The reaction was terminated by filtration using a Tomtec 96 harvester (Orange, CT) with glass fiber filters. Bound radioactivity was counted on a Pharmacia Biotech beta-plate liquid scintillation counter (Piscataway, NJ) and expressed in counts per minute. IC₅₀ values were determined using at least six concentrations of test compound, and calculated using Graphpad/Prism (ISI, San Diego, CA). K_i values were determined by the method of Cheng and Prusoff. [See Y. Cheng, and W. H. Prusoff, *Biochem. Pharmacol.*, **22**:3099-3108 (1973).]

[0123] B. Results. Affinity and Selectivity of the Ligands. Table 1 contains the K_i values for compounds **5** and **6**. K_i is the parameter that measures the inhibition of radioligand

binding to the receptor by the test compound. As with M6G, each ligand tested was mu selective. With respect to the type I compounds, the rank order of affinity for the most active compounds was **6b** = **5a** > **5d** > **6a**. Each of these compounds possessed a free phenolic hydroxyl group. Compared to M6G their affinities were increased 1.5 to 2.4-fold at mu, 2.9 to 10.3 at delta and 1.4 to 369-fold at the kappa receptor. Compounds **5a** and **5b** each possessing a carbomethoxy group at the C-5' position showed a 1.7 to 2.7-fold selectivity for the kappa receptor over the delta receptor. All of the other ligands showed selectivity for the delta receptor over the kappa receptor. The replacement of the carbomethoxy group at C-5' in compound **5a** with an acetoxymethyl group in compound **5d** decreased the affinity for the kappa receptor by a factor of 270. The affinity of the remaining compounds for the mu, delta and kappa receptors possessing either 3-acetoxy groups or 3-methyl ether groups was significantly decreased when compared to M6G. In each instance, hydrolysis of the ester functional groups in the sugar moiety greatly diminished affinity of the ligands for the kappa receptor, while having a significantly less pronounced effect on the affinity of the ligands for the mu and delta receptors.

[0124] With respect to the mu binding affinity of type II compounds, the morphine analogue **10** (2.80 nM) possessing a free phenolic hydroxyl group and a fully esterified glucuronic acid moiety had the highest affinity. This observation is consistent with those results observed for the type I analogue **3a**. Interestingly, the codeine derivative **9b** (7.43 nM) showed significantly higher affinity than any type I codeine compound. Compound **11a** (14.6 nM) and **11b** (41.5 nM) showed reduced affinity. In comparison to M6G, compound **10** showed a 4.5-fold higher affinity for the mu receptor and compound **9b** showed a 1.7-fold higher affinity. The type II compounds were significantly more selective than the type I compounds. The selectivity of compound **11b** for the mu receptor approached that of M6G, although it possessed a 3.2-fold reduction in binding affinity. These results suggest that the carbon bridge between the morphine or codeine nucleus and the sugar residue may be critical for mu receptor selectivity. It is conceivable that the additional conformational mobility imparted by this bridge allows these molecules to interact with the mu receptor more similarly to M6G, which possesses a C-6 alpha sugar residue.

[0125] With the exception of compound **14** (19.92 nM), the K_i values for type III compounds at the mu receptor were between 0.21 and 0.59 nM. These compounds were between 20-fold and 64-fold higher affinity for the mu receptor than M6G. Type III compounds were at least 9-fold higher affinity than the highest affinity type I compound and

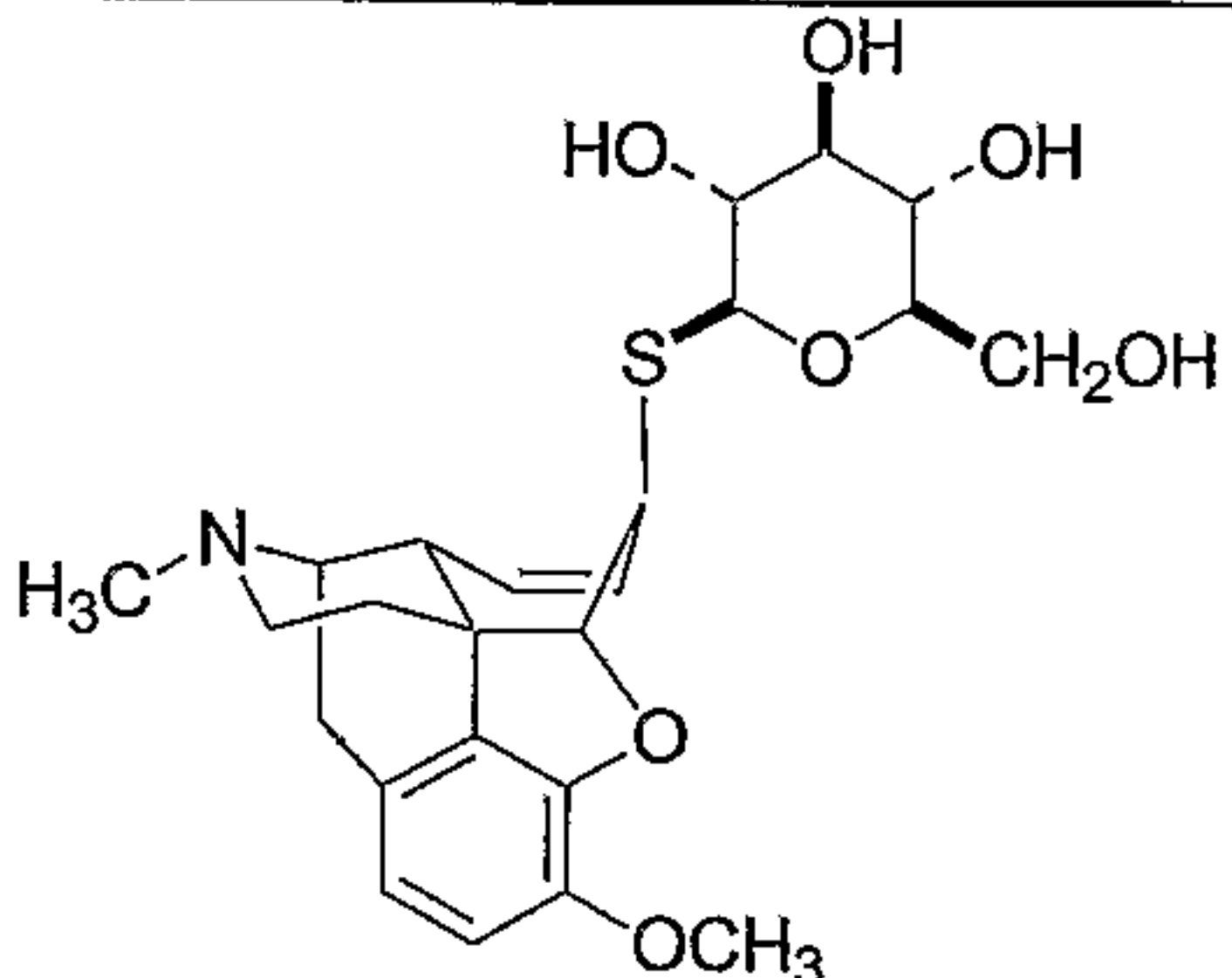
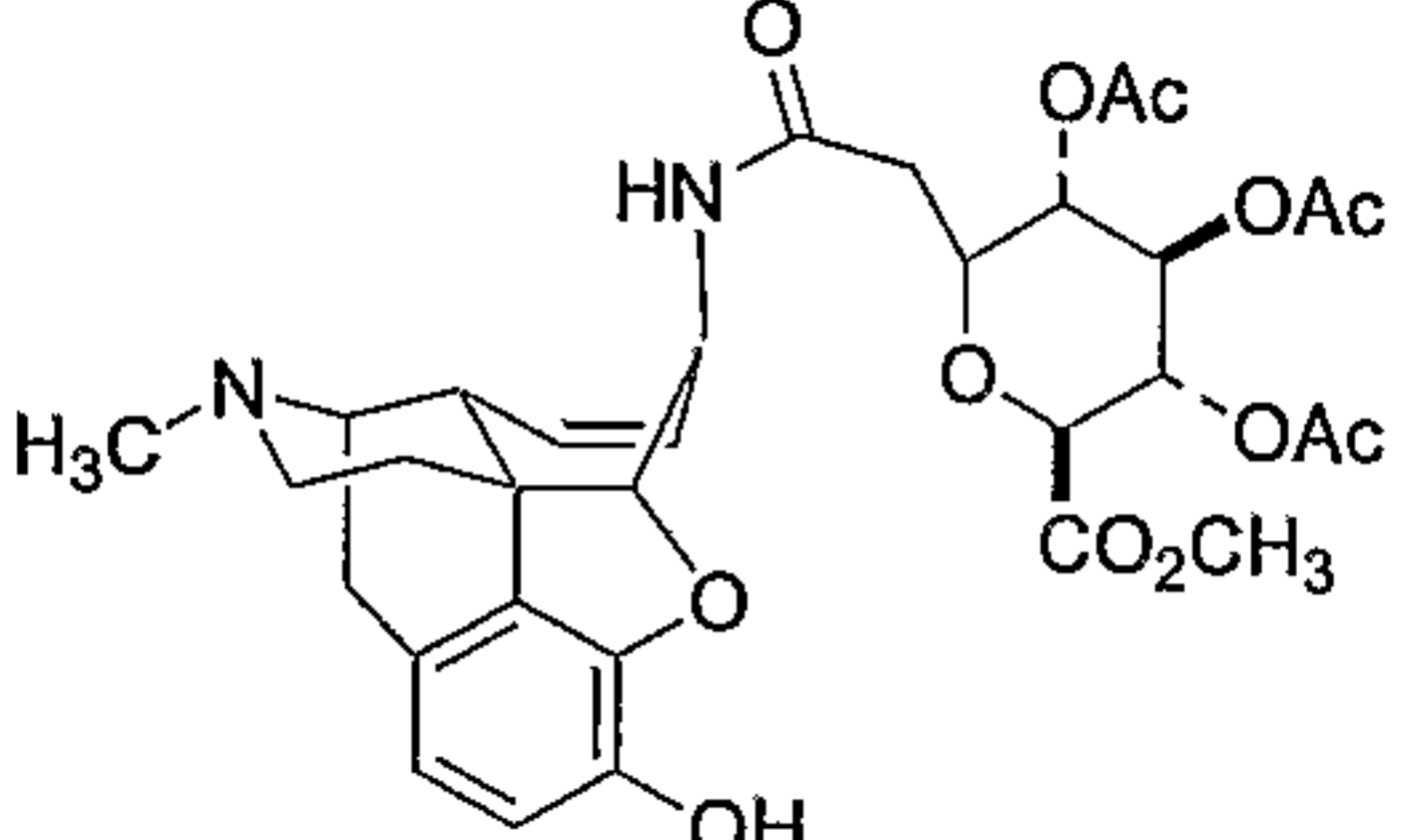
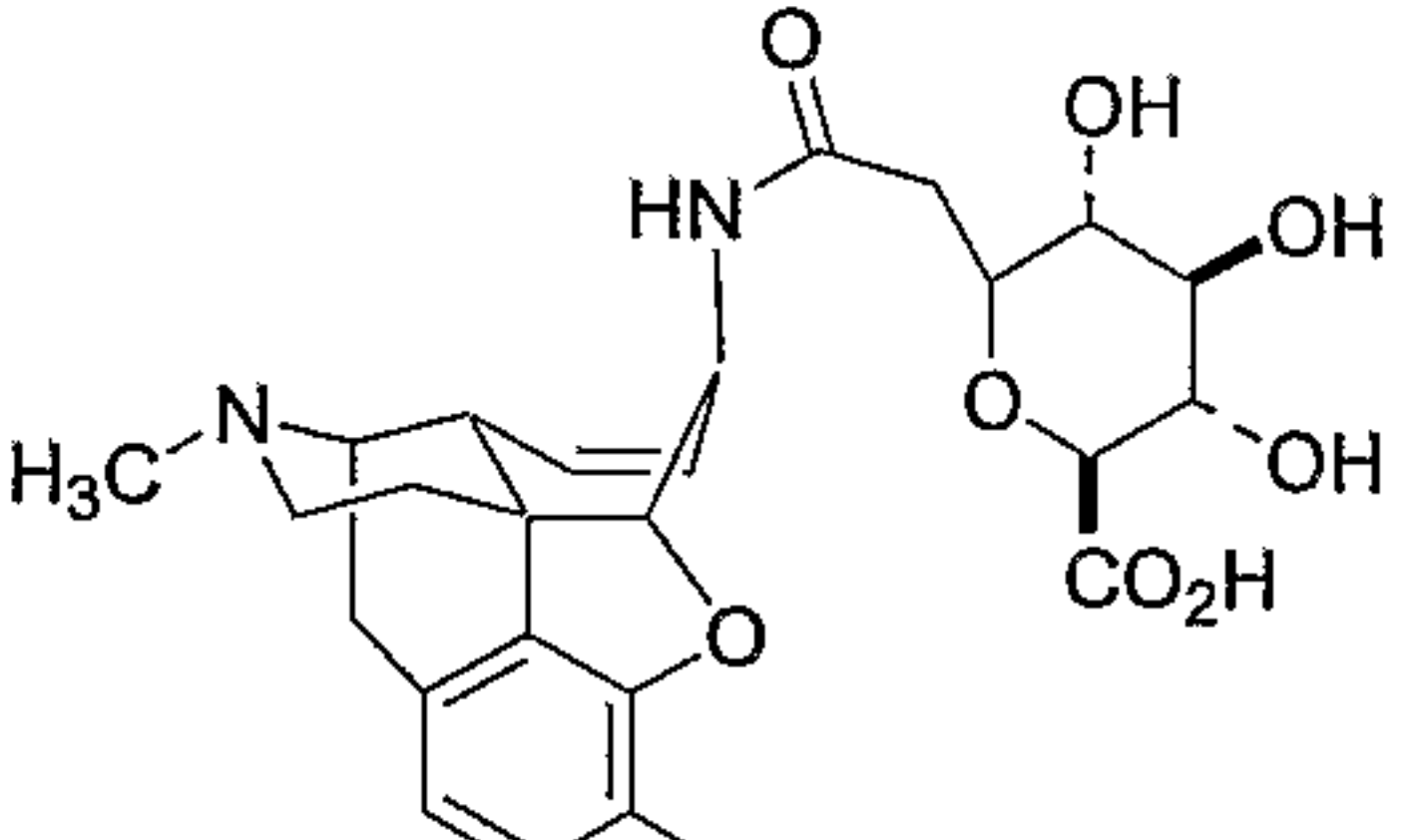
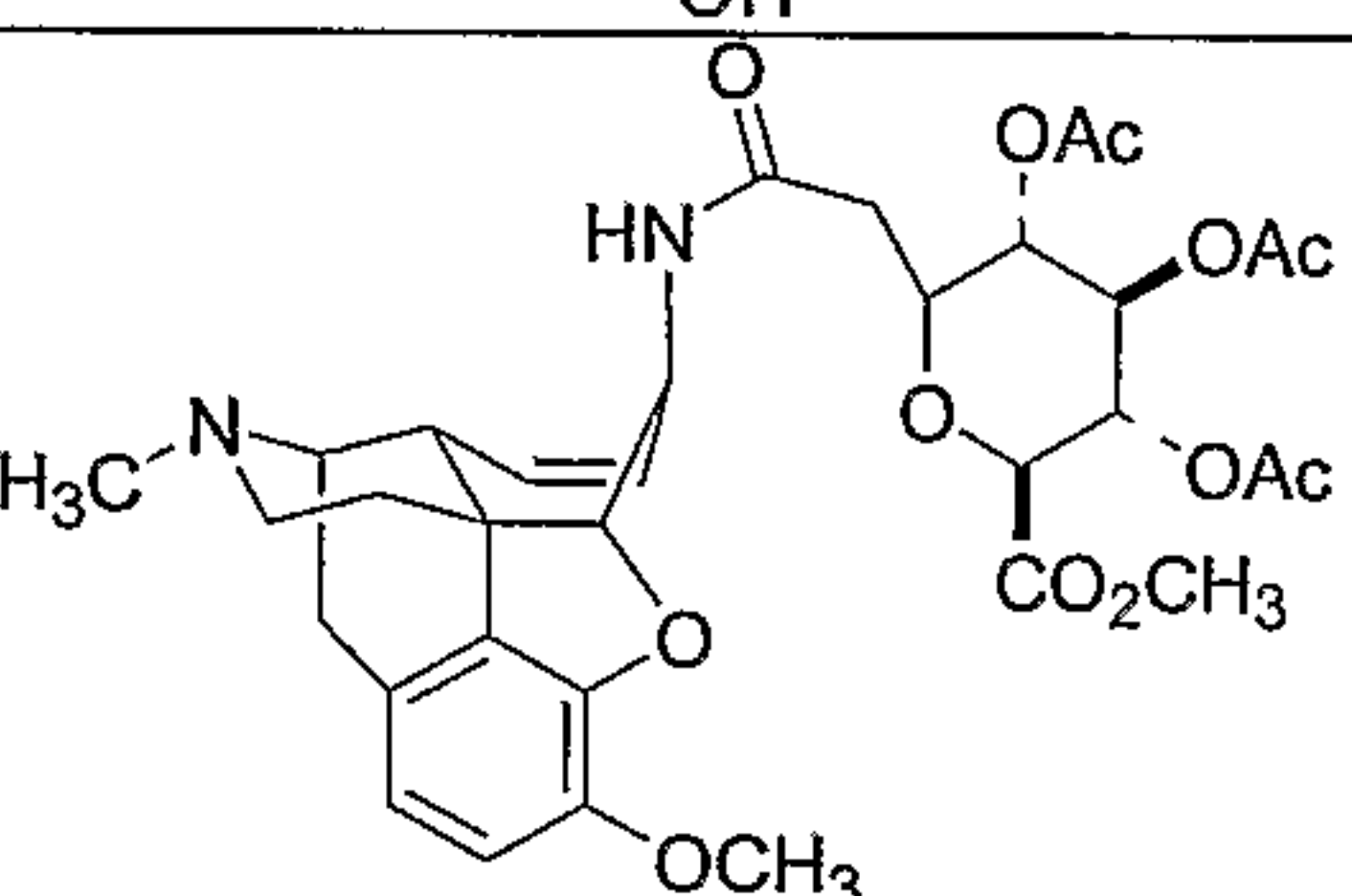
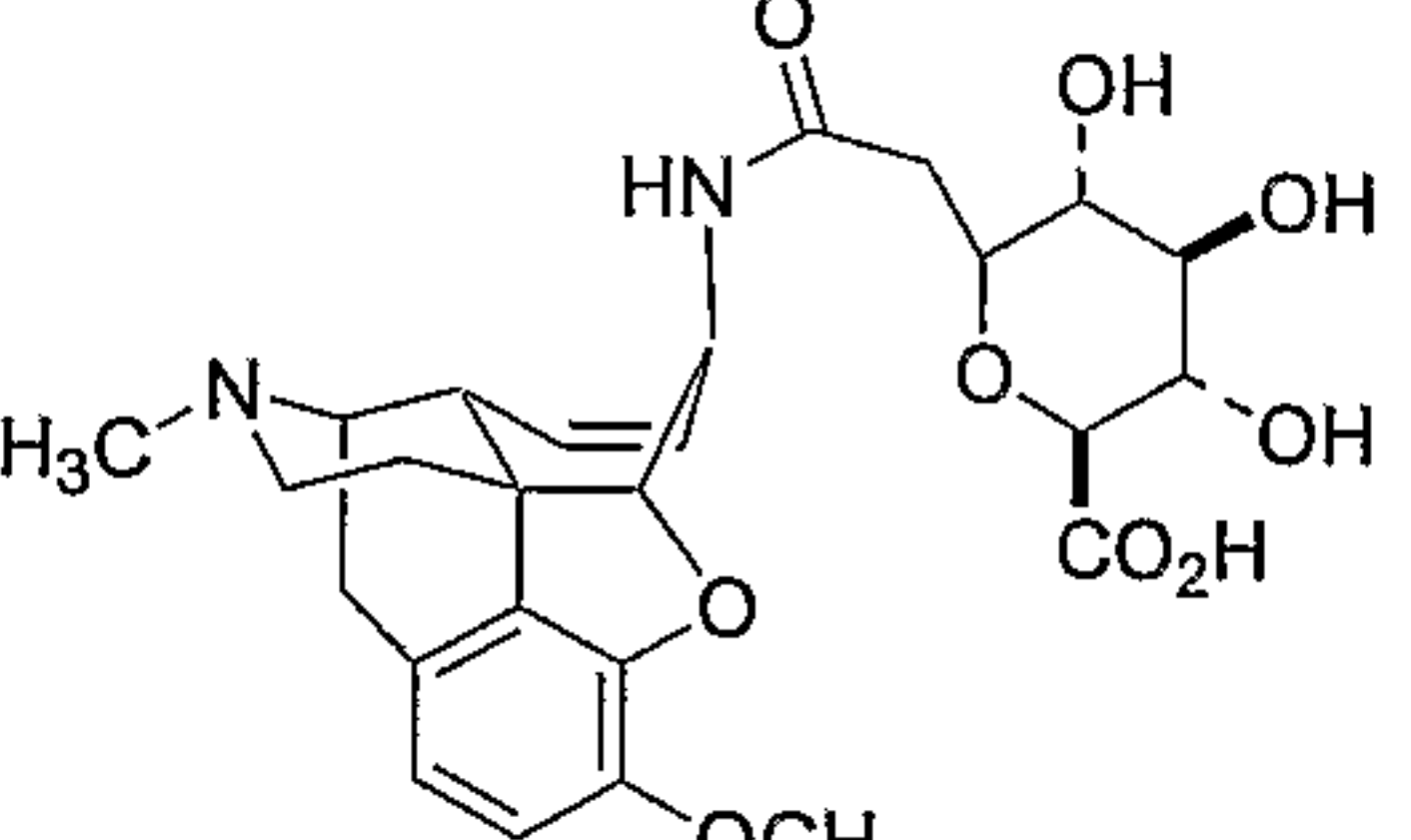
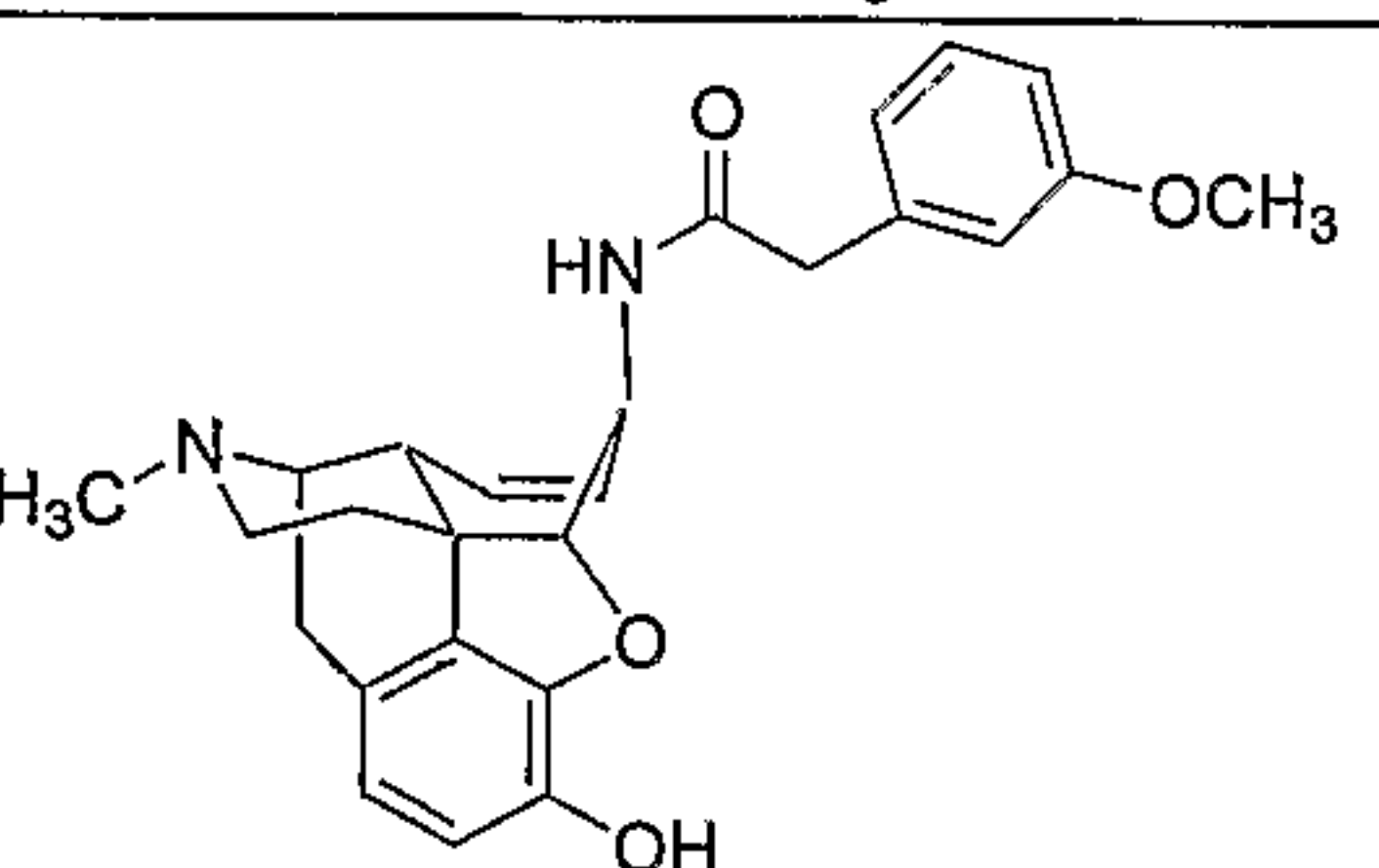
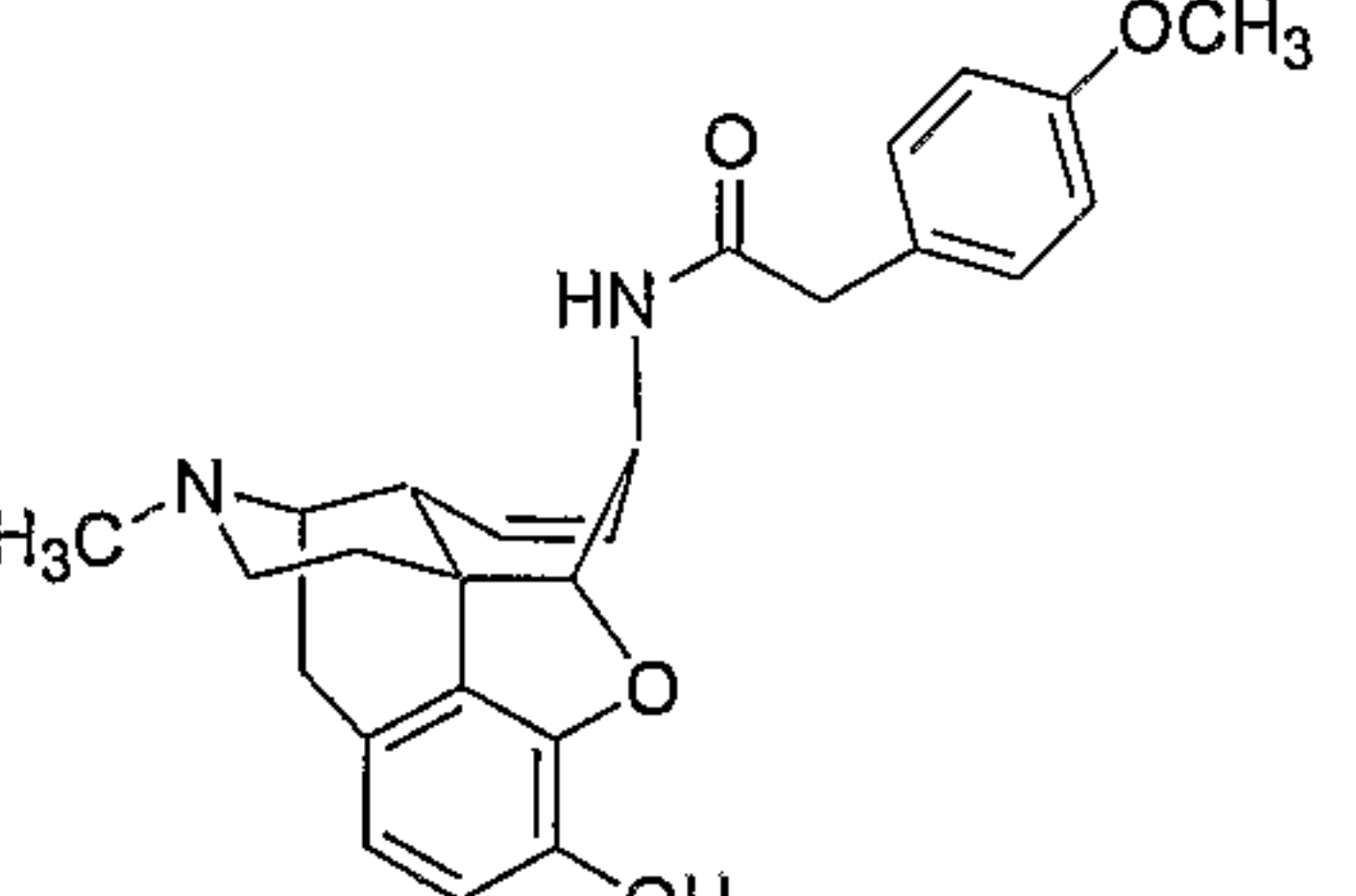
at least 4.7-fold higher affinity than the highest affinity type II compound. These results suggest that the C-6 substituent in these ligands was interacting with a hydrophobic region of the mu binding pocket. This observation is further supported by the decrease in affinity observed in compound **14** (19.92 nM). In most instances, type II compounds showed an increased mu versus delta selectivity and a reduced mu versus kappa selectivity.

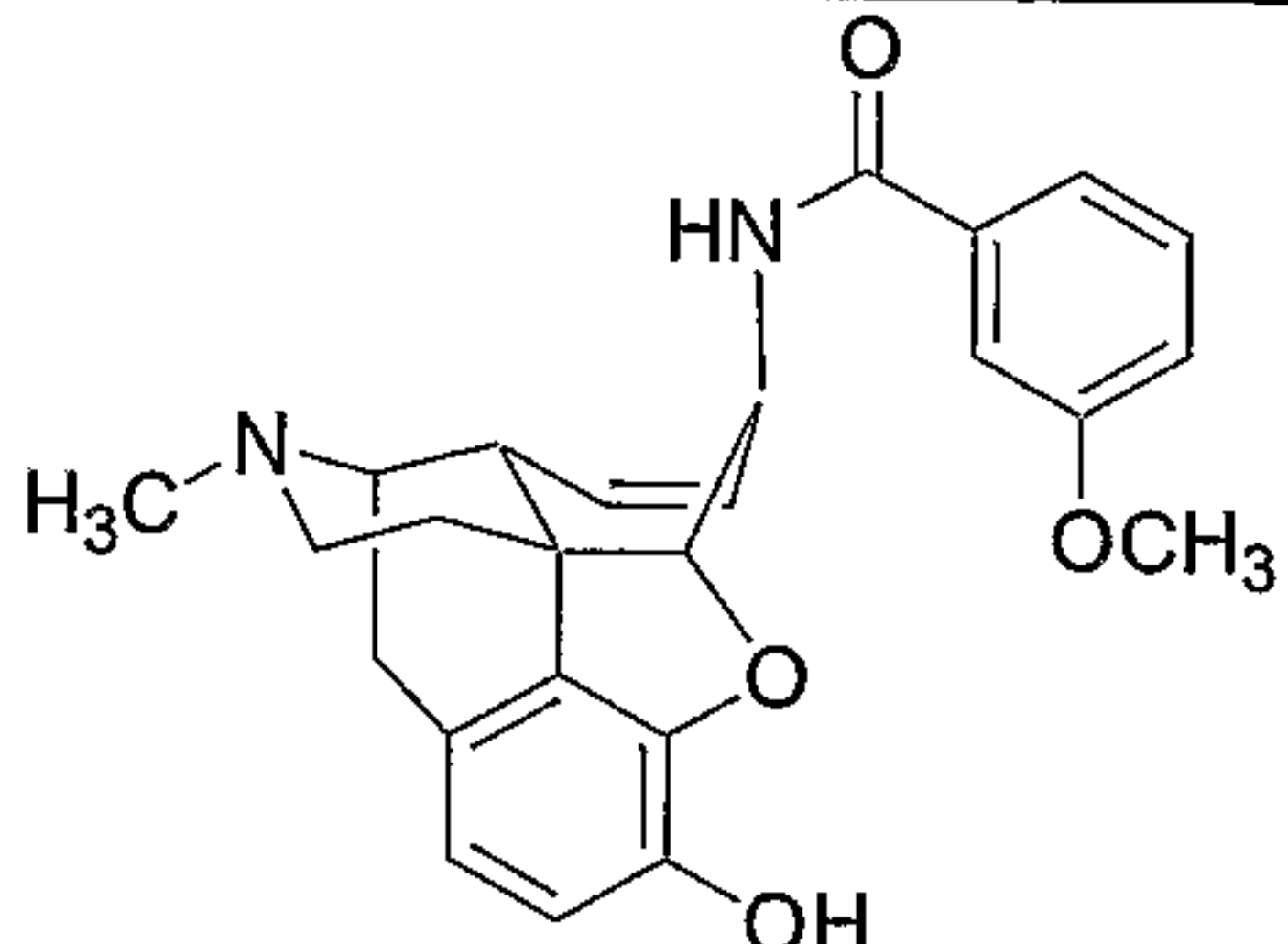
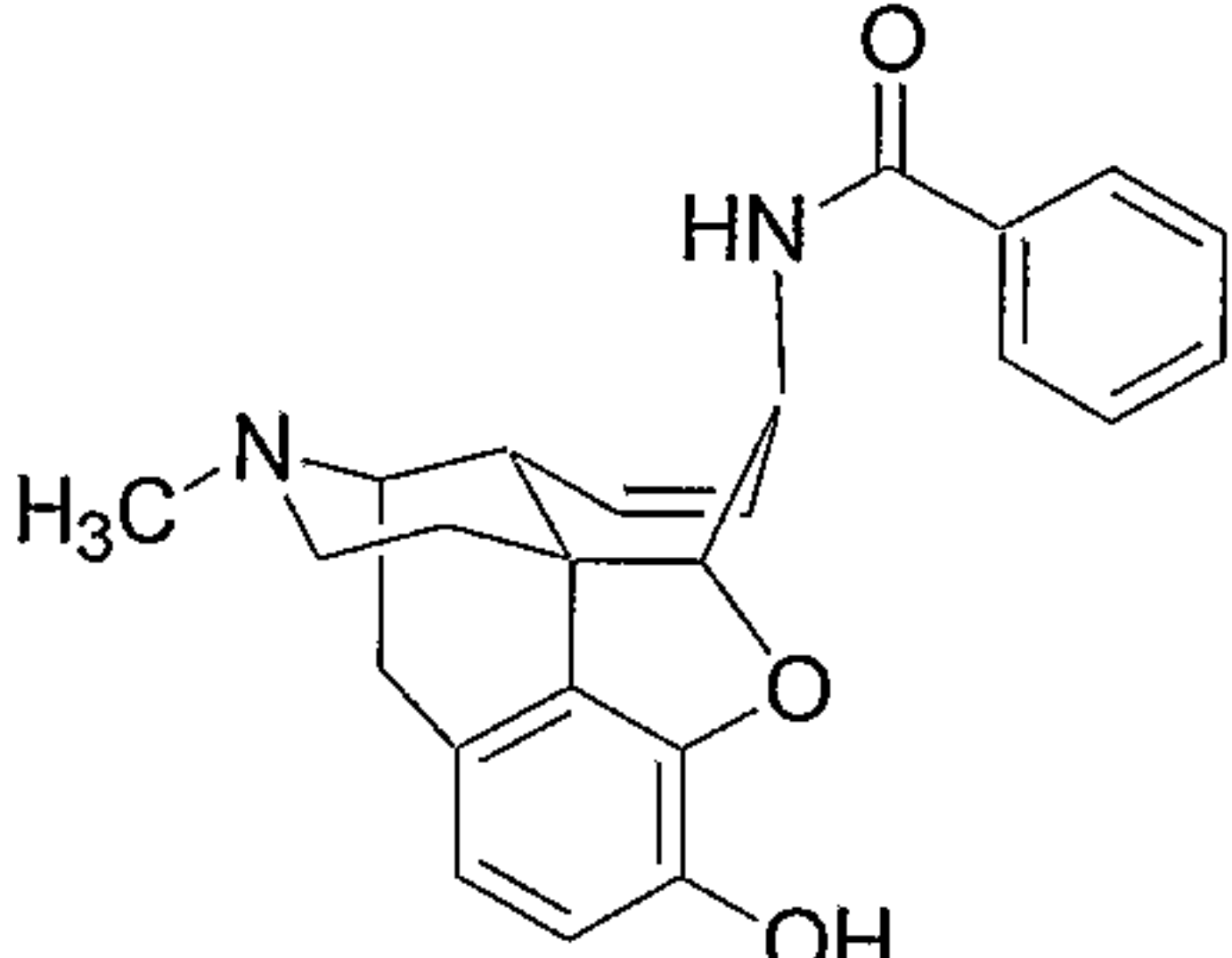
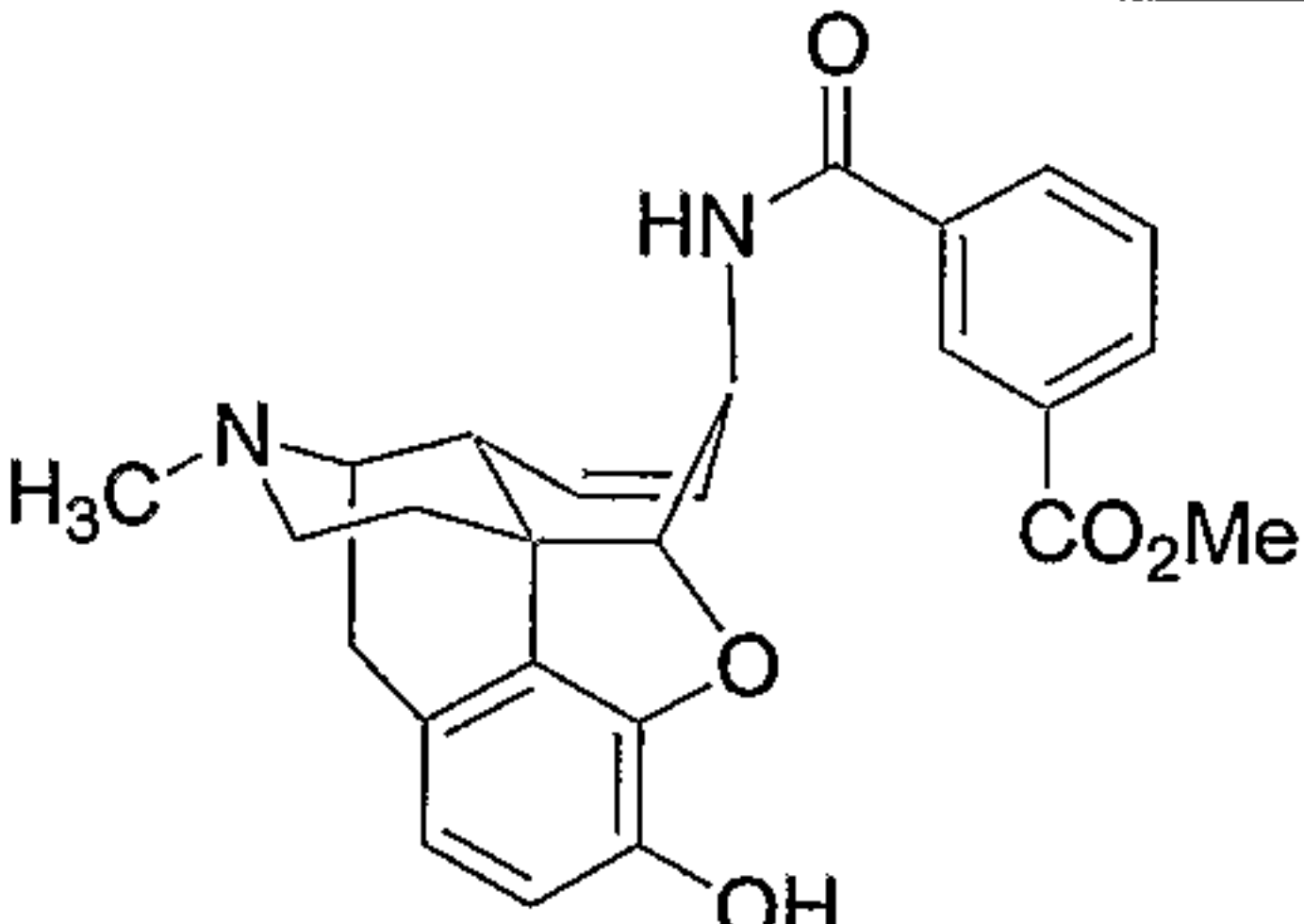
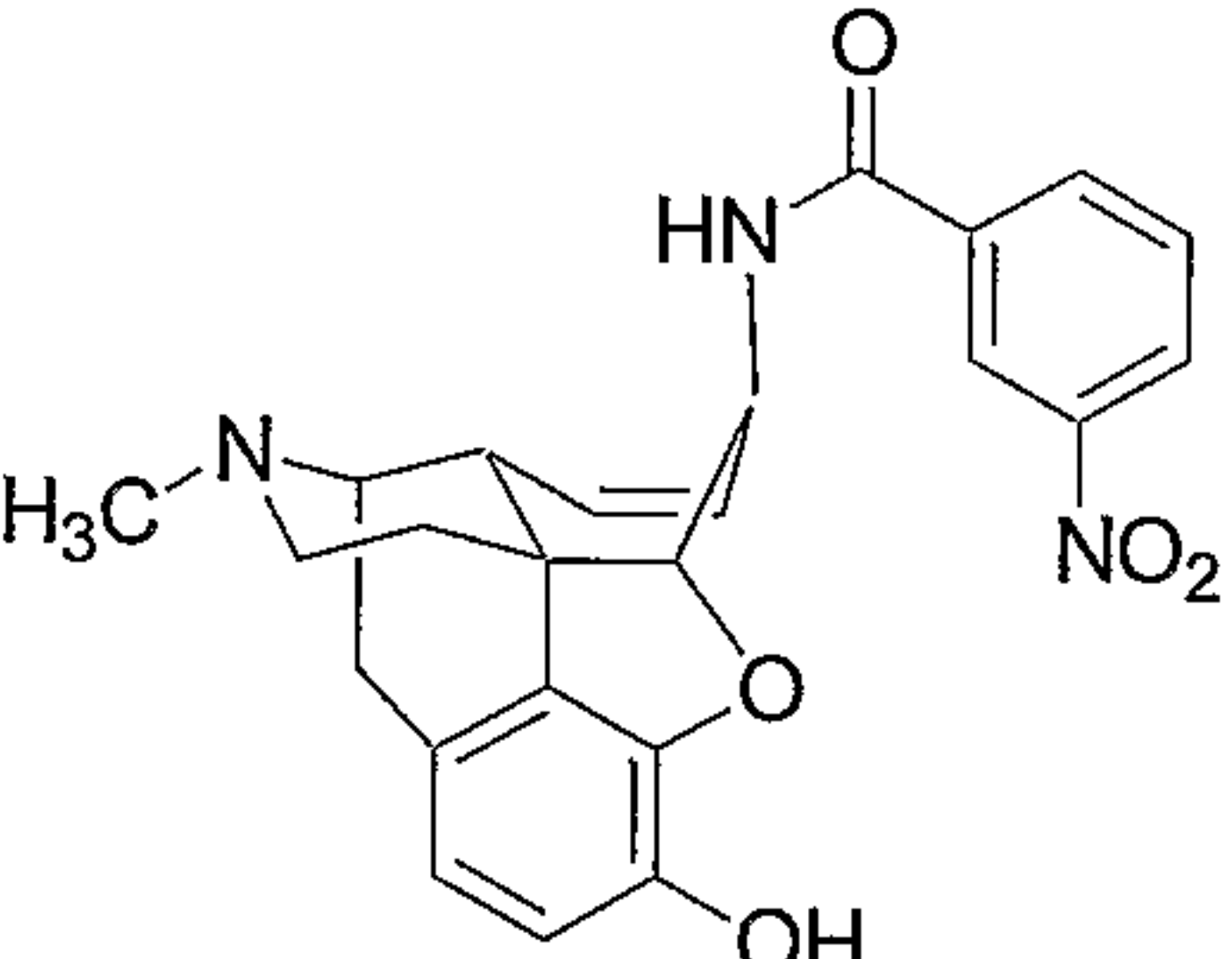
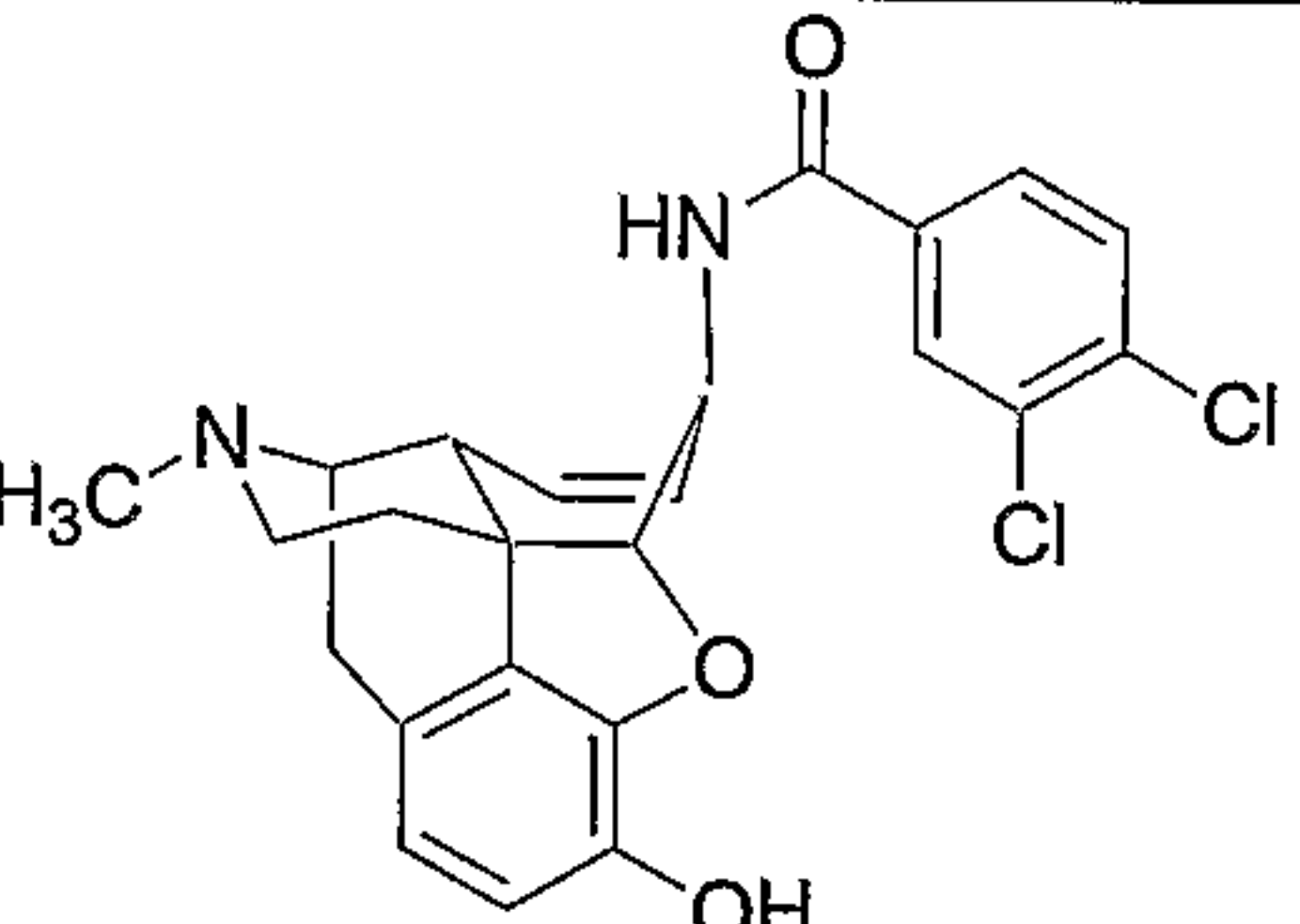
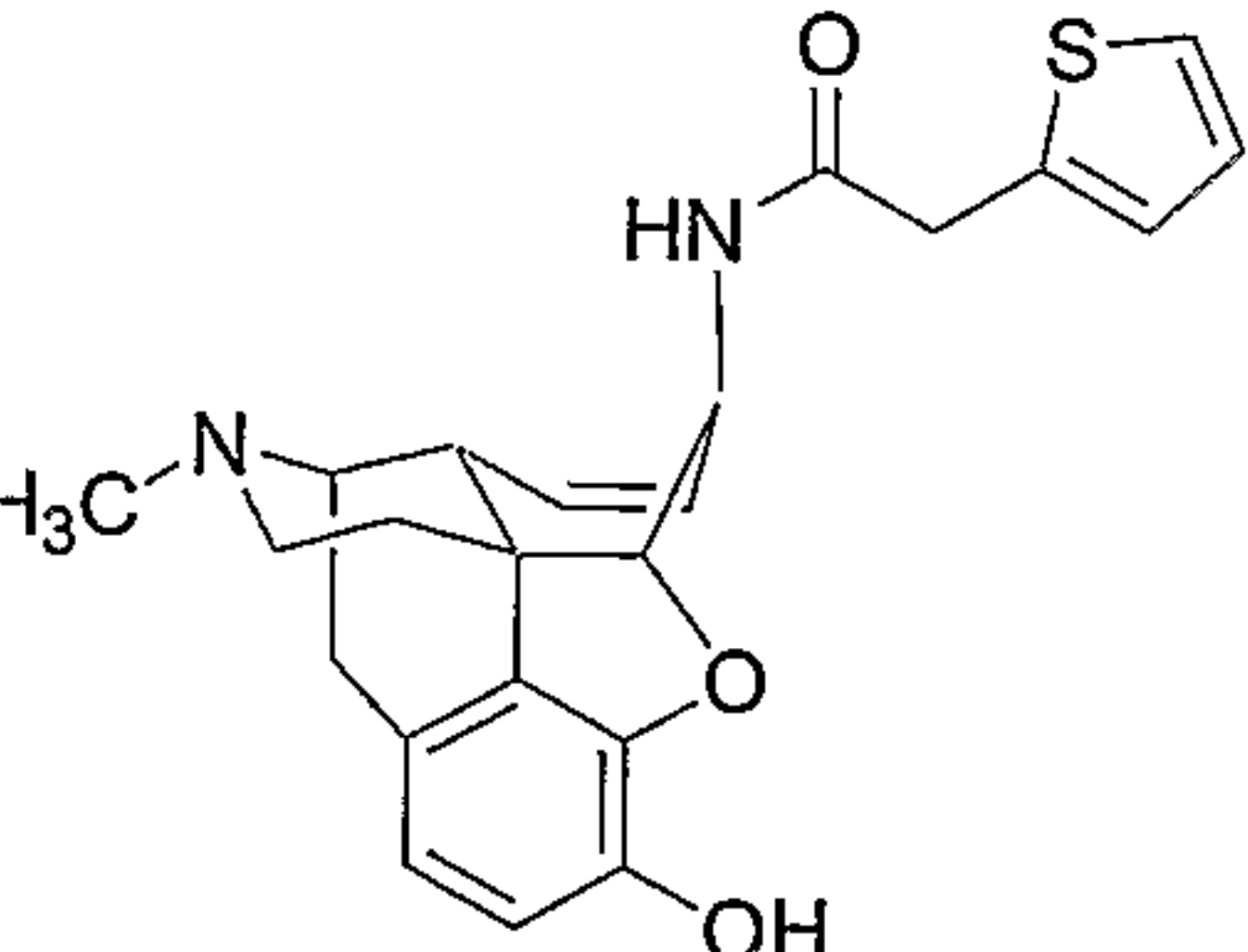
Replacement of the N-methyl substituent of the bridgehead N with cyclopropyl methyl or cyclobutyl methyl or similar substituents will typically afford antagonists of the receptors for the activity described below.

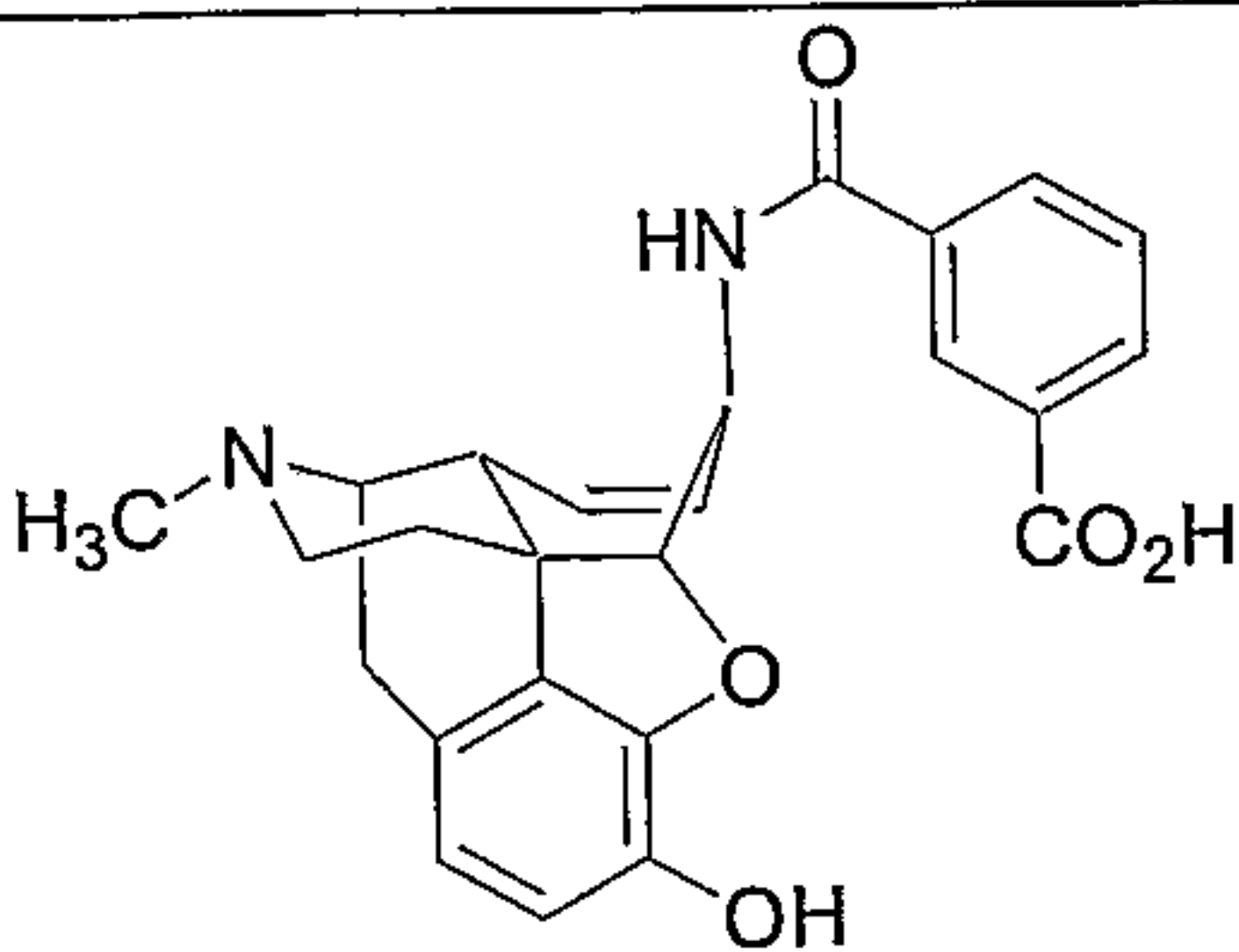
Table 1. Inhibition constants from competition binding assays of M6G derivatives at the mu, delta and kappa opioid receptors.

entry	cmpd	Ki (nM)			δ/μ	κ/μ
		μ	δ	κ		
morphine		1.1±0.05	140±2	46.9±14	127	42
M6G		12.85±0.95	160.96±0.73	4058.75±230	13	317
3a		5.37±0.14	15.6±2.4	11.0±0.06	2.9	2.0
3b		100±1.9	528±47	189±14	5.3	1.9
3c		305.04±66.04	762.07±166.54	1385.66±197.40	2.5	4.5

entry	cmpd	Ki (nM)			δ/μ	κ/μ
		μ	δ	κ		
3d		7.78±0.48	19.49±0.31	2973.60±947.83	2.5	382
3e		64±1.1	438±5	499±6.6	6.8	7.8
3f		164.61±27.66	465.77±118.71	2186±878.08	2.8	13
4a		8.73±0.85	31.4±2.3	288±12	3.6	33
4b		5.35±0.78	56.23±2.15	136.0±16.93	10.4	25
4c		463±57	2679±205	>10,000	5.8	>21

entry	cmpd	Ki (nM)			δ/μ	κ/μ
		μ	δ	κ		
4d		127.12±22.72	1138.22±353.73	2476.68±536.30	9	19.5
10		2.80±0.1	16.2±1.2	26.2±0.6	5.8	9.4
11a		14.6±2.4	53.8±3.1	325±17	3.7	22
9b		7.43±.55	176±27	499±49	24	67
11b		41.5±5.3	984±61	>10,000	24	241
13a		0.35±0.08	9.5±2.58	0.96±0.2	27	2.7
13b		0.59±0.19	8.89±2.1	2.84±0.96	44	4.8

entry	compd	Ki (nM)			δ/μ	κ/μ
		μ	δ	κ		
13c		0.21±0.07	8.96±1.95	2.65±1.25	42	12.8
13d		0.40±0.03	24.95±2.33	4.13±1.21	62.5	10.3
13e		0.23±0.05	3.39±0.03	1.53±0.2	15	6.7
13f		0.20±0.04	18.0±5.63	2.63±1.1	36	13
13g		0.20±0.04	0.94±0.02	0.75±0.2	4.7	3.8
13h		0.33±0.02	14.42±1.26	0.58±0.17	44	1.8

entry	cmpd	Ki (nM)			δ/μ	κ/μ
		μ	δ	κ		
14		19.92±4.29	50.78±8.86	>10K	2.5	502

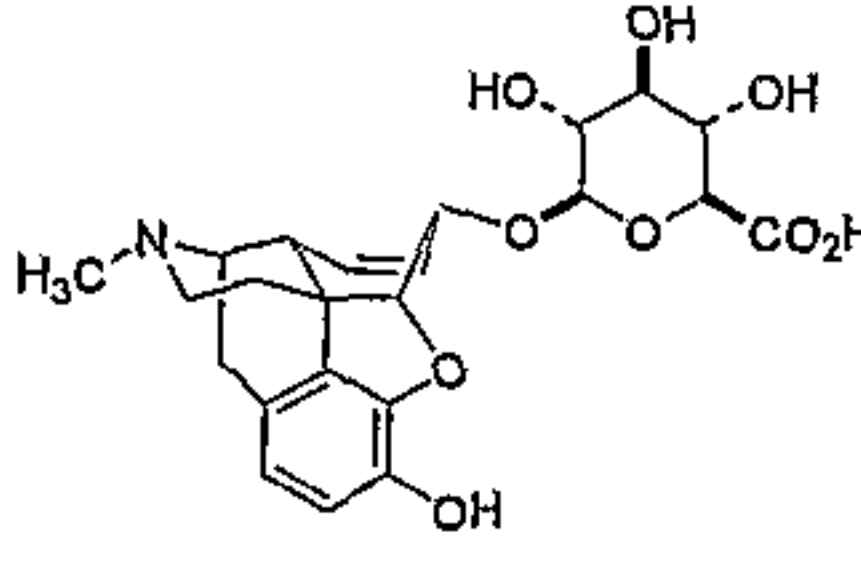
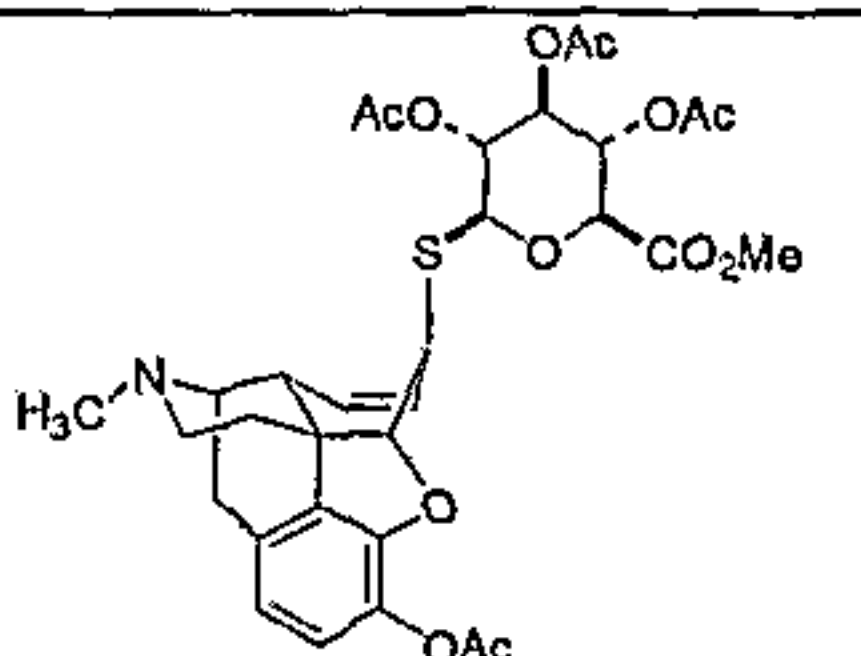
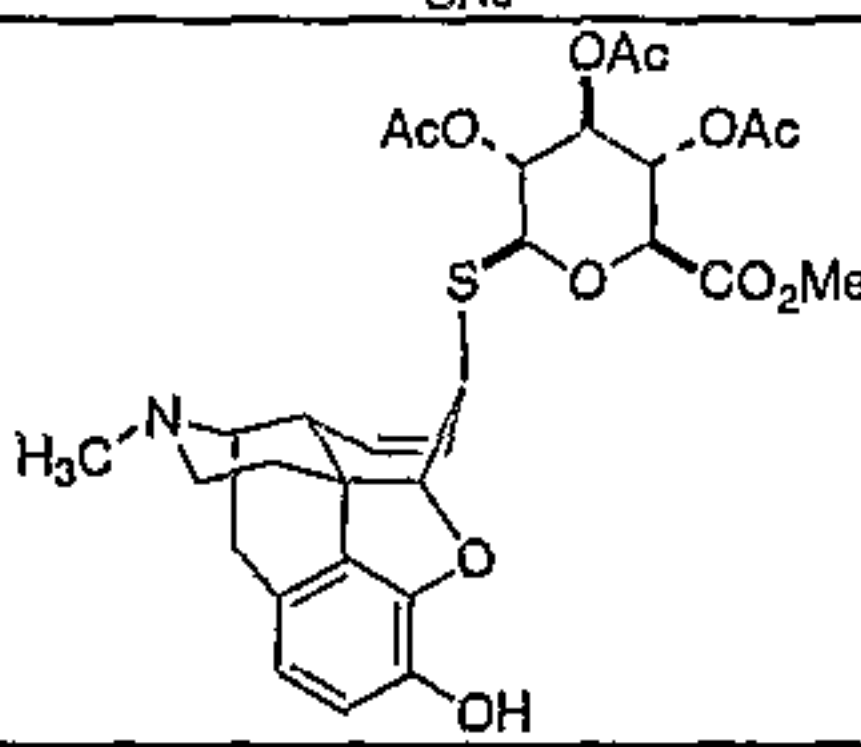
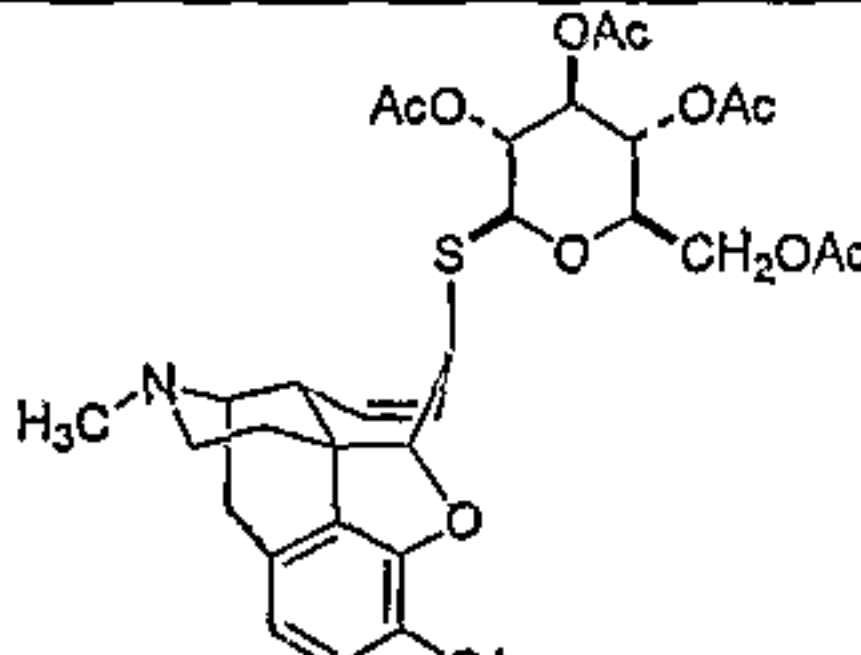
Example 28: [³⁵S]GTP γ -S binding studies to measure coupling to G proteins

[0126] A. **Methods.** Radiolabelled S binding was conducted basically as described by [J. R. Traynor and S. R. Nahorski., *Mol. Pharmacol.*, **47**:848-854 (1995)]. Cells were scraped from tissue culture dishes into 20 mM Hepes, 1 mM EDTA, then centrifuged at 500 x g for 10 min. Cells were resuspended in this buffer and homogenized using a Polytron homogenizer. The homogenate was centrifuged at 27,000 x g for 15 min and the pellet resuspended in Buffer A, containing 20 mM Hepes, 10 mM MgCl₂, 100 mM NaCl, pH 7.4. The suspension was recentrifuged at 27,000 x g and suspended once more in Buffer A. For the binding assay, membranes (8-15 μ g protein) were incubated with [³⁵S]GTP γ -S (50 pM), GDP (10 μ M), and the appropriate compound, in a total volume of 1.0 mL, for 60 min at 25 °C. Samples were filtered over glass fiber filters and counted as described for the binding assays. Statistical analysis was conducted using the program Prism.

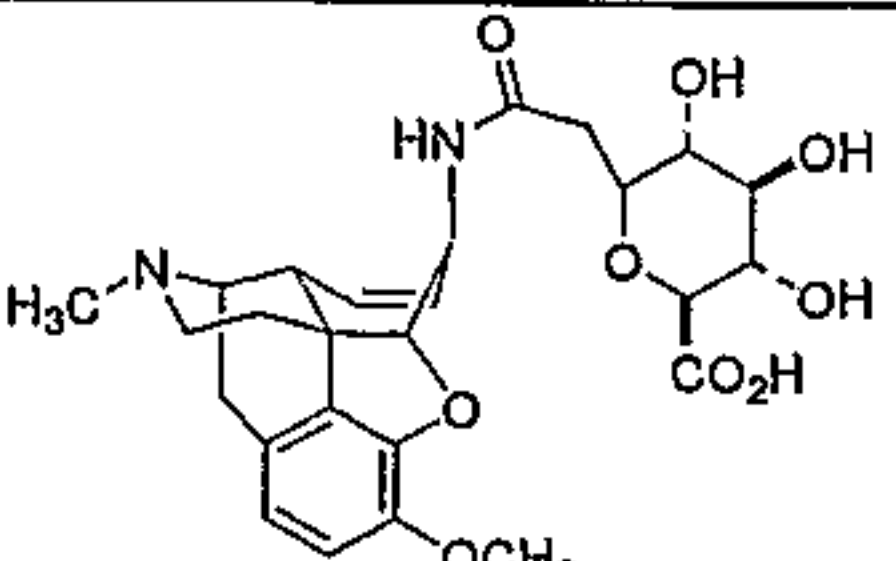
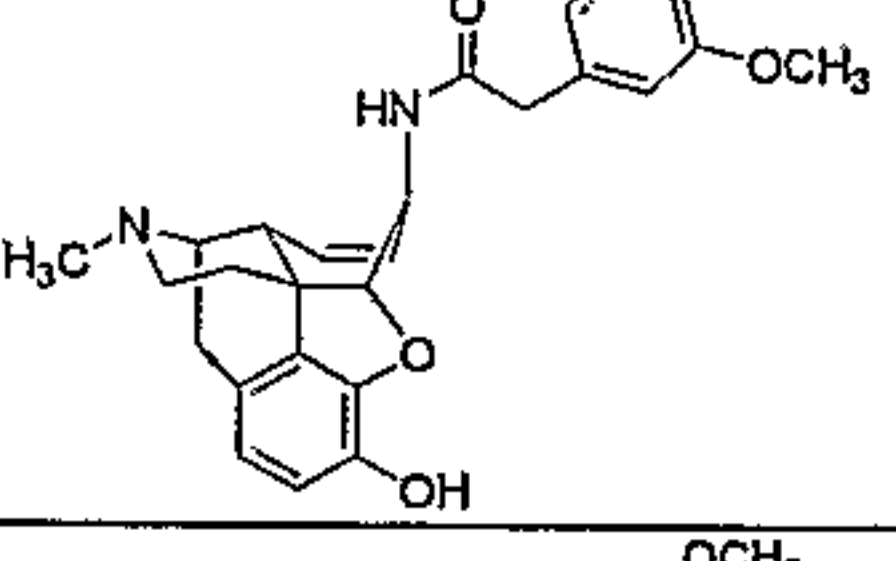
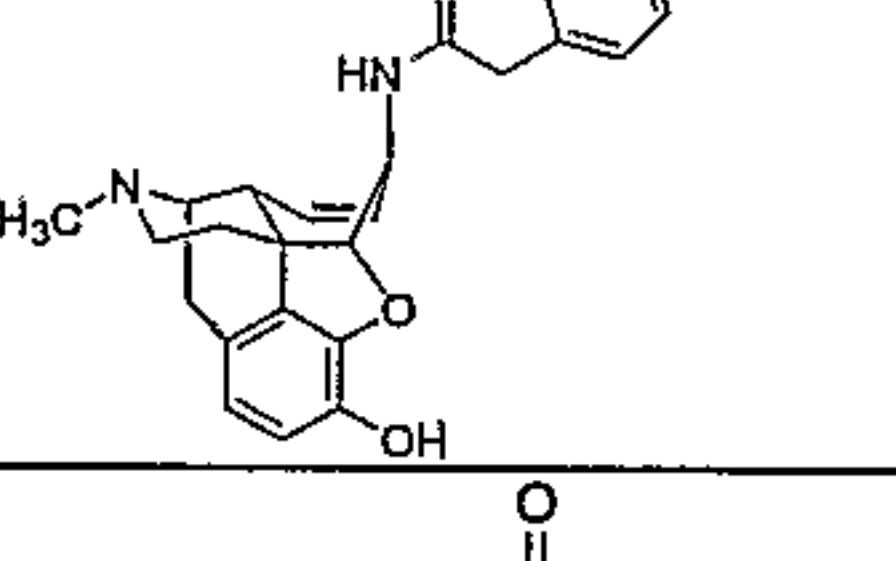
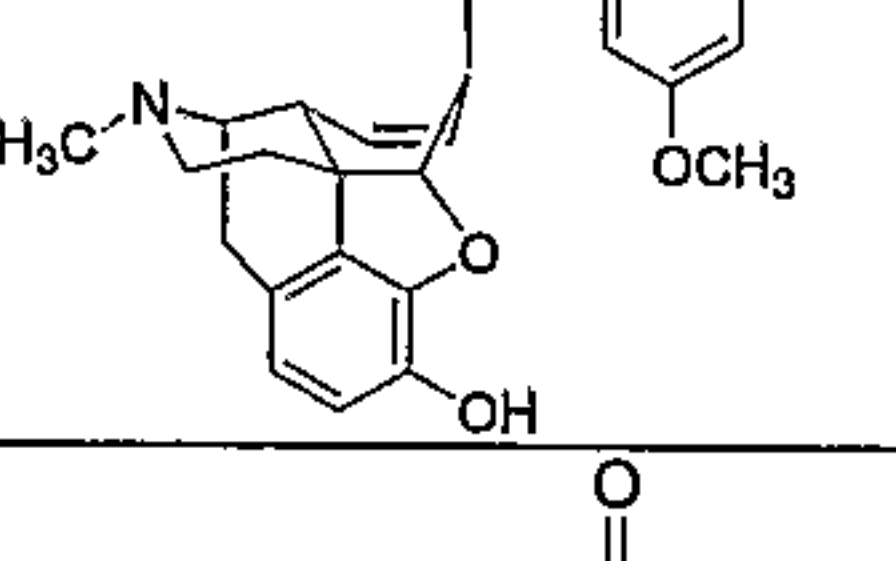
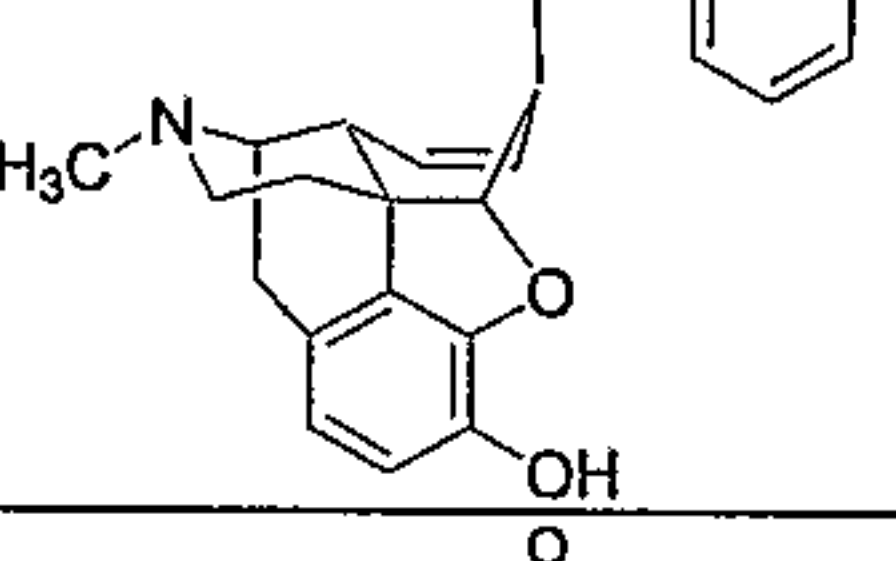
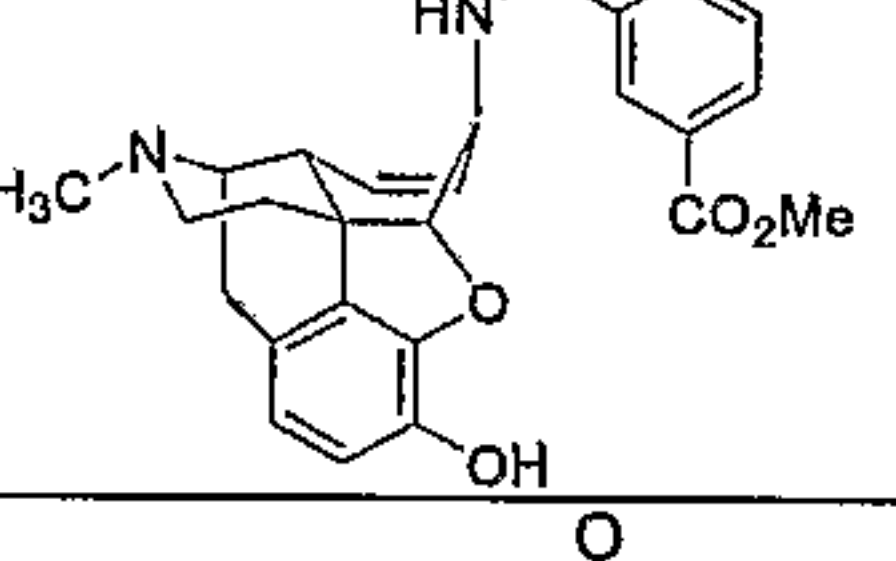
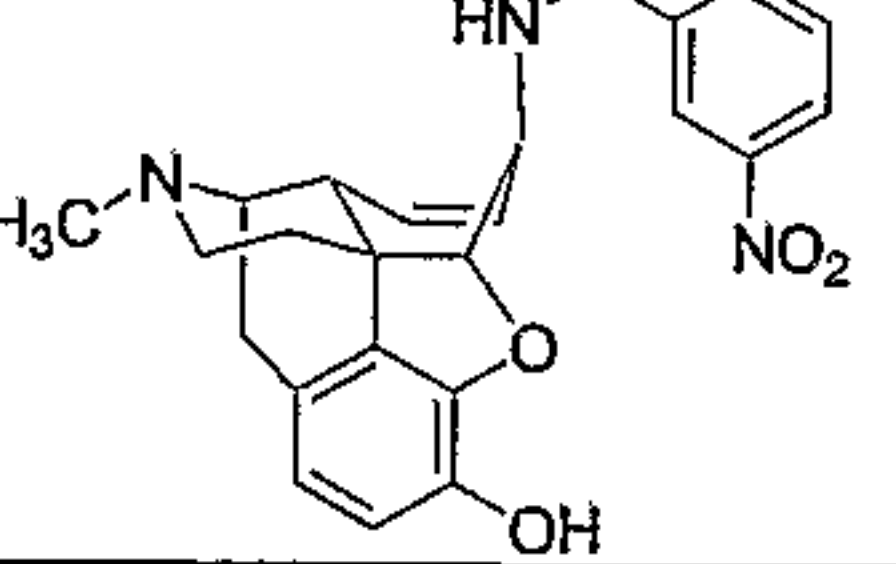
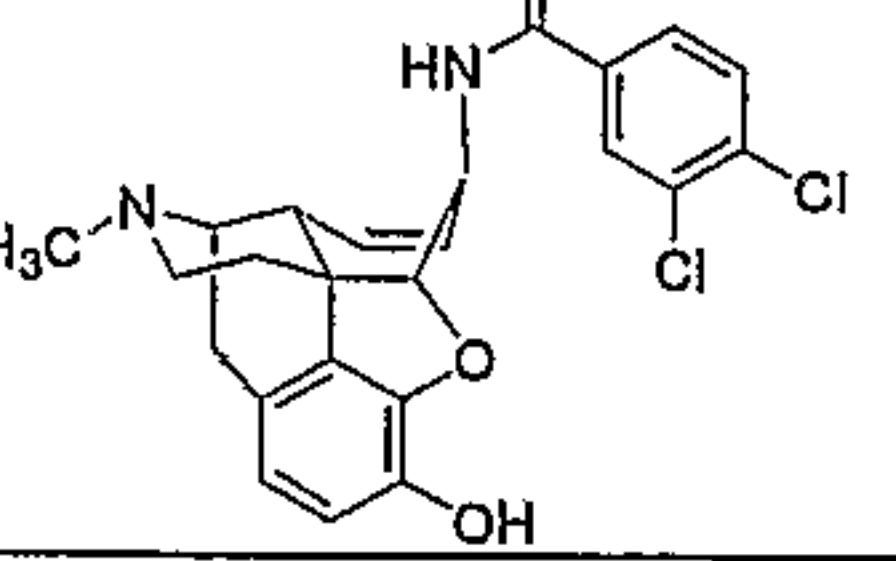
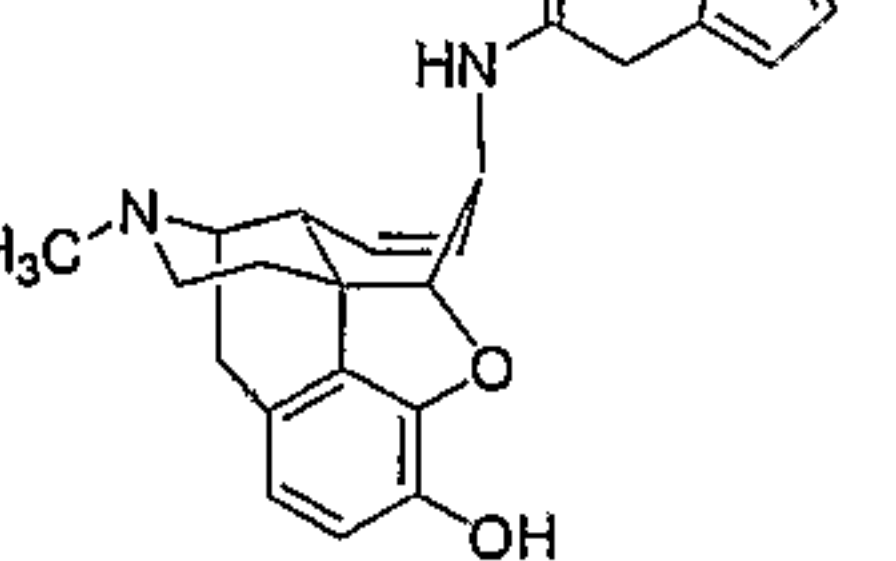
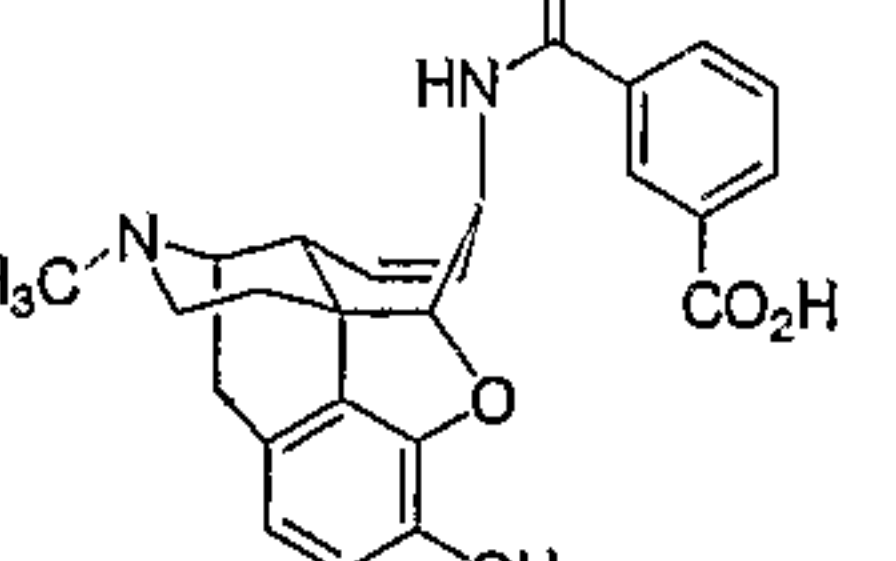
[0127] B. **Results.** Potency and Efficacy of Ligands. In order to evaluate the opioid receptor-mediated activation of its associated G protein, the compounds were evaluated using [³⁵S]GTP γ S assays. These data are summarized in Table 2. In this assay, the compound's potency or affinity for the receptor is defined by its EC₅₀ for stimulating [³⁵S]GTP γ S binding. Agonist efficacy is defined as the degree to which the compound maximally stimulates [³⁵S]GTP γ S binding relative to the control. The EC₅₀ value represents the concentration of a compound that produced 50% maximal stimulation of [³⁵S]GTP γ S binding by that compound. Full agonists stimulate [³⁵S]GTP γ S binding to a maximal extent and partial agonists cause a reduced level of binding. Table 2 gives the E_{max} and EC₅₀ values for stimulation of [³⁵S]GTP γ S binding at human mu, delta and kappa opioid receptors. With the exception of compound 6c all of the compounds stimulated [³⁵S]GTP γ S binding at the mu and delta receptors. The compounds were much less efficacious at the kappa receptor. This trend was also observed for M6G. The most efficacious compounds at the mu receptor were compounds **3b** (88.0%), **3d** (76.0%), **4b** (64.5%), and **4a** (46.6%) (see Table 2). Each of

these compounds possessed a free phenolic hydroxyl group. These compounds were all more efficacious than M6G. The same general trend was observed at the delta receptor with compounds possessing a free phenolic hydroxyl showing increased efficacy. The most efficacious compounds were **3b** (104.4%), **4a** (78.70%), **3e** (64.3%), and **4b** (51.5%). Protection of the phenolic hydroxyl group with an acetate group or a methyl group diminished the efficacy and potency at each receptor. Compounds that effected maximal stimulation may be viewed as agonists at a given receptor. Those ligands that elicited less than maximal binding may be viewed as partial agonists or antagonists if no stimulation was observed. The overall rank order of the EC₅₀ values correlated with the K_i values. With respect to the type II compounds, ligands **10** and **9b** produced maximum stimulation of [³⁵S]GTPgammaS binding by the mu receptor and reduced stimulation of [³⁵S]GTPgammaS binding at the delta and kappa receptors. With respect to type III compounds **13a-h** and **14** each of the compounds stimulated [³⁵S]GTPγS binding at the mu, delta and kappa receptors. The compounds were generally more efficacious at the mu and kappa receptors as opposed to the delta receptor. Compounds that effected maximal stimulation may be viewed as agonists at a given receptor. Those ligands that elicited less than maximal binding may be viewed as partial agonists or antagonists if no stimulation was observed. The overall rank orders of the EC₅₀ values correlated with the K_i values.

Table 2. Stimulation of ³⁵S-GTP-γ-S binding by M6G derivatives

entry	cmpd	mu		delta		kappa	
		EC ₅₀	% stimulation	EC ₅₀	% stimulation	EC ₅₀	% stimulation
M6G		72.3±26.7	45.0 ± 5.0	190.35±22.9	80.0 ± 0	>10K	
3a		1424±239	37.8±6.7	1323±304	46.83±1.98	flat	flat
3b		43.7±16.48	88.3±19.5	80.16±0.16	104.4±19.95	29.11±8.23	23.52±0.92
3c		4794±1615	44.1±4.9	3659±1510	39.3±0.8	1722±634	36.9±1.9

entry	cmpd	mu		delta		kappa	
		EC ₅₀	% stimulation	EC ₅₀	% stimulation	EC ₅₀	% stimulation
3d		33.7 ± 11.3	76.0 ± 3.0	63.8 ± 14.6	45.5 ± 1.5	52.0 ± 4.9	26.5 ± 2.5
3e		732.2±47.1	19.3±0.3	1009±178	64.3±8.3	2667±64	24.34±4.2
3f		993.7±13.3	41.9±2.1	871.5±241.6	44.9±1.2	>10K	flat
4a		90.6±22.94	46.6±10.1	50.13±36.7	78.70±0.92	flat	flat
4b		91.5 ± 23.4	64.5 ± 0.5	191.7 ± 14.8	51.5± 6.5	320.9±93.1	42.5±2.5
4c		flat	flat	1331±20.5	44.25±5.4	flat	flat
4d		1059±22	42.0±6.0	1740±312	27.7± 3.3	4628±1773	21.0 ± 0
10		9.4±3.2	104.3±1.2	29.57±3.7	62.35±9.36	119±59.6	45.2±3.4
11a		113.9±5.55	44.5±7.1	67.62±0.9	69.81±0.58	1213±19	49.5±1.3
9b		83.9±4.3	96.8±8.22	424.9±100	76.49±19.94	1844.5±54. 5	30.65±3.86

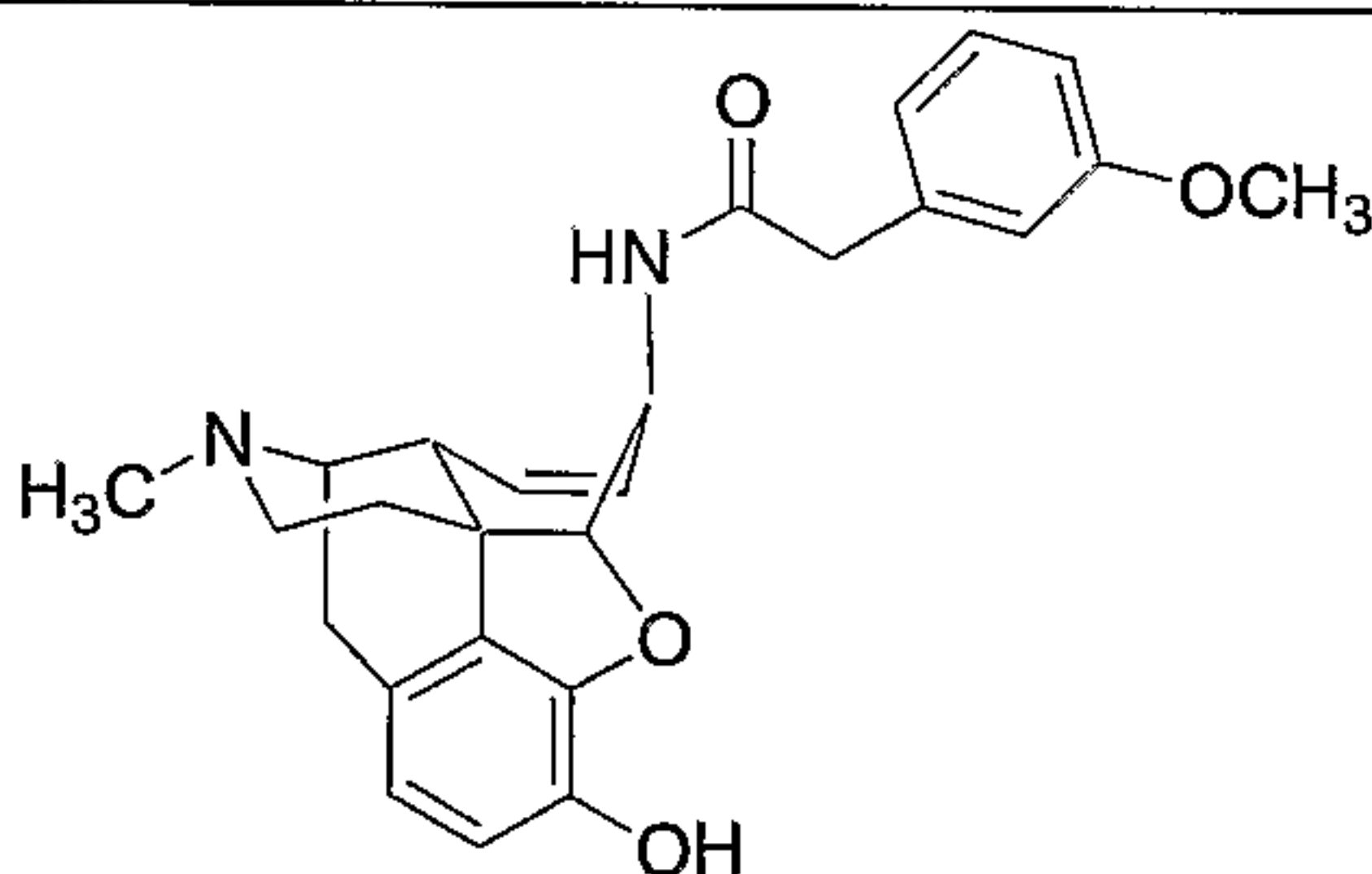
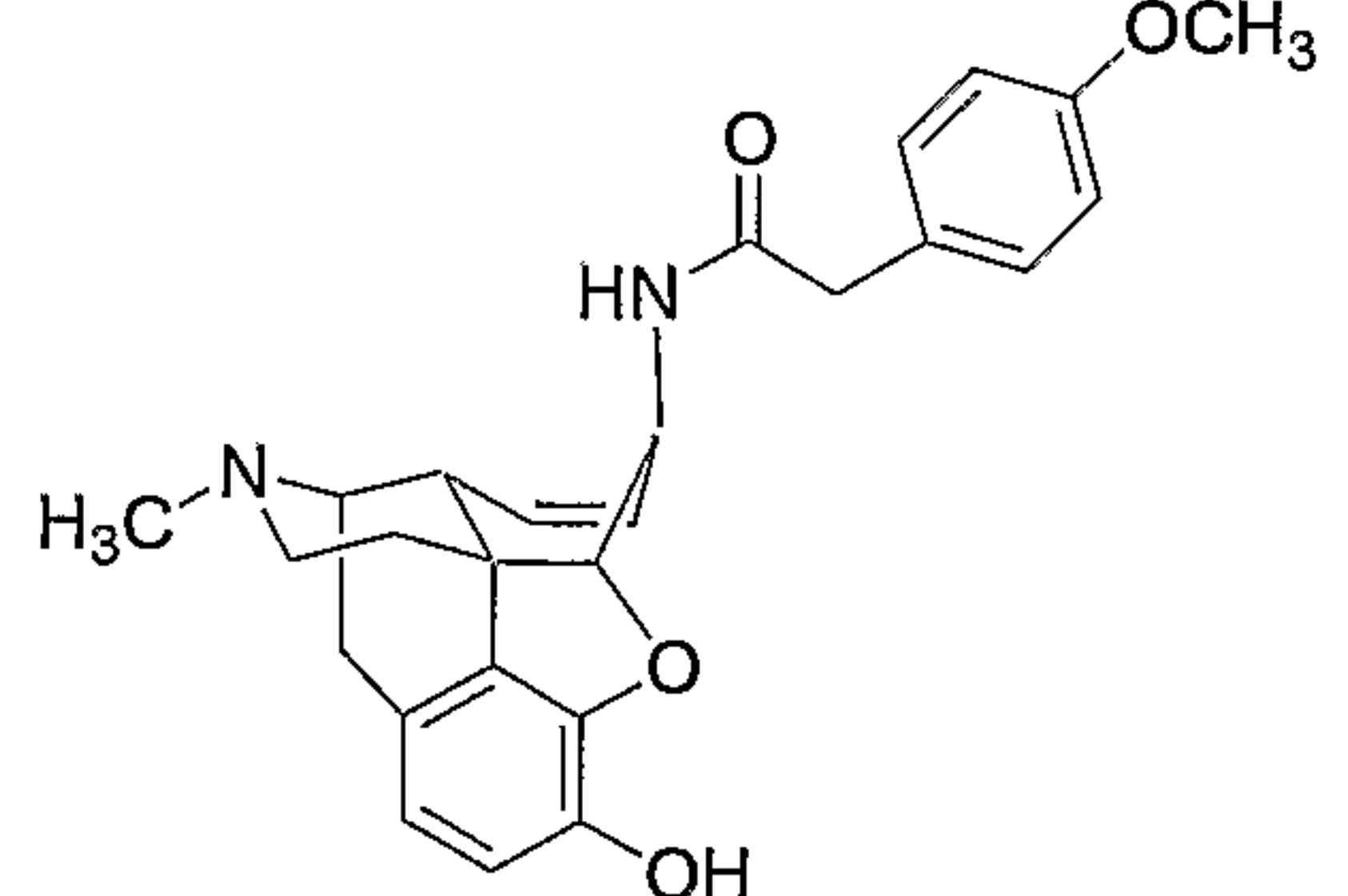
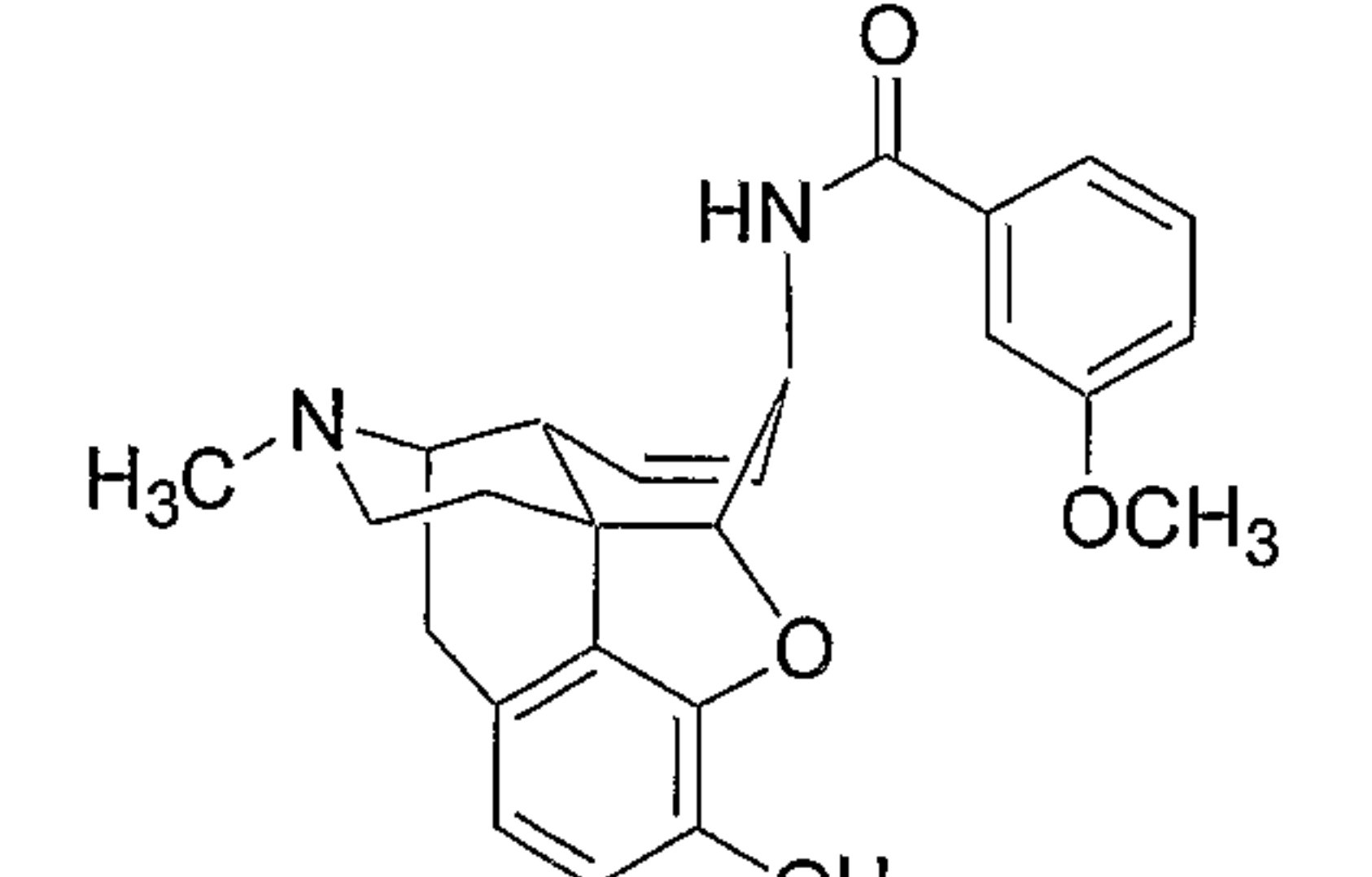
entry	cmpd	mu		delta		kappa	
		EC ₅₀	% stimulation	EC ₅₀	% stimulation	EC ₅₀	% stimulation
11b		672.3±6.4	27.1±3.4	1031±34.2	48.92±5.5	flat	flat
13a		1.7 ± 0.17	99.0 ± 4.0	18.8 ± 2.21	51.0 ± 4.0	4.8 ± 0.1	89.0 ± 6.0
13b		4.8 ± 2.05	72.5 ± 14.5	25.2 ± 3.0	59.5 ± 3.5	5.0 ± 1.0	81.5 ± 1.5
13c		2.8 ± 0.24	87.5 ± 6.5	37.8 ± 1.9	65.5 ± 5.5	9.8 ± 0.02	86.0 ± 0.0
13d		5.5 ± 0.9	90.5 ± 9.5	62.7± 24.0	61.3 ± 2.3	5.3 ± 1.3	81.1 ± 8.9
13e		2.4±0.32	98.1±7.9	6.20±0.42	99.63±2.19	11.22±3.51	88.6±8.6
13f		1.9 ± 0.16	95.5 ± 7.5	24.5 ± 3.0	94.1 ± 10.9	1.2 ± 0.1	90.3 ± 4.8
13g		0.1 ± 0.00	95.5 ± 10.5	1.3 ± 0.3	106.5 ± 11.5	0.03 ± 0.02	78.5 ± 1.5
13h		6.0 ± 2.1	95.8 ± 19.3	32.4 ± 2.1	57.3 ± 2.8	4.5 ± 0.2	98.0 ± 1.0
14		65.1 ± 21.8	71.0 ± 8.0	74.0 ± 12.7	69.5 ± 3.5	5096	71 ± 12

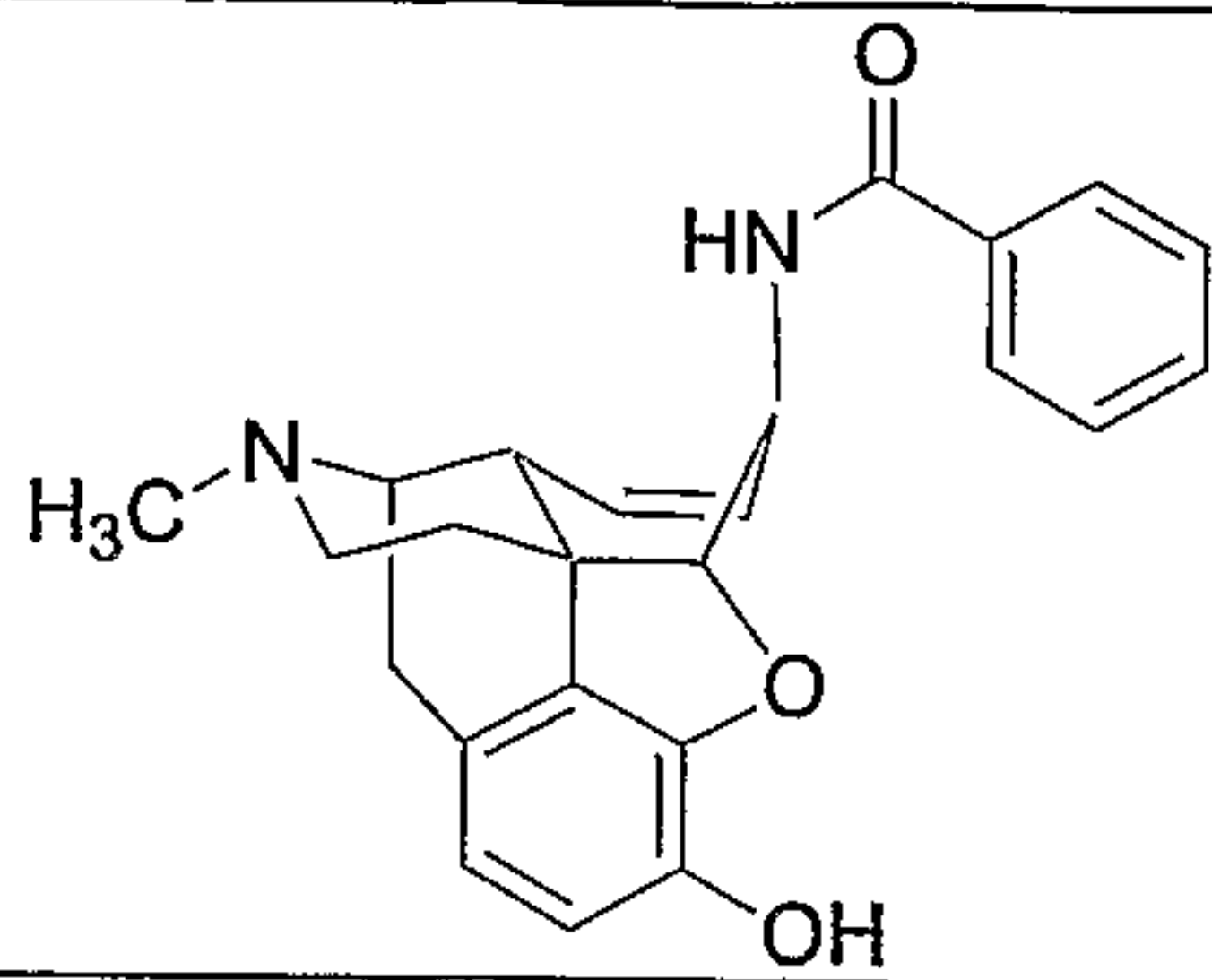
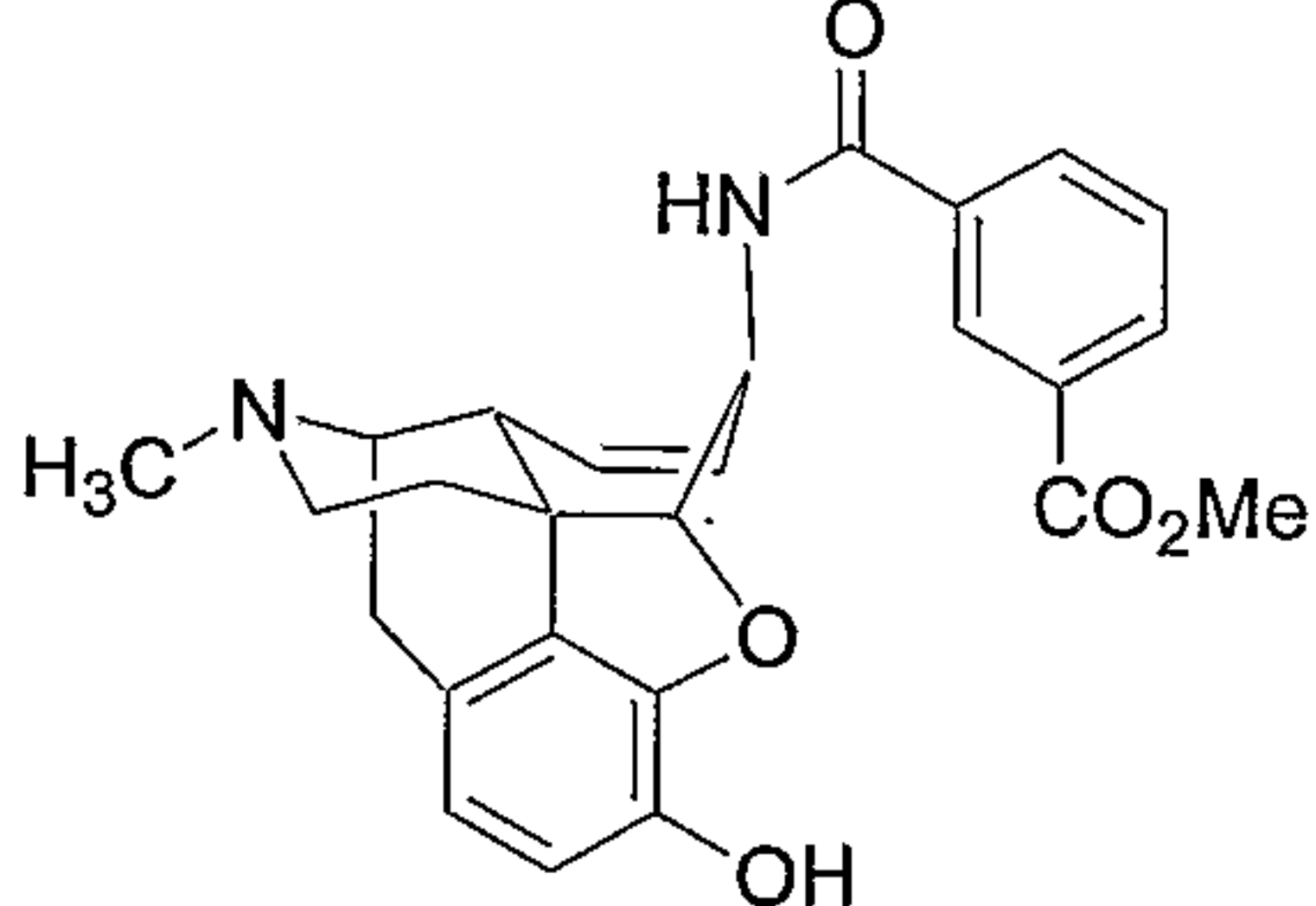
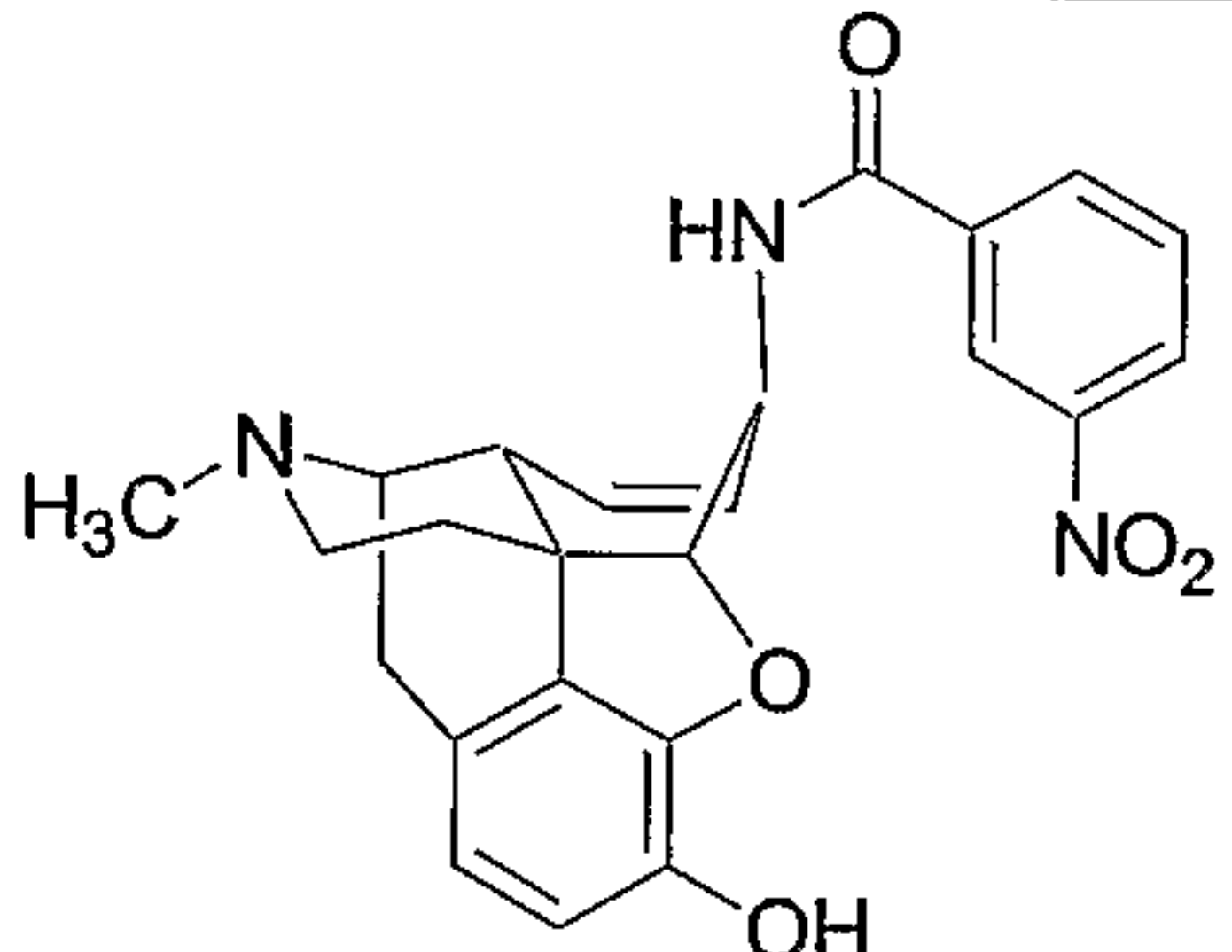
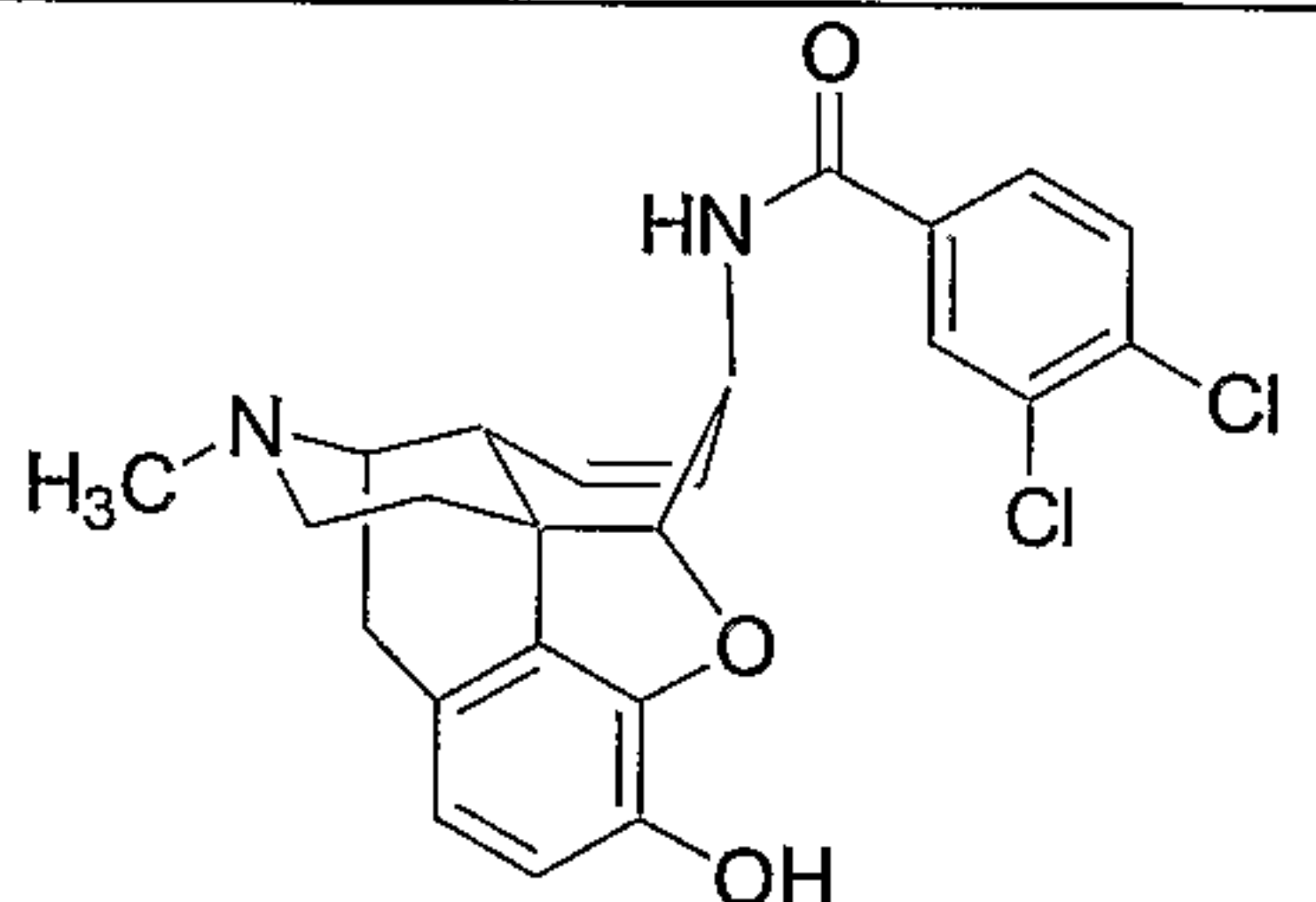
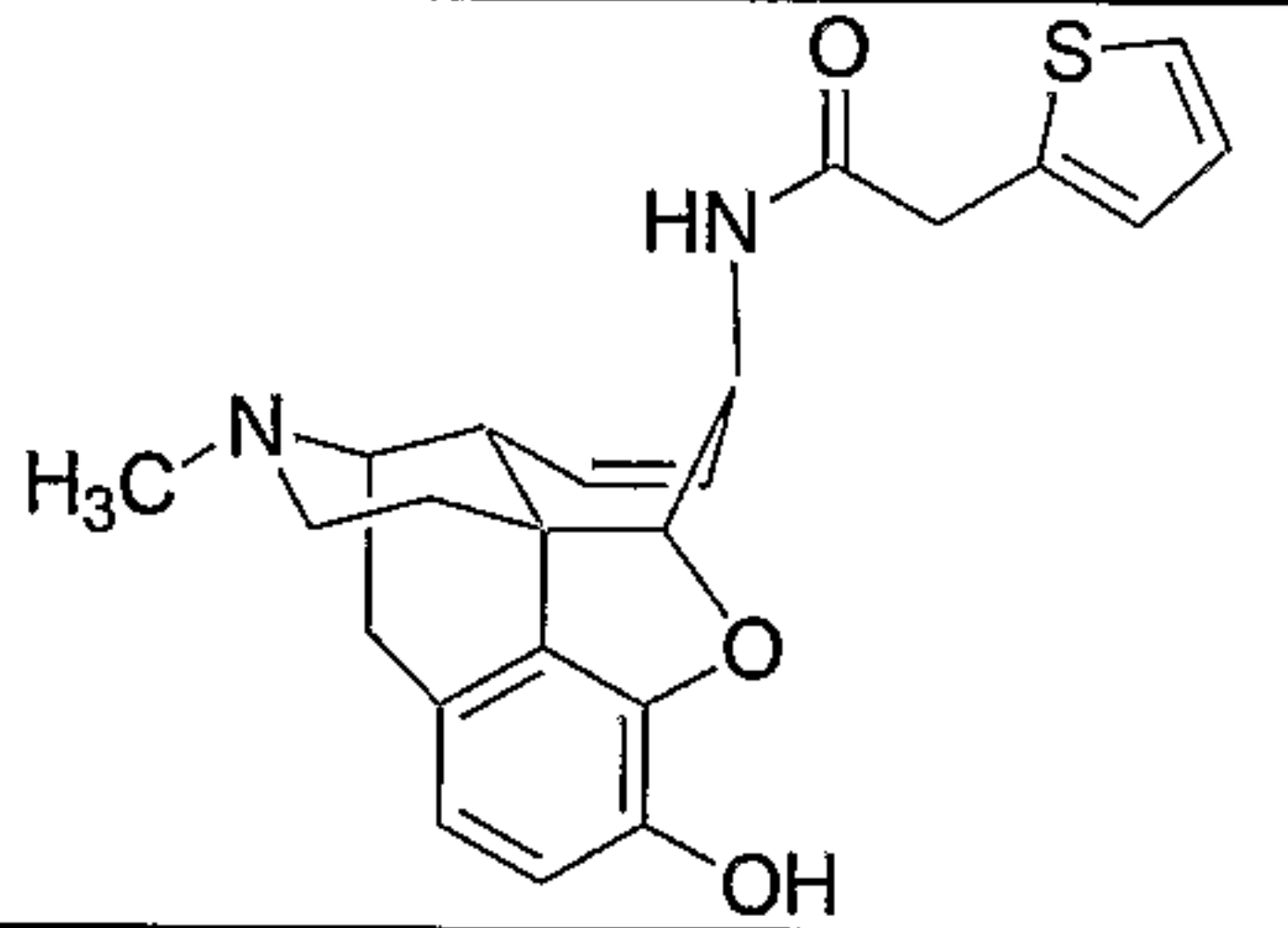
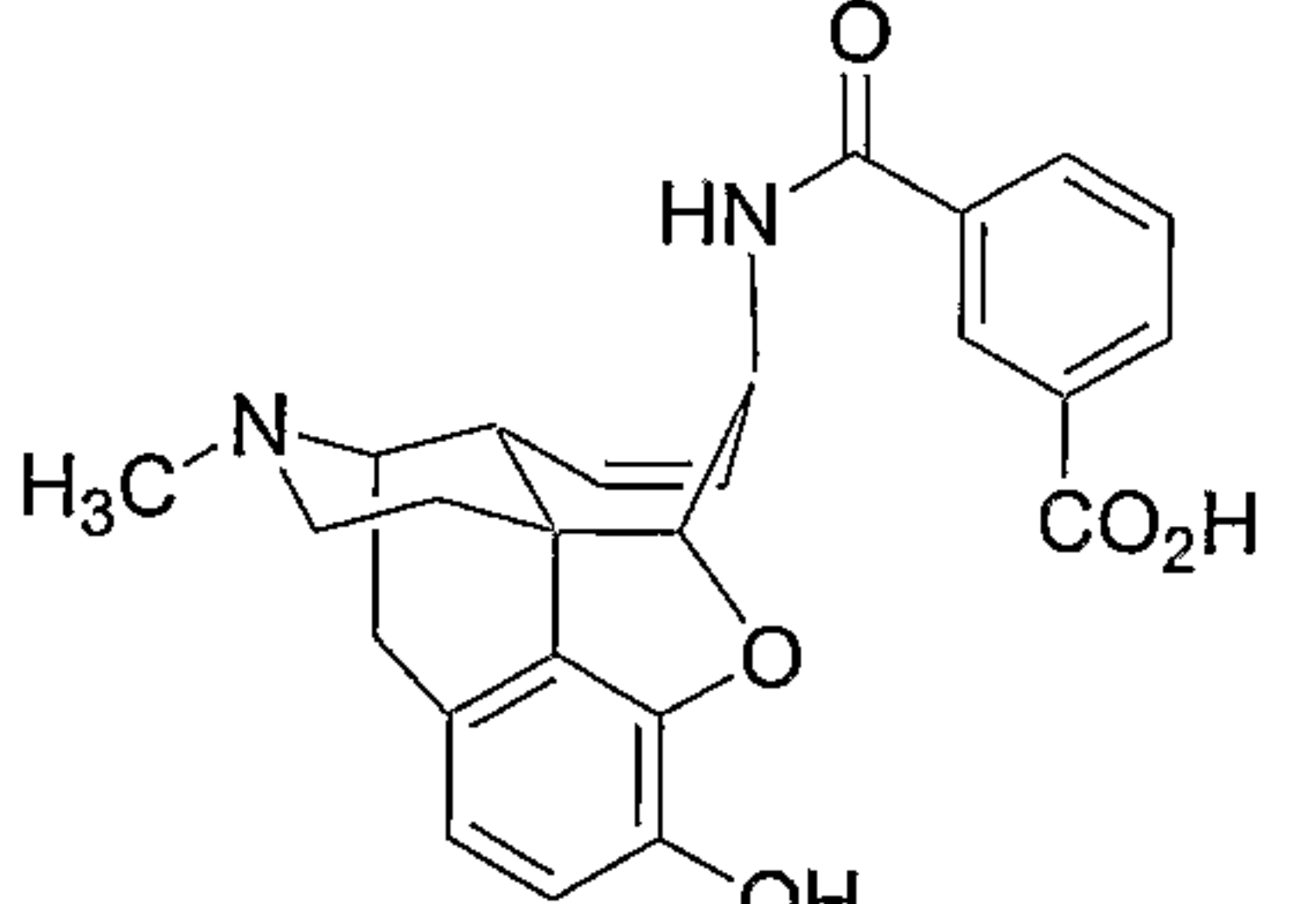
Example 29: Mu Receptor Internalization

[0128] A. **Methods.** Mu receptor internalization was evaluated according to the method of [D. E. Keith *et al.*, *Mol. Pharm.*, **53**:377-384 (1998)]. In general terms, this phenomenon was studied using flow cytometric analysis in which surface receptors can be quantified by staining with FITC-labeled FLAG M1 and measuring fluorescence. Drugs that were effective at causing internalization caused reduced staining relative to the control.

[0129] B. **Results.** Type III compounds were evaluated for their ability to effect mu receptor internalization because of the role this process may play in the development of tolerance and dependence (*see* Table 3). From the data, it can be seen that the dichloro compound **13g** (47%) and the nitro compound **13f** (59%) were both more effective than etorphine (61%) at causing mu receptor internalization. The other amides were moderate to weak internalizers of the mu receptor. It should be pointed out that morphine (93%) does not cause mu receptor internalization at normal plasma concentrations (1-50 nM). The concentration of the compounds used in these experiments was 1 μ M.

Table 3. Mu receptor internalization for selected ligands.

entry	structure	% control
13a		76.14
13b		84.84
13c		74.53

entry	structure	% control
13d		72.11
13e		81.83
13f		58.69
13g		47.11
13h		91.11
14		95.85

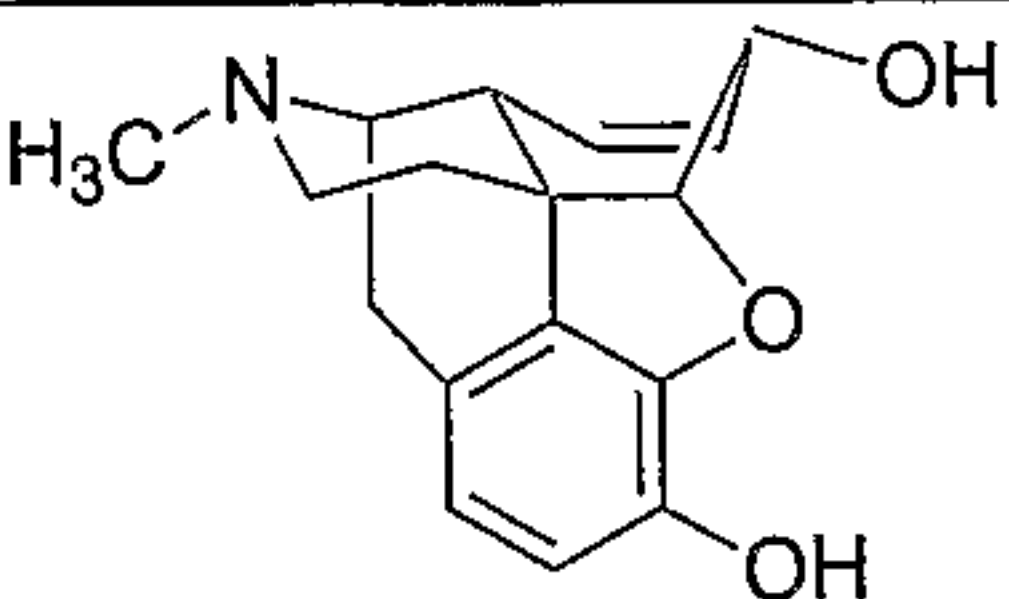
Example 30: Chemical and Metabolic Stability Evaluation

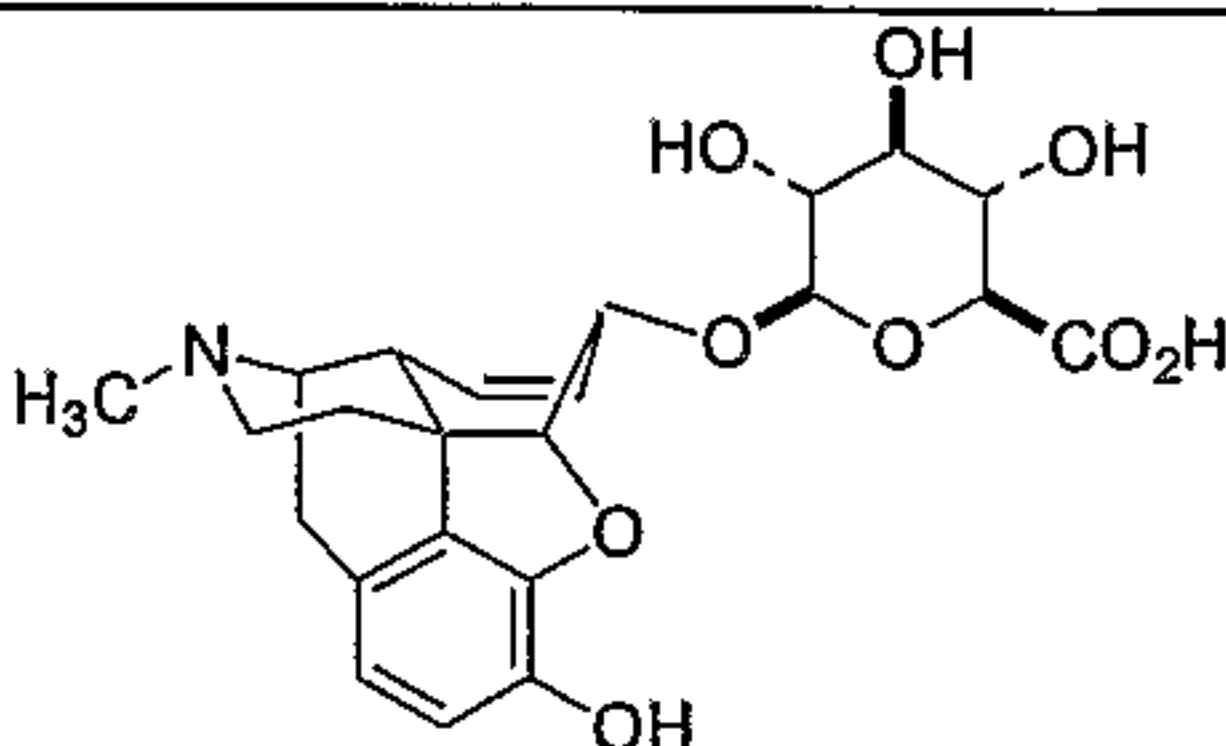
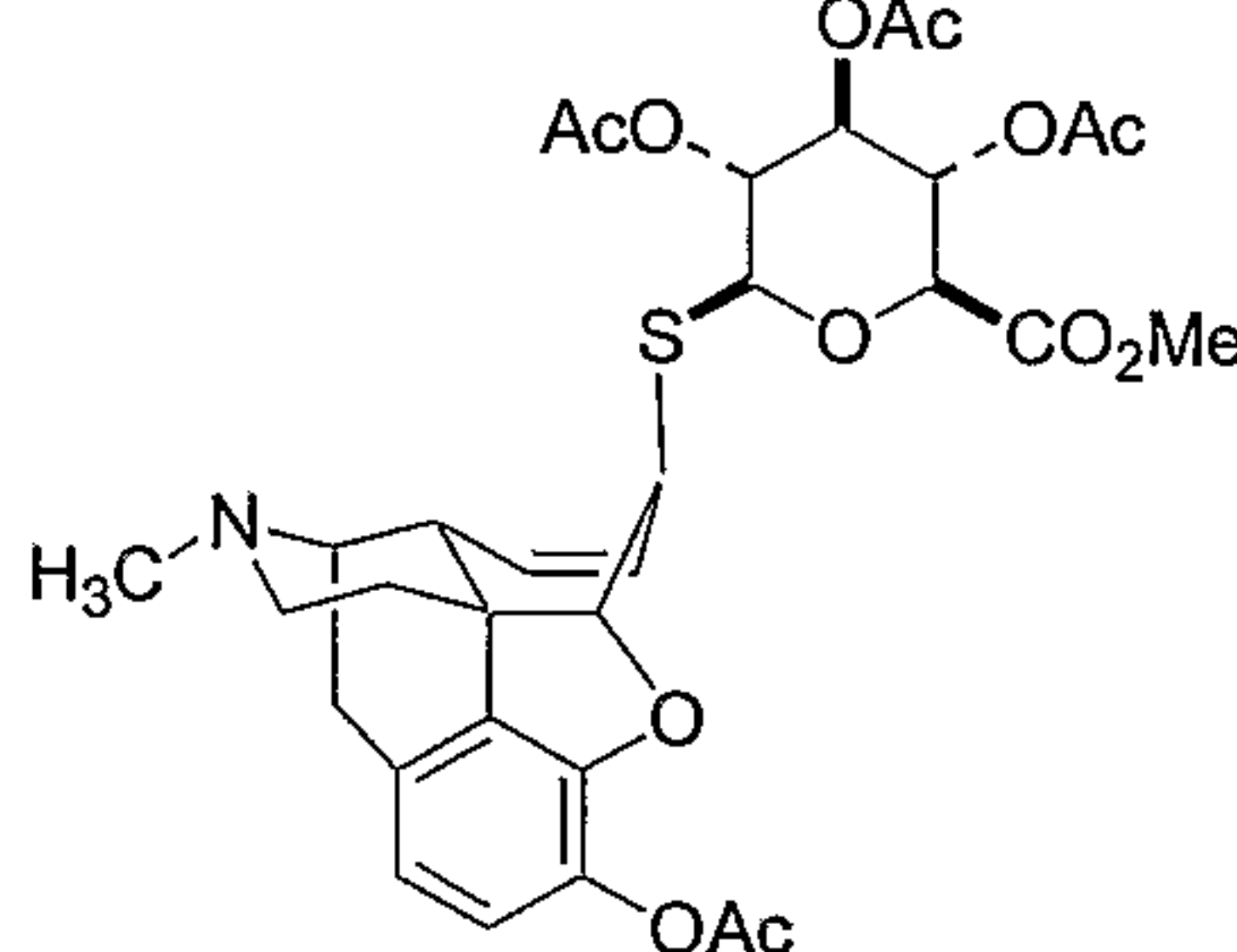
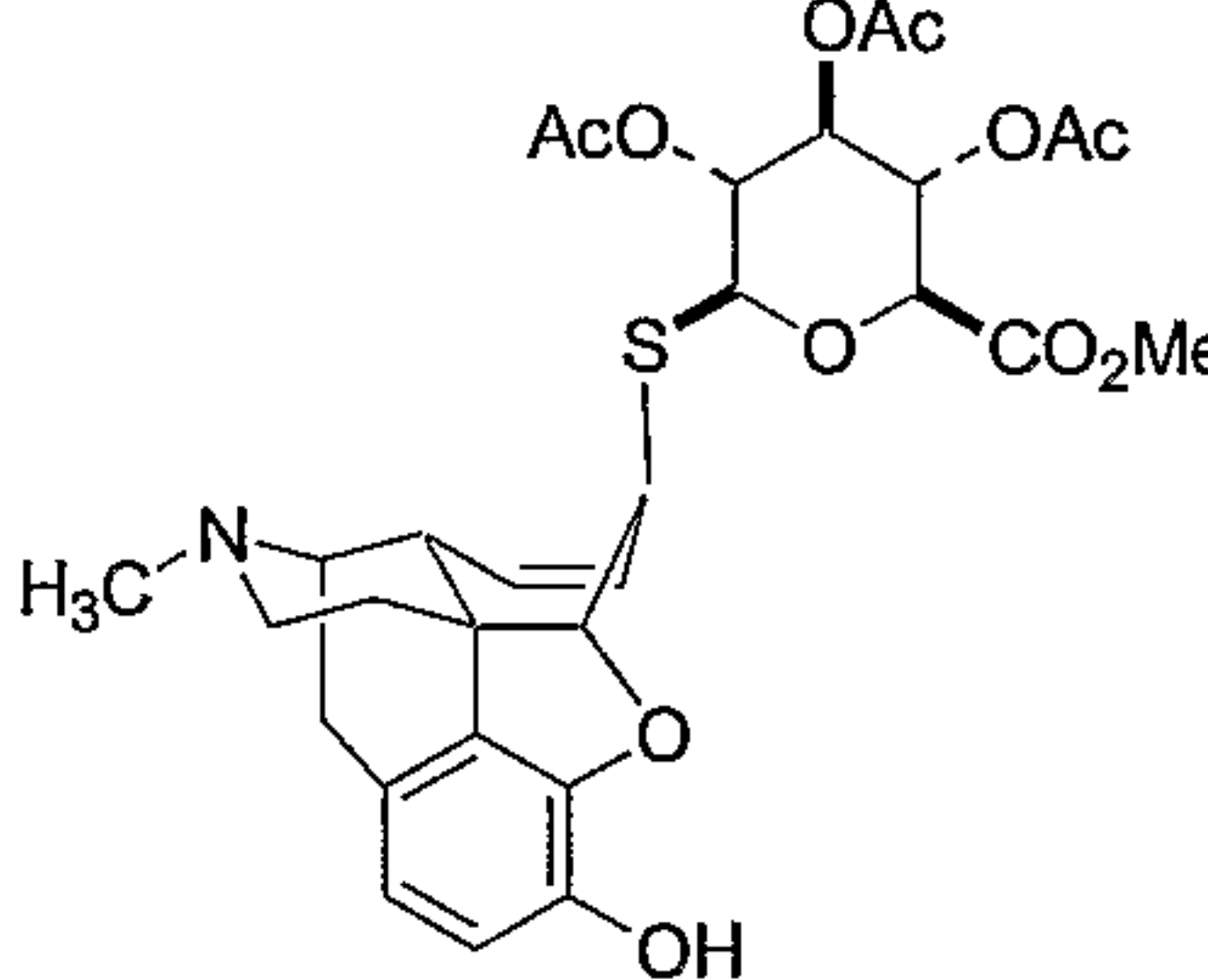
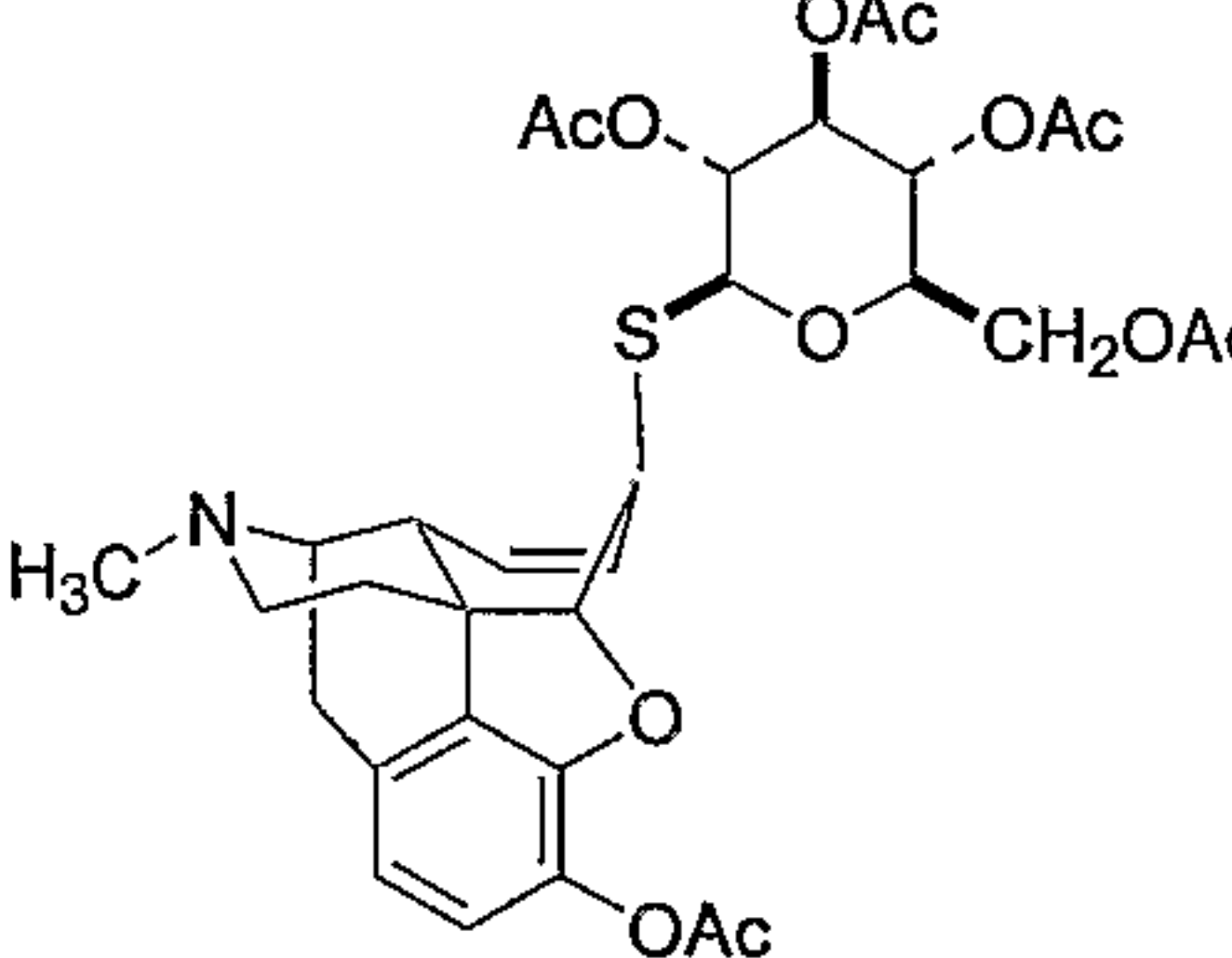
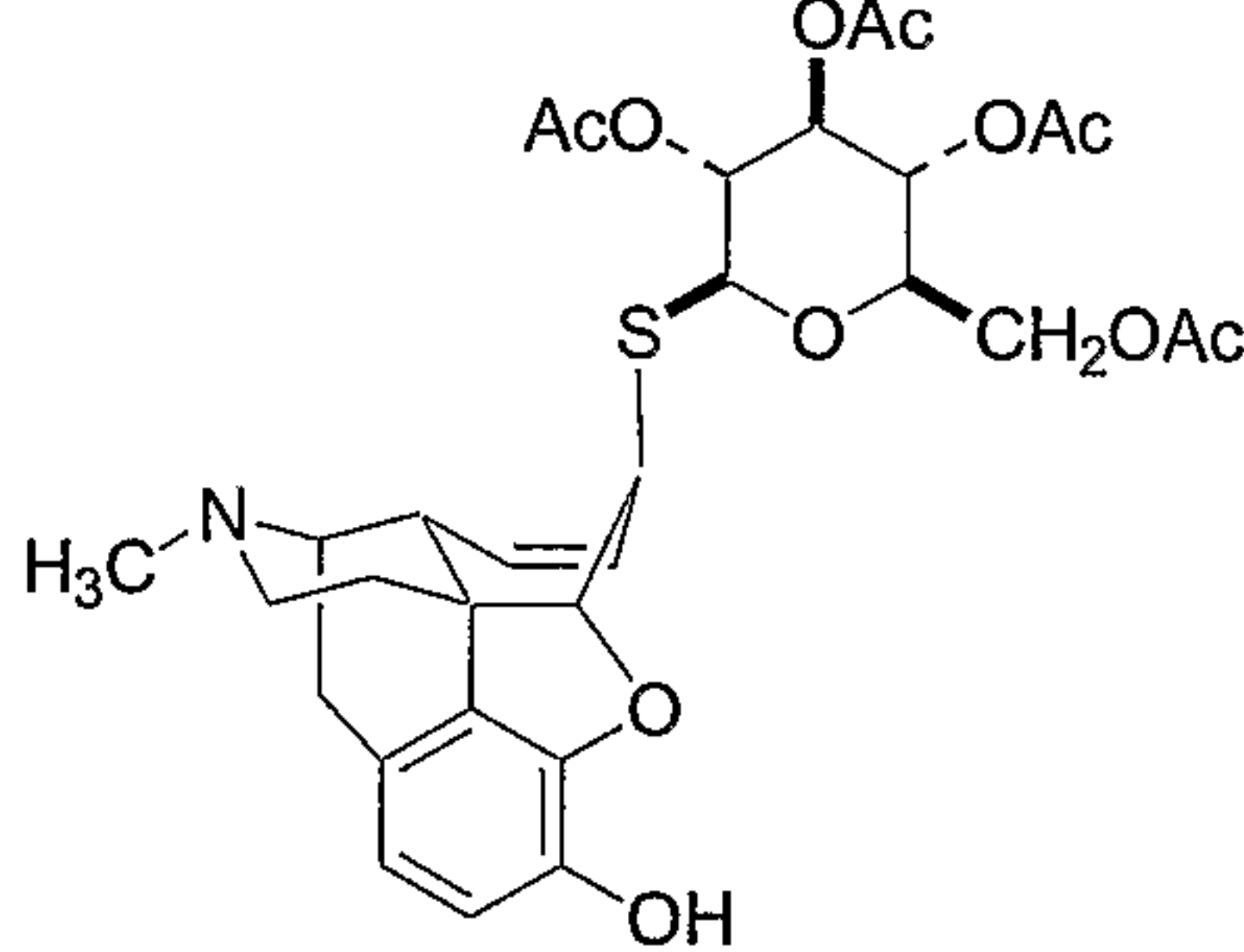
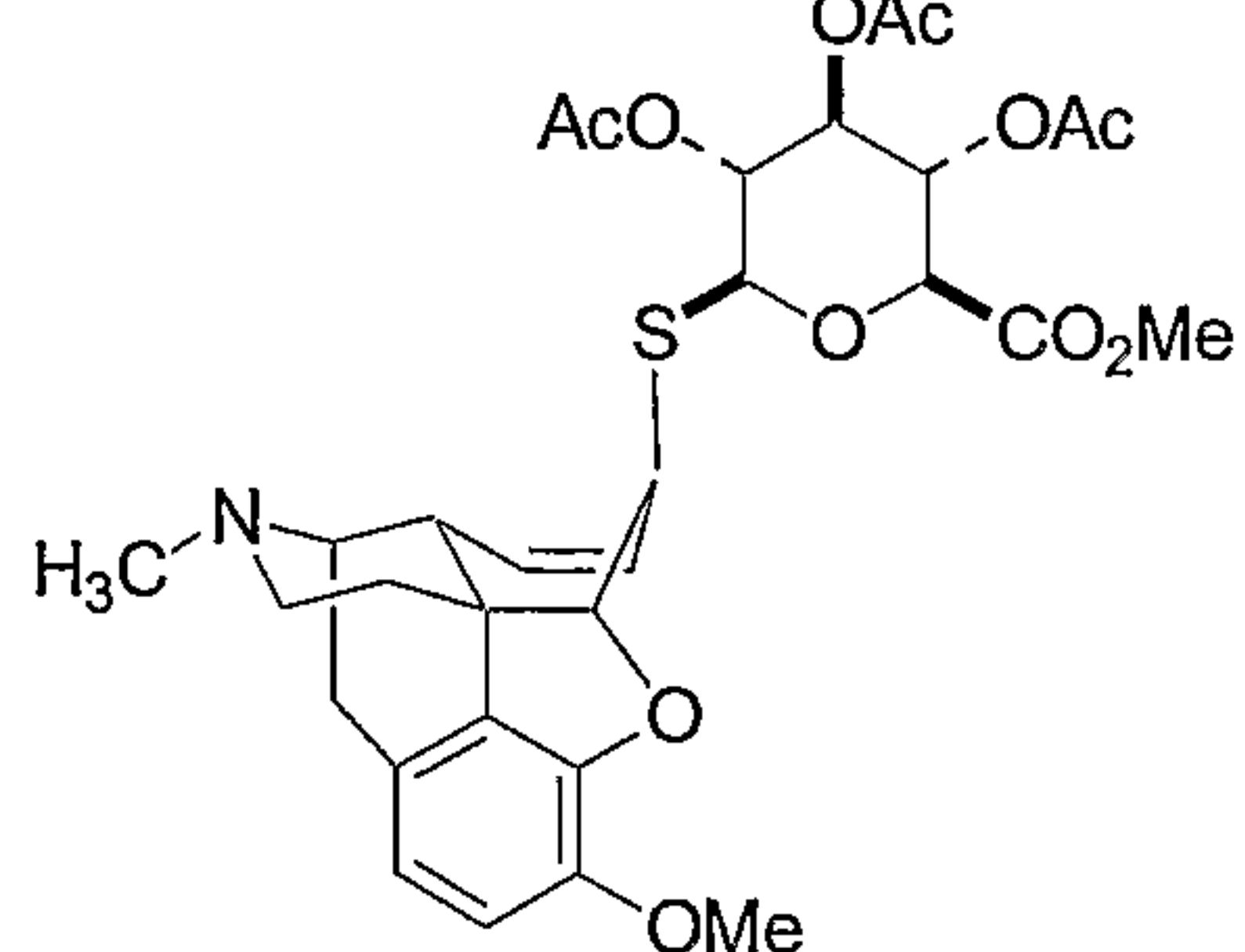
[0130] A. **Methods.** The chemical stability of selected compounds were examined at pH 7.4 and pH 2.0. Compounds (0.1 M) at either pH 7.4 or 2.0 in the presence of 10 uM potassium phosphate buffer were concentrated after 5 min, 1 h, 2 h, 3 h, 24 h, 48 h or 72 h.

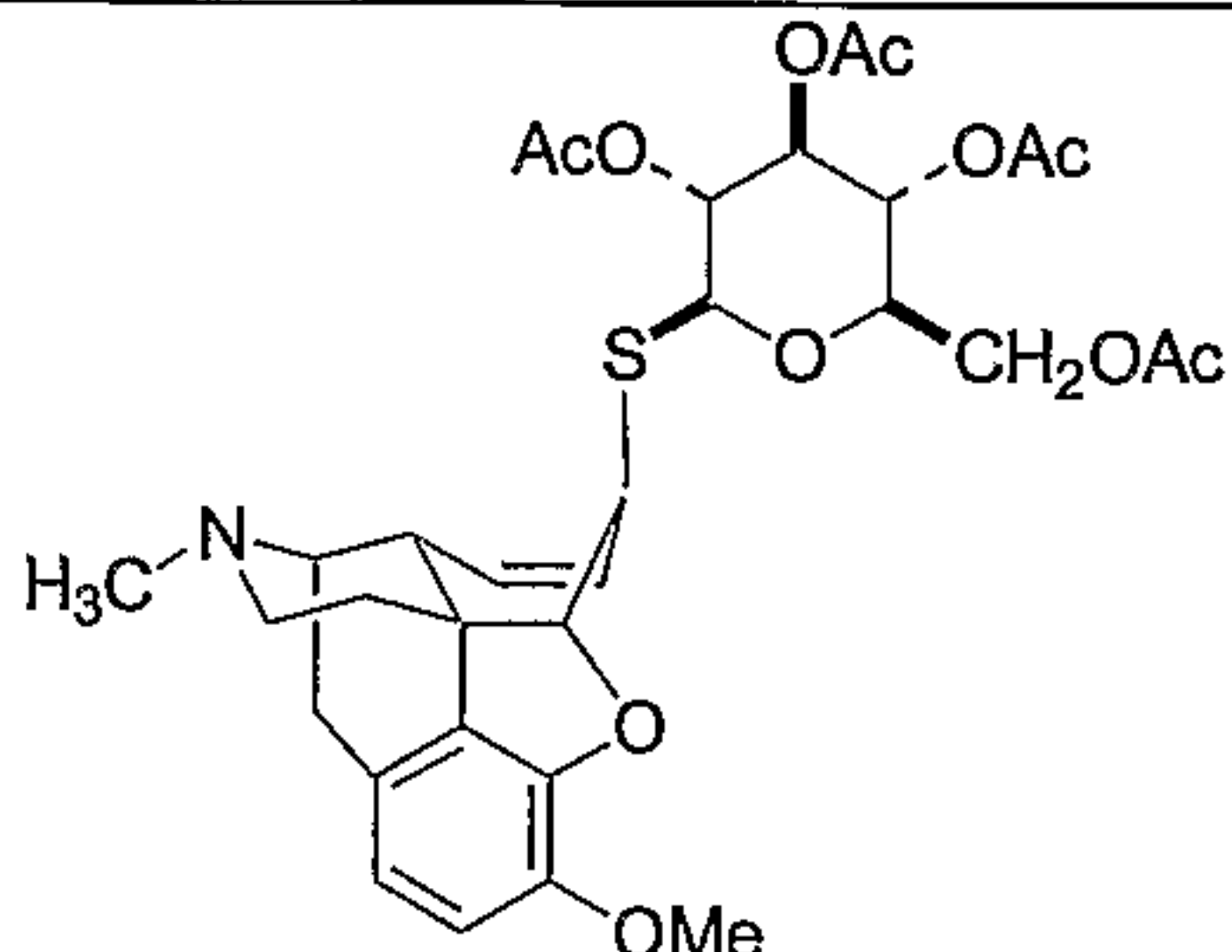
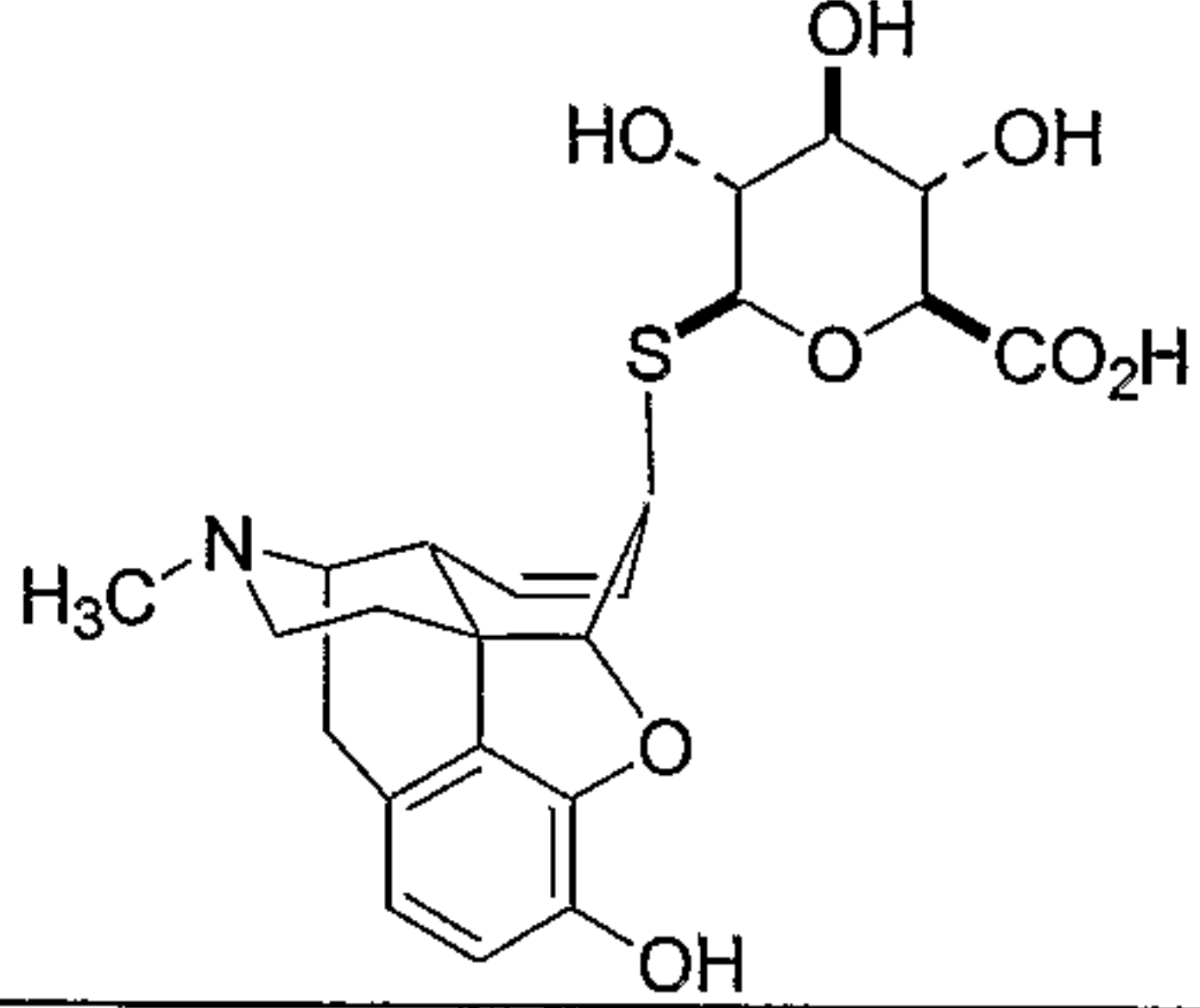
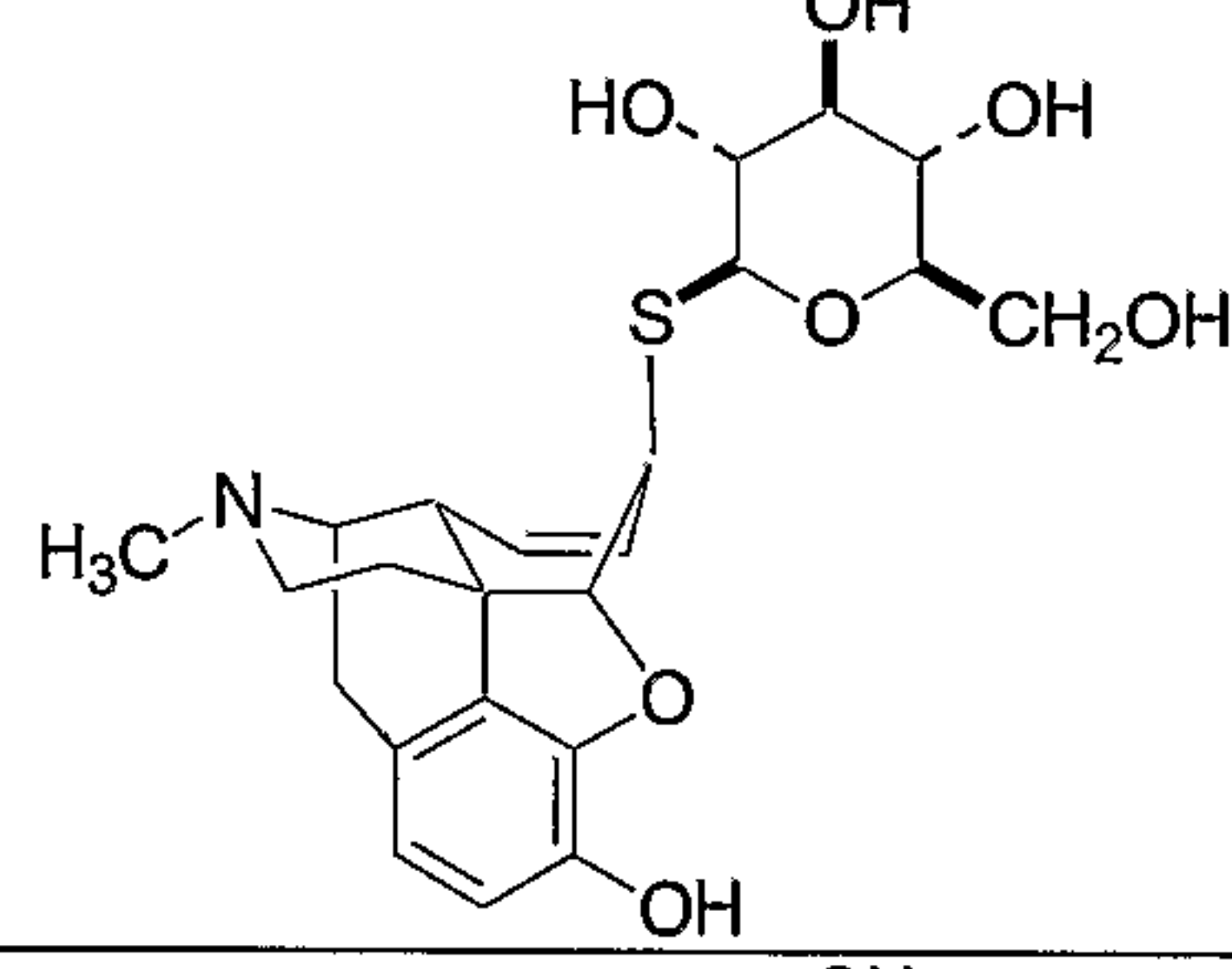
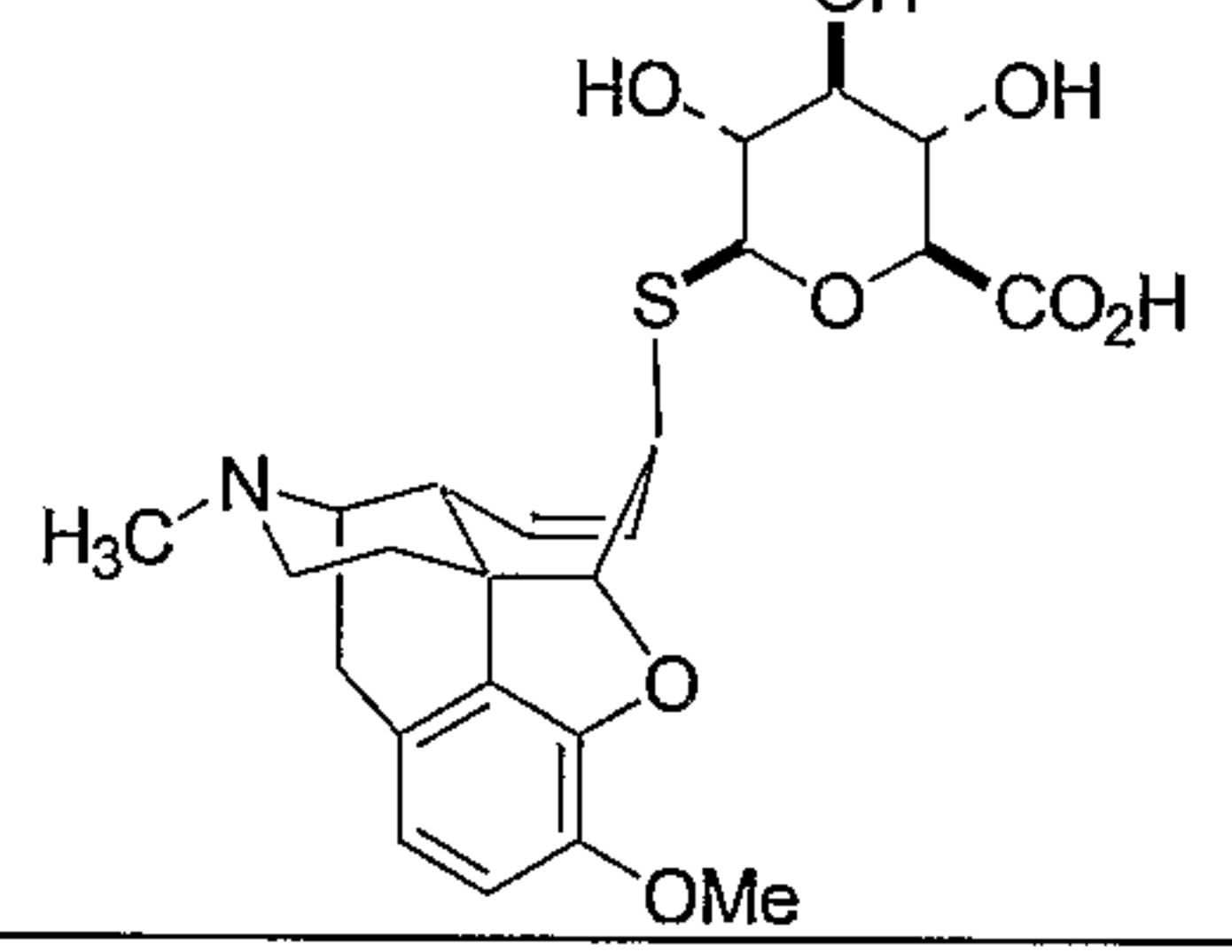
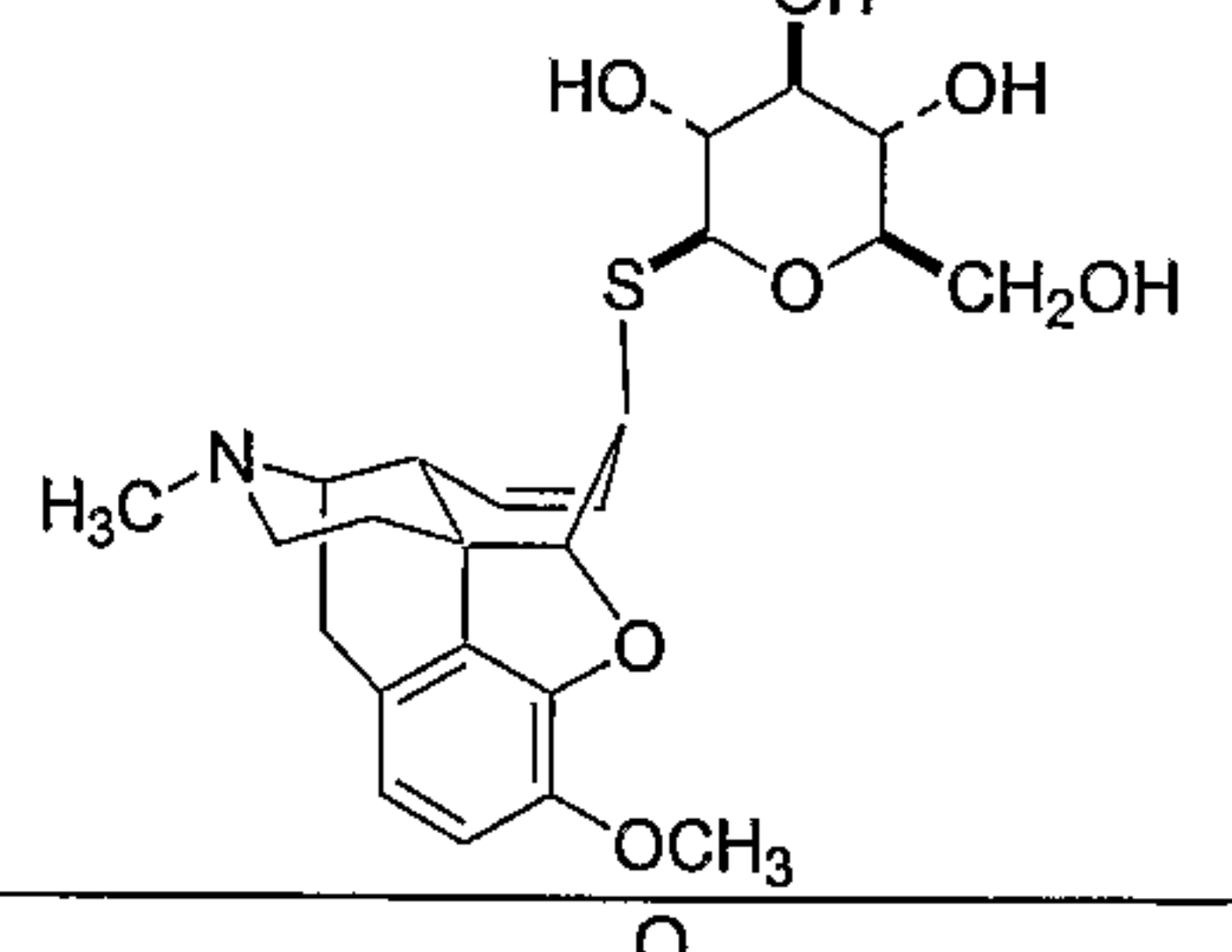
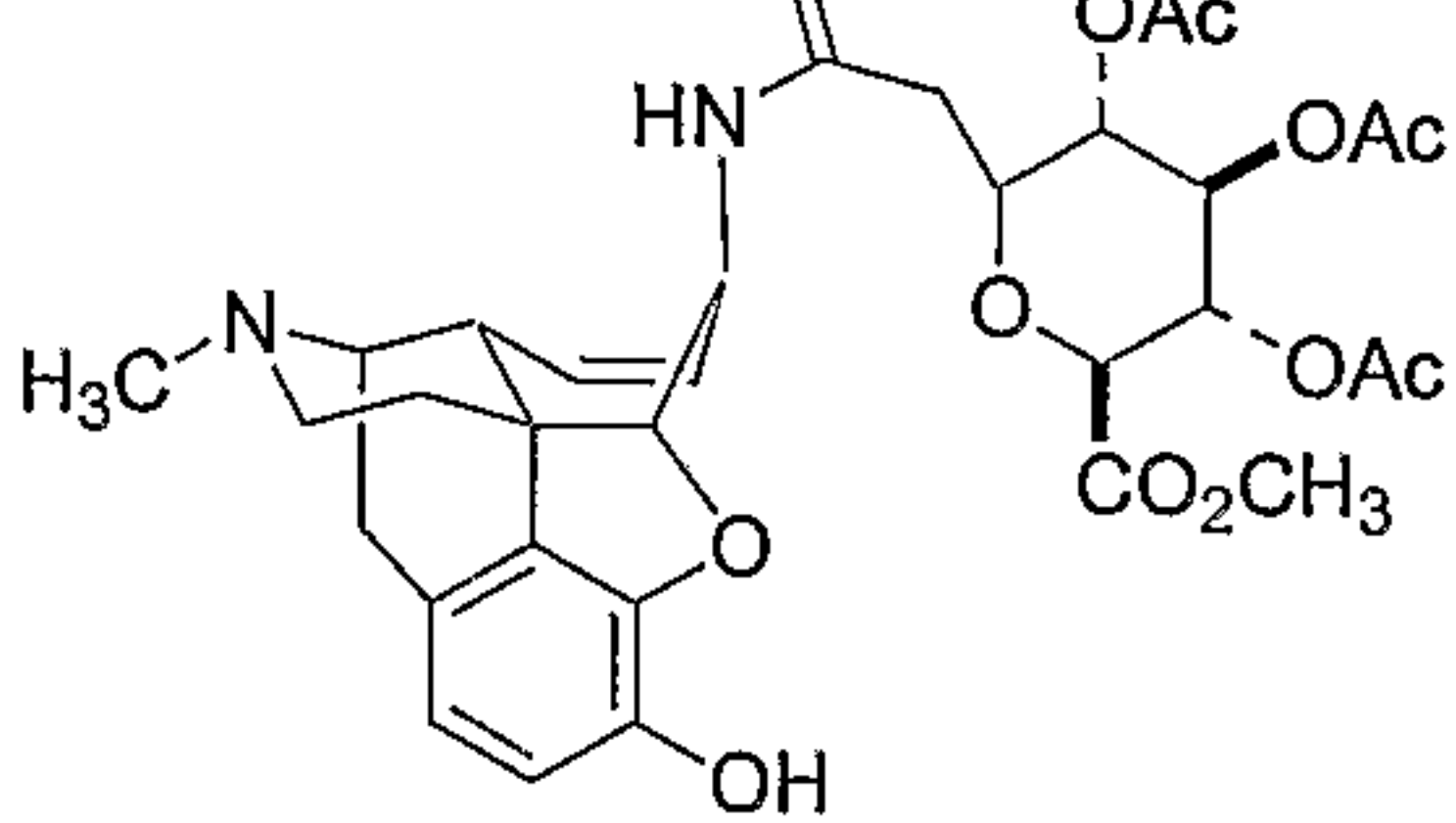
Then HPLC was used to analyze the decomposition of the starting material. The metabolic stability of selected compounds was examined in human liver S9 and microsomes. Human liver pooled S9 (HLS9) stability and mouse liver microsomes (MLM). Assay buffer contains 3.2 mg/mL HLS9 or 1.2 mg/mL MLM, 0.1 M potassium phosphate buffer (pH 7.4), 0.1 mM compounds, 0.5 mM NADP⁺, 0.5 mM glucose-6-phosphate, 5U/mL glucose-6-phosphate dehydrogenase, 1 mg/mL DETAPAC, 7 mM MgCl₂ for a final incubation volume of 0.25 mL. After 0, 10, 25, 40 or 60 min the reactions were stopped by the addition of 1 mL CH₂Cl₂/IPA (3:1 v:v). After centrifugation, the extraction solvent (organic phase) was evaporated off with a nitrogen stream, resolved by 200 uL methanol, vortexed, centrifuged, transferred to HPLC vial inserts. HPLC was used to analyze the decomposition of the starting material by comparing area under the curve to at before addition of microsomes to the area under the curve at the given time interval (0, 10, 25, 40 or 60 min).

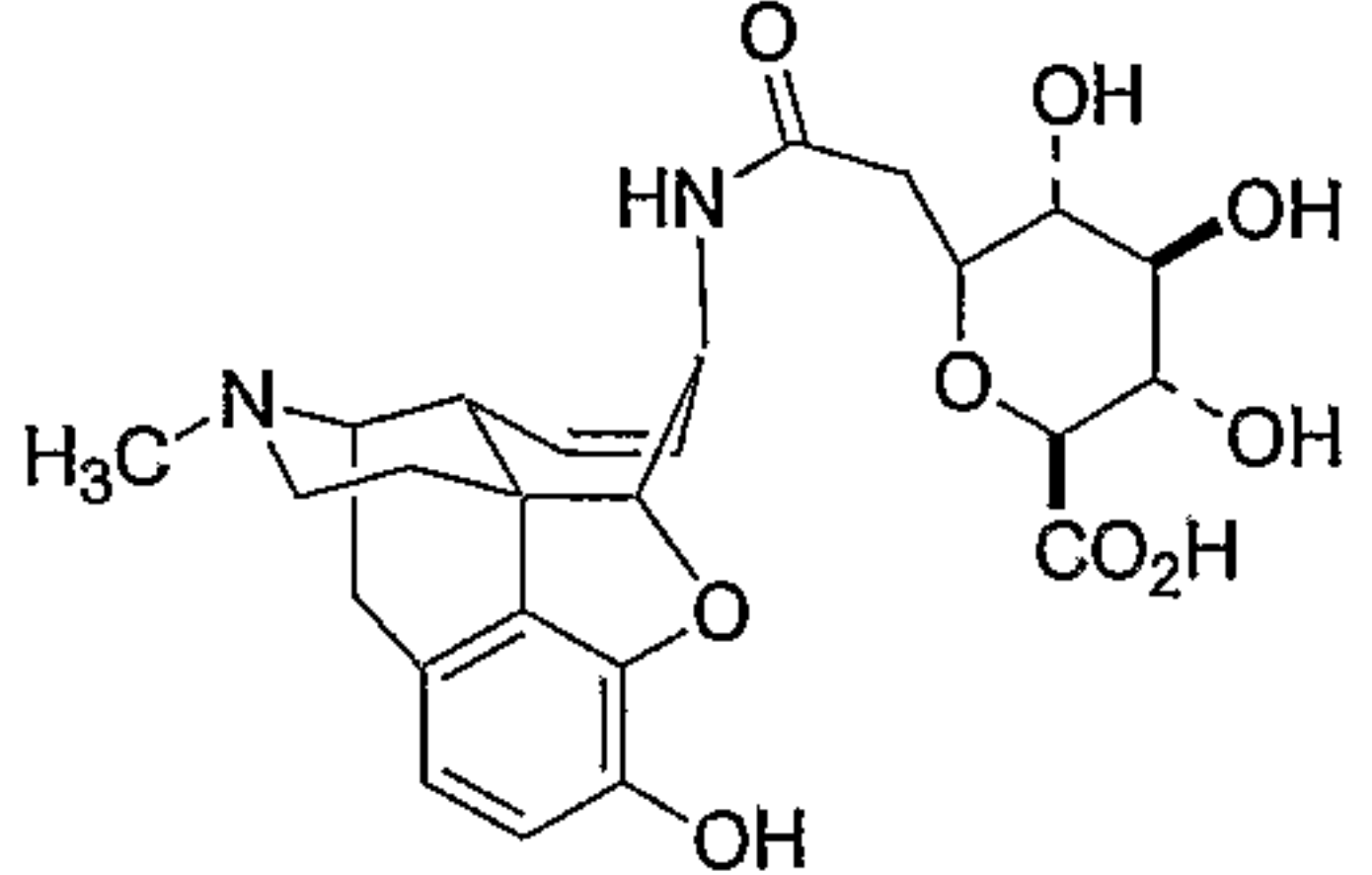
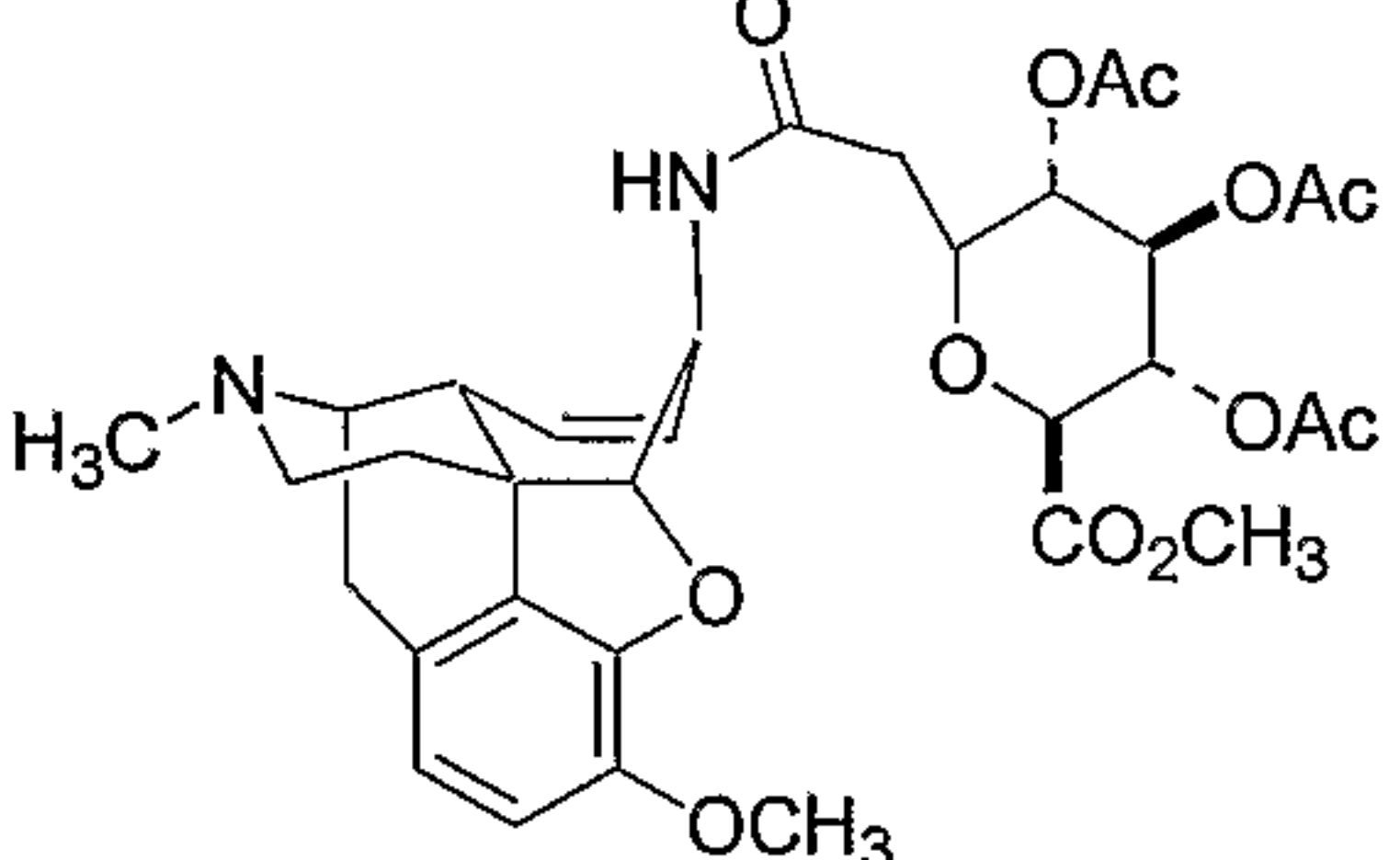
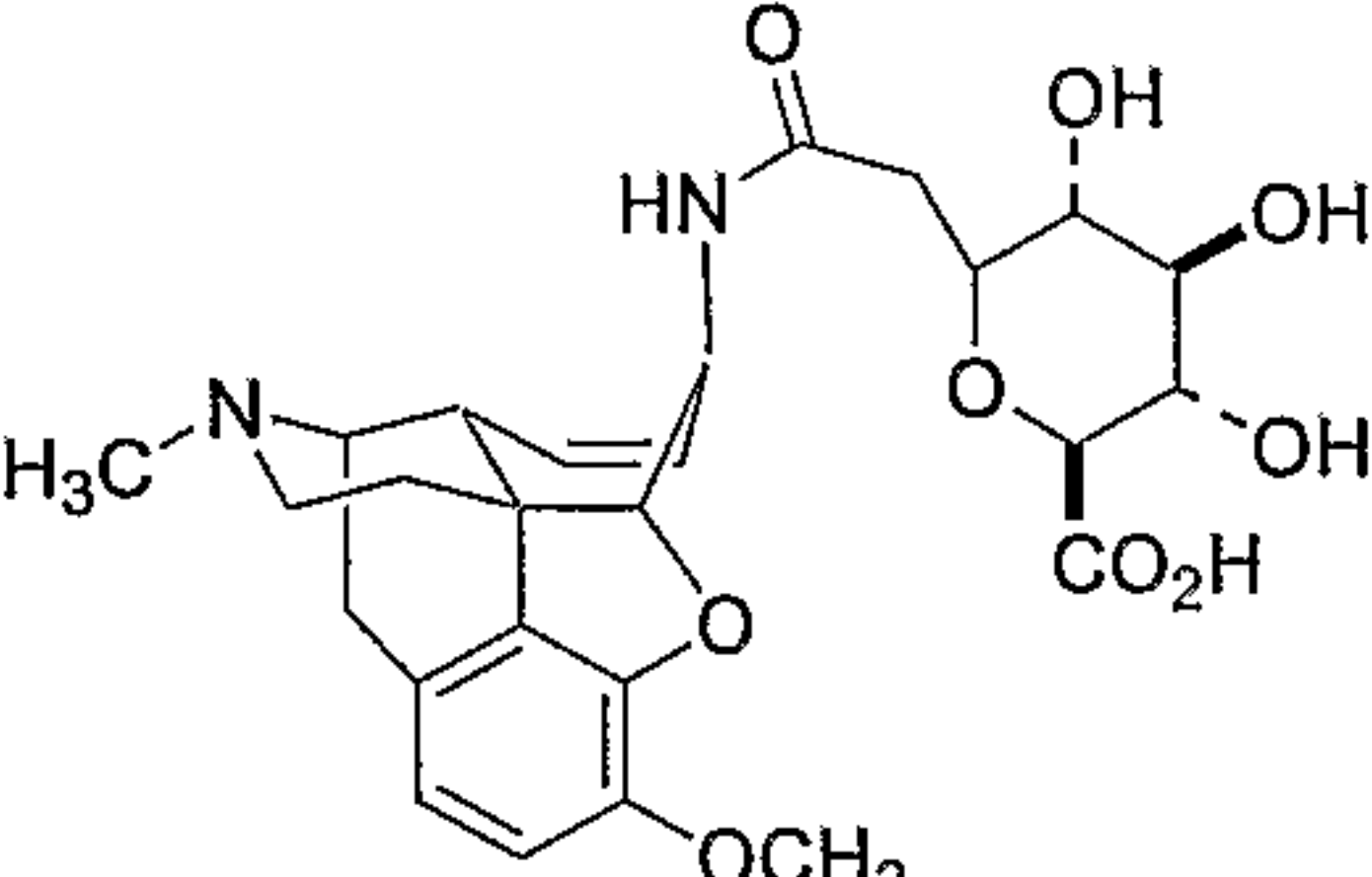
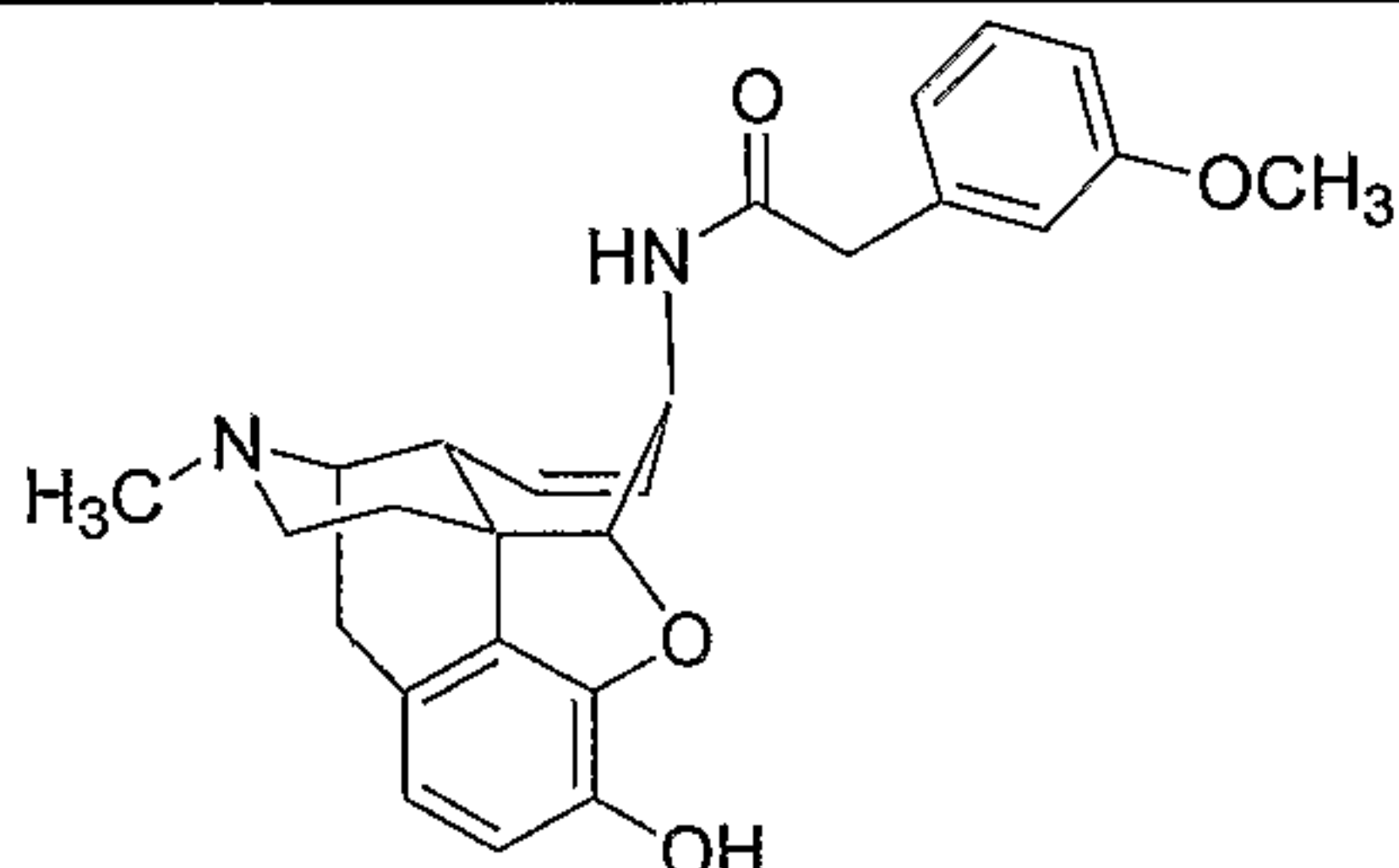
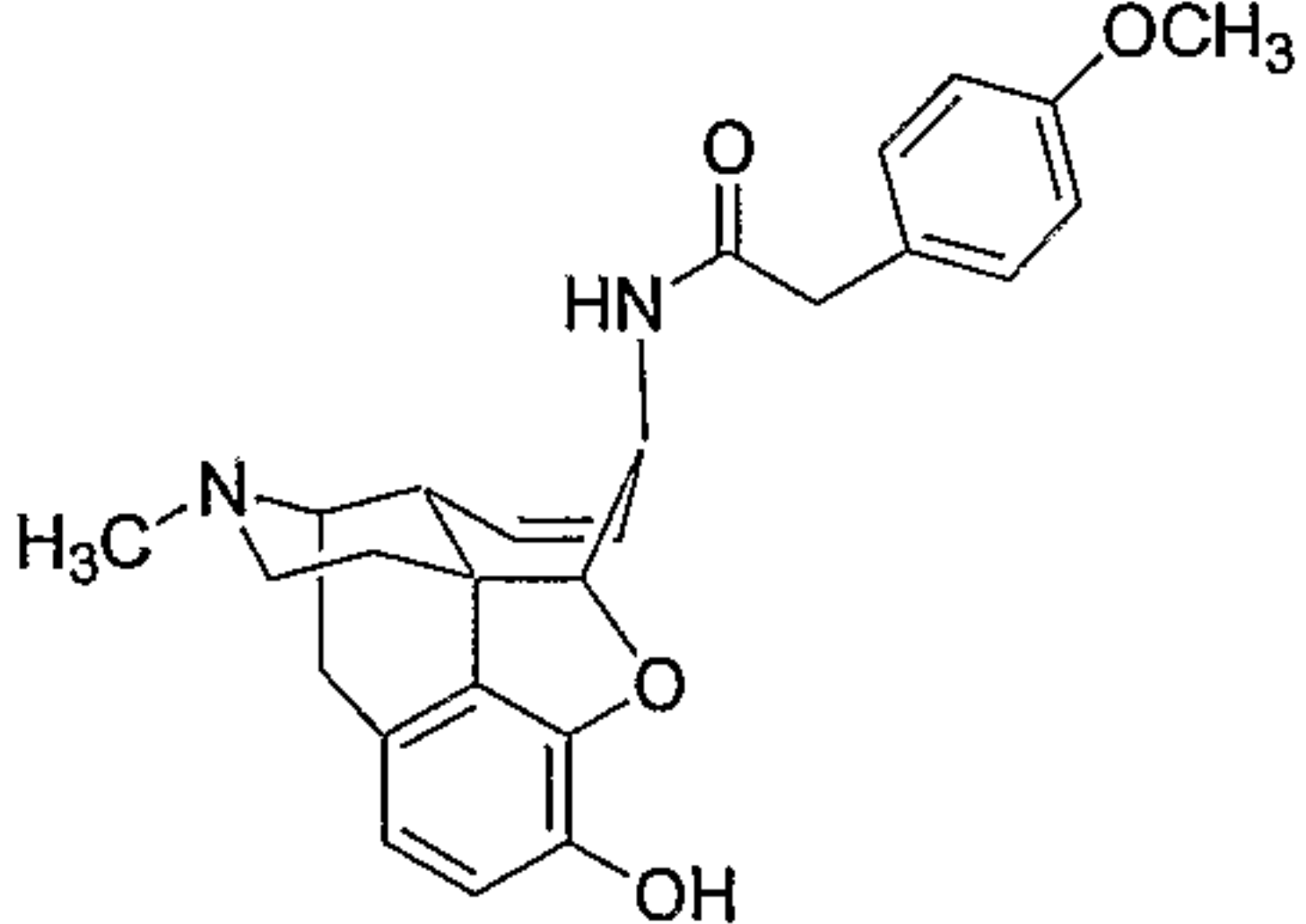
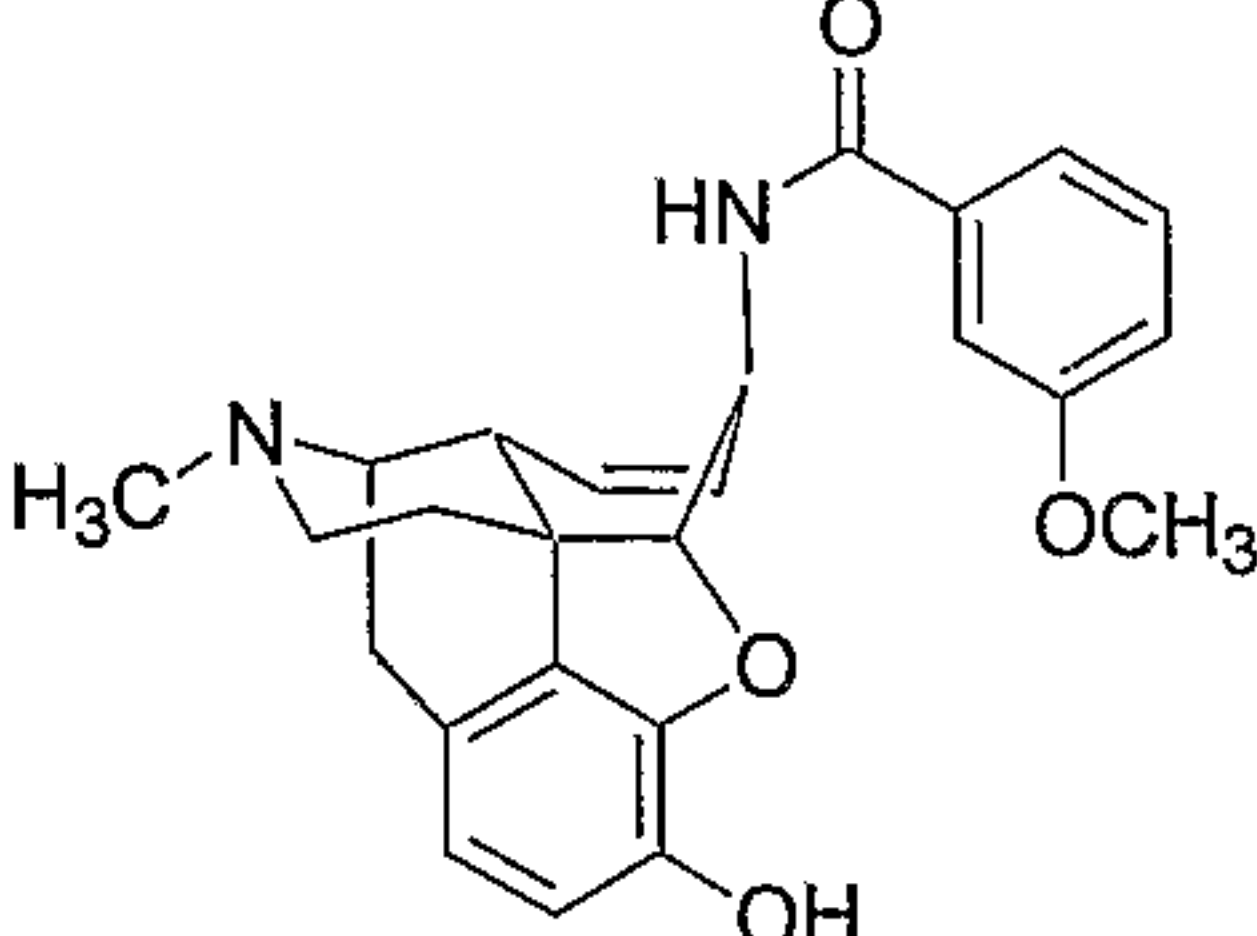
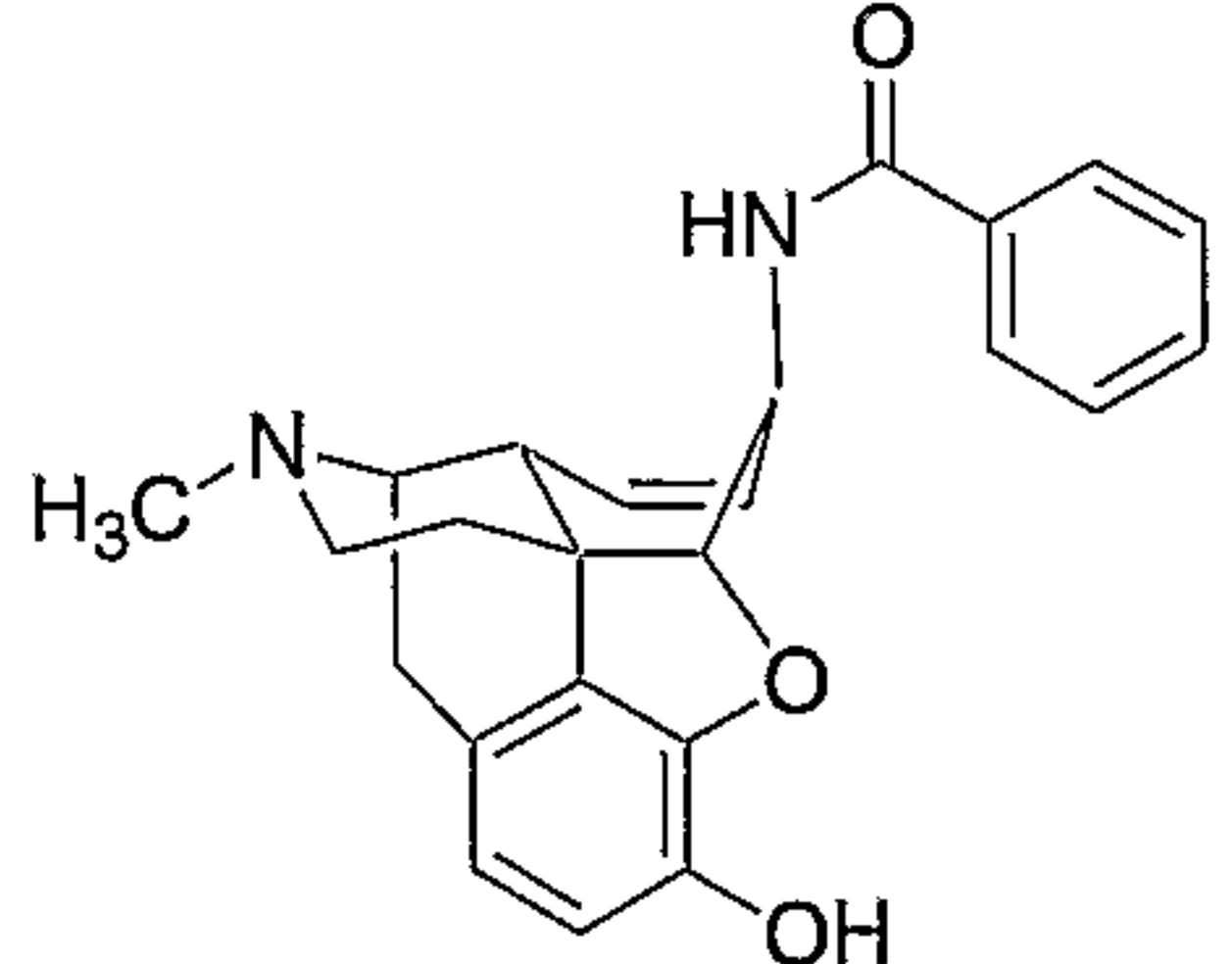
[0131] **B. Results.** Select type I and III compounds were evaluated in the presence of mouse liver microsomes (MLM), human liver microsomes S-9 (HLS9) and at pH 2 and 7.4 (*see* Table 4). A longer half-life is correlated with greater stability under the given conditions. In compounds of type I, the M6G sulfur analogue **4a** showed equal stability to M6G in the presence of HLS9 and at pH 2 and 9. The presence of ester protecting groups reduced the stability of type I molecules. The stability of compound **3a** to HLS9 is greater than compound **3b** (17.86 min) suggesting that the 3-position acetate group is the most labile ester group in type I molecules. This hypothesis was verified by HPLC co-injection. No differences could be detected in the stabilities of deprotected compounds **4a-d** Type III compounds were significantly more stable than type I compounds under all conditions tested. The presence of the methyl ester group in compound **13e** reduced the stability of this compound to HLS9 and at pH 7.4 when compared to other type III compounds. Sufficient amounts of type II compounds could not be obtained for evaluation. The presence of ester protecting groups in type II compounds should render them less stable than type III compounds. The amide linkage is expected to impart improved stability over the S-glycosidic linkage.

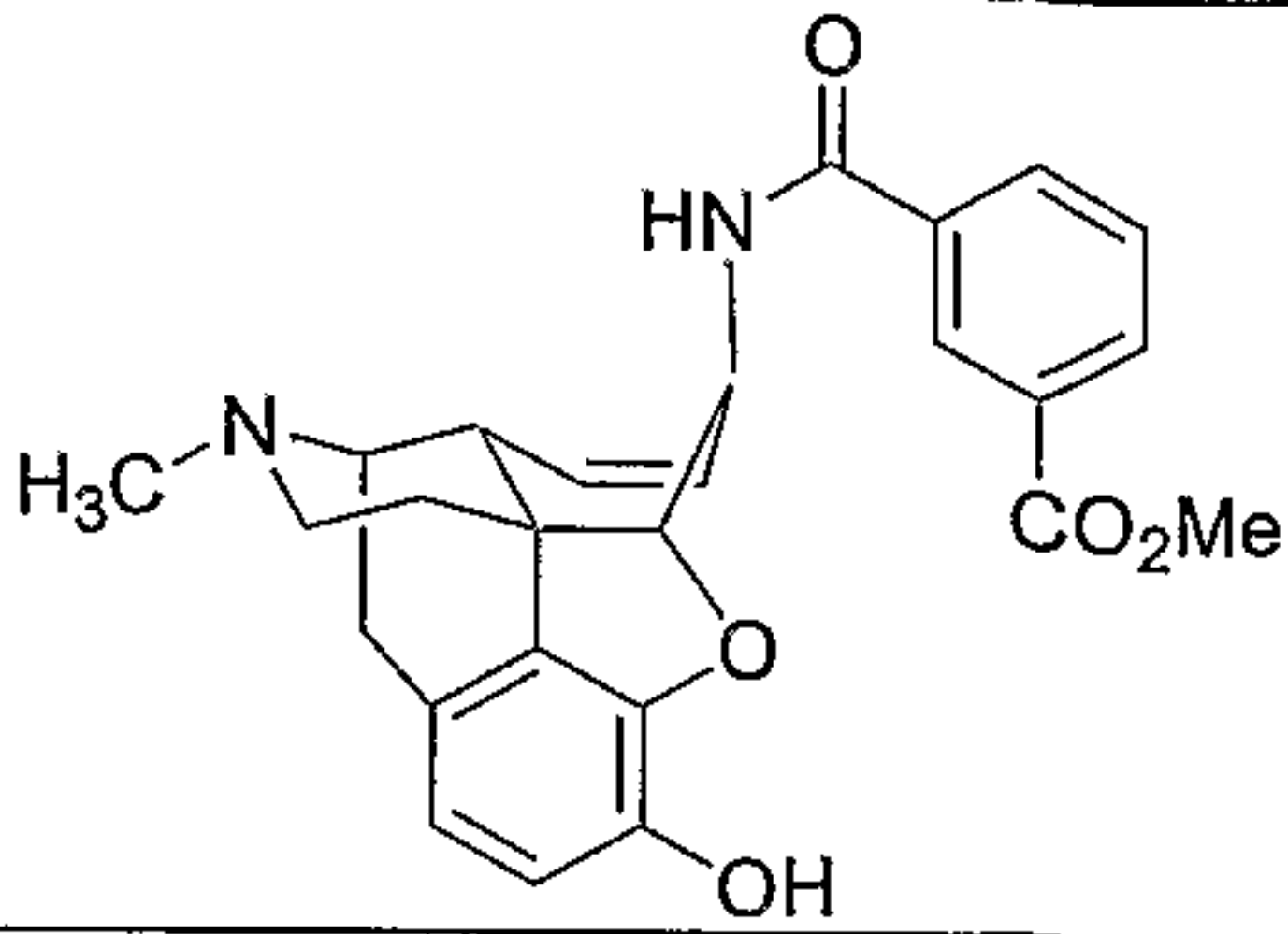
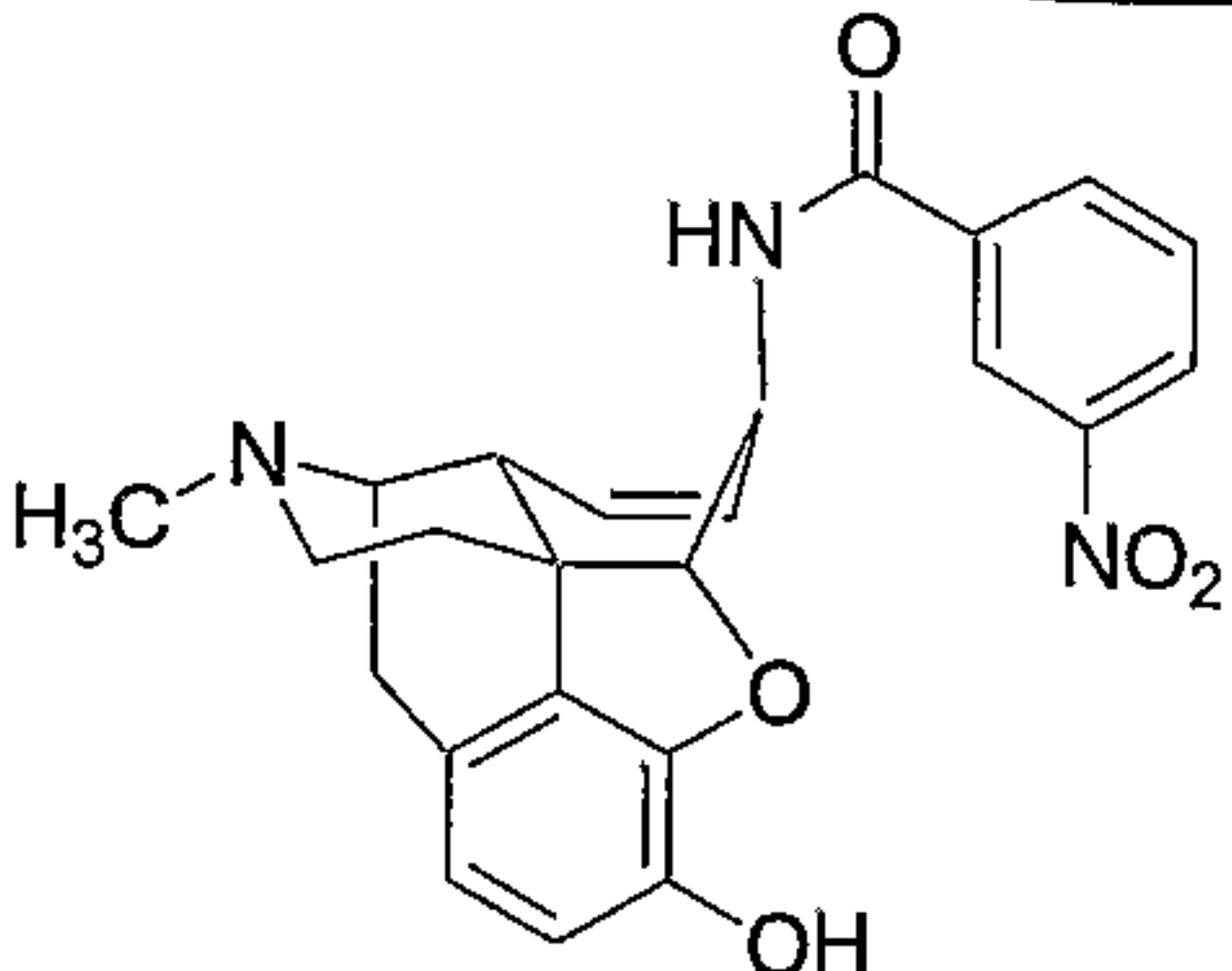
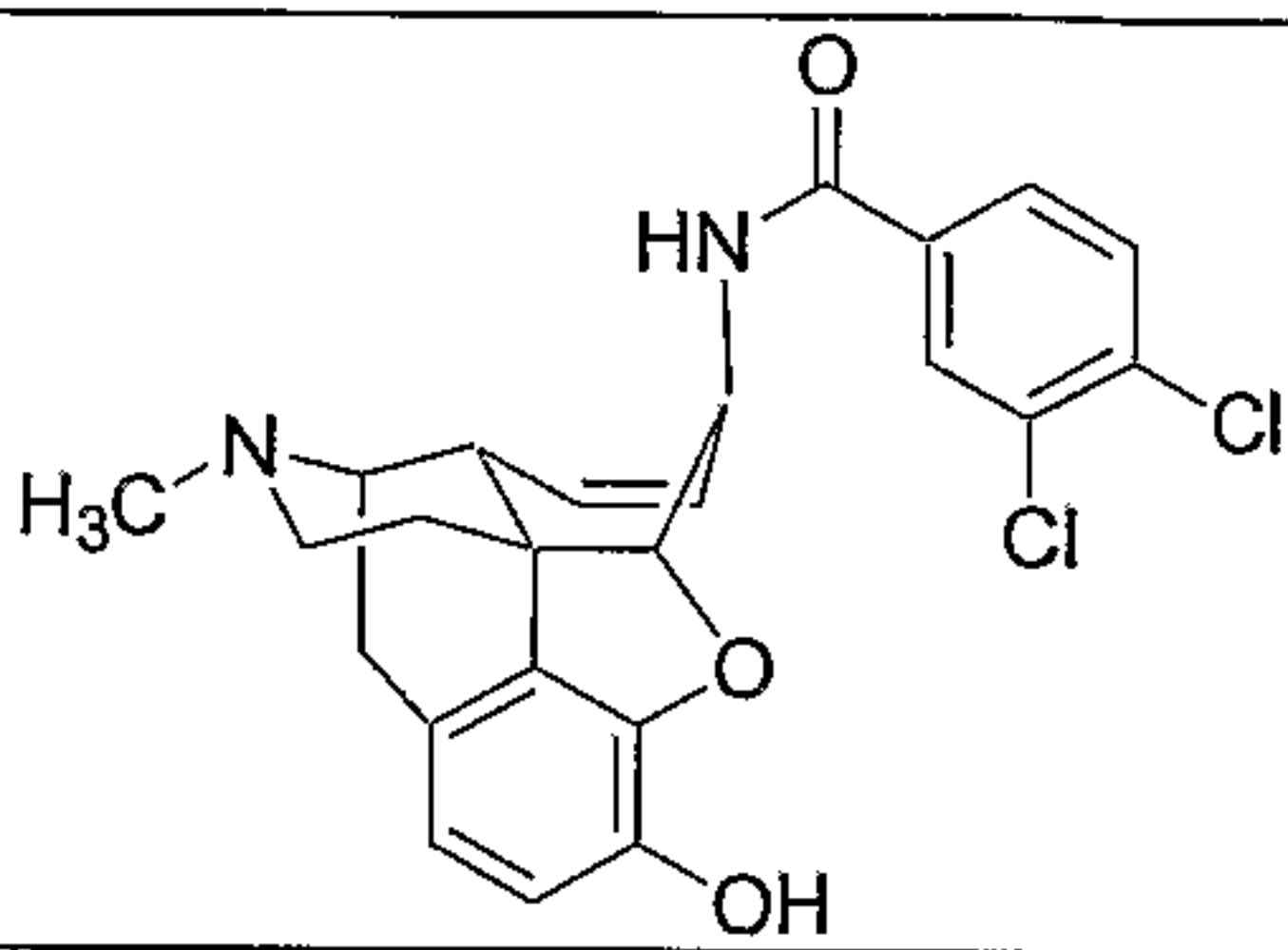
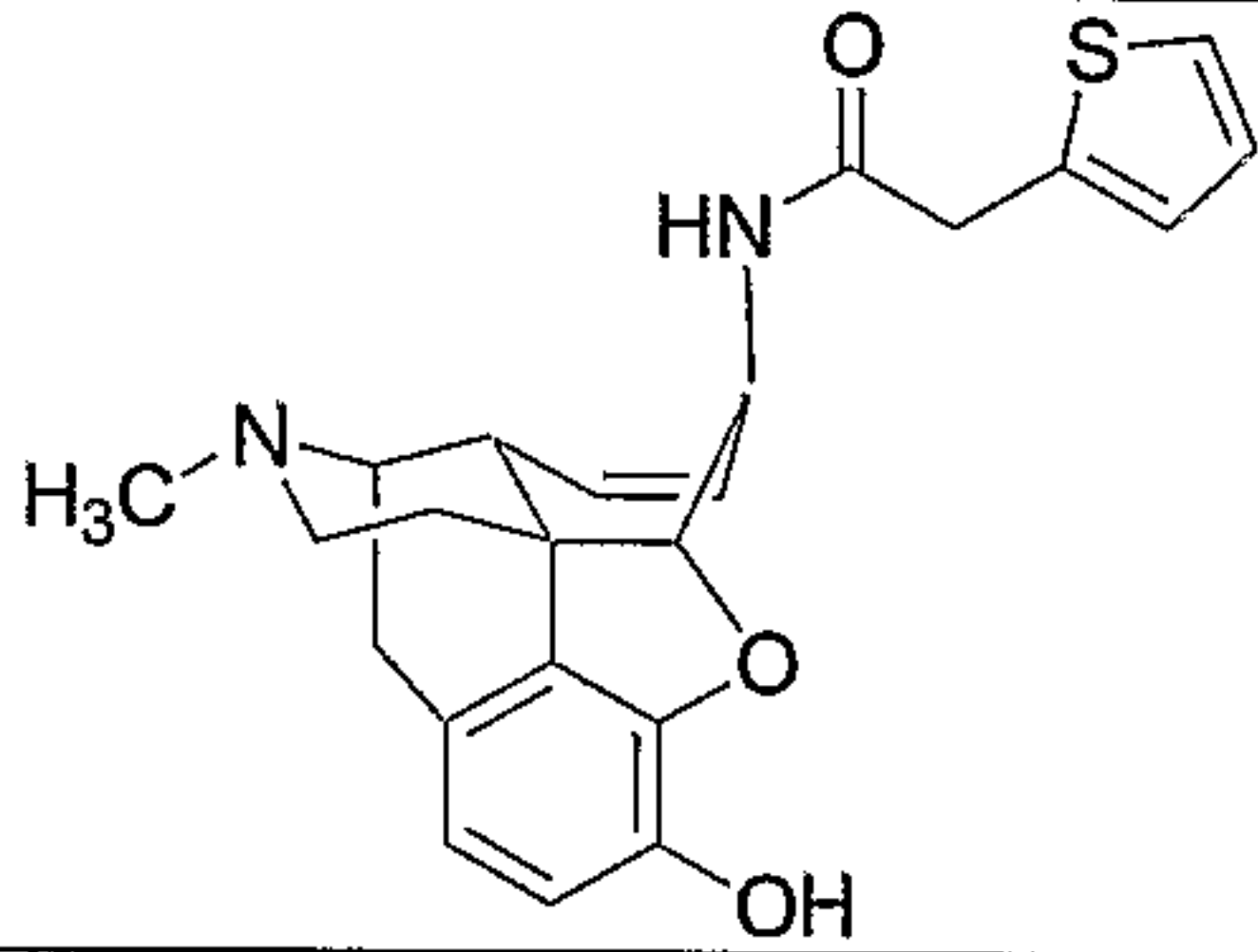
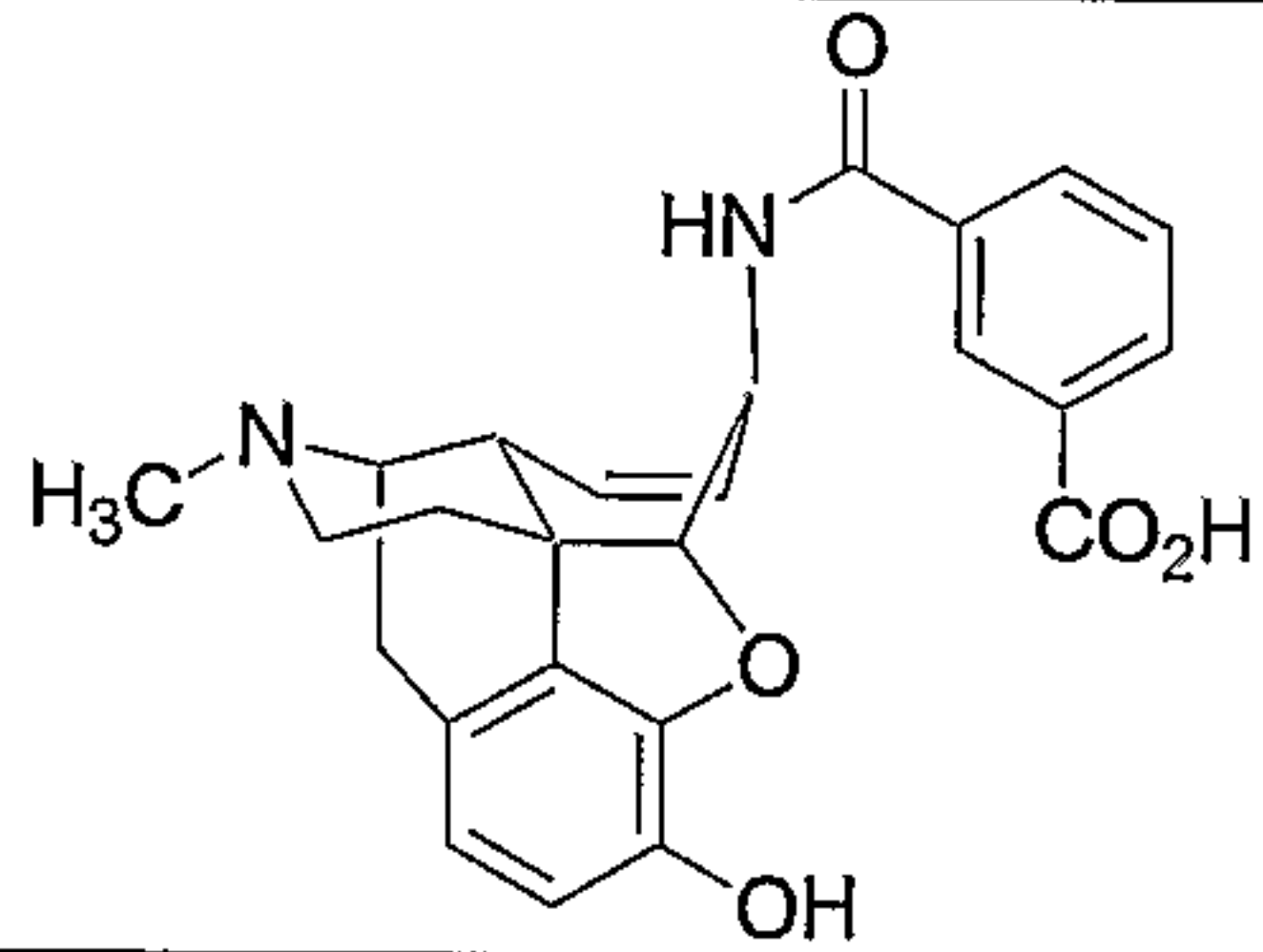
Table 4. Stability analysis of selected ligands.

entry	cmpd	MLM t _{1/2} (min)	HLS9 t _{1/2} (min)	pH 2.0 t _{1/2} (min)	pH 7.4 t _{1/2} (min)
morphine		--	--	--	--

entry	cmpd	MLM t _{1/2} (min)	HLS9 t _{1/2} (min)	pH 2.0 t _{1/2} (min)	pH 7.4 t _{1/2} (min)
M6G		stable	stable	stable	stable
3a		16.74	17.86	835.6	stable
3b		39.95	stable	stable	94.1 h
3c		14.11	11.76	--	--
3d		94.65	156.5	--	--
3e		≤12.5	37.44	1042.0	51 h

entry	cmpd	MLM t _{1/2} (min)	HLS9 t _{1/2} (min)	pH 2.0 t _{1/2} (min)	pH 7.4 t _{1/2} (min)
3f		491.8	628.8		
4a		stable	stable	stable	stable
4b		stable	stable	--	--
4c		stable	stable	--	--
4d		stable	stable	--	--
10		--	--	--	--

entry	cmpd	MLM t1/2 (min)	HLS9 t1/2 (min)	pH 2.0 t1/2 (min)	pH 7.4 t1/2 (min)
11a		--	--	--	--
9b		--	--	--	--
11b		--	--	--	--
13a		stable	stable	--	--
13b		310.2	stable	--	--
13c		stable	stable	--	--
13d		stable	stable	--	--

entry	cmpd	MLM t _{1/2} (min)	HLS9 t _{1/2} (min)	pH 2.0 t _{1/2} (min)	pH 7.4 t _{1/2} (min)
13e		stable	202.8	stable	828.1
13f		1123.5	361.1	--	--
13g		stable	231.4	--	--
13h		670.2	stable	--	--
14		stable	stable	--	--

Example 31: Determination of Analgesic Activity of Morphine Analogs 3a and 13e

A. Methods.

[0132] 1. Animals. Male ICR mice weighing 20-25g at the start of the experiment were used. Animals were group-housed under standard laboratory conditions and were kept on a 12:12 hr day-night cycle (lights on at 08:00). Animals were handled for 1-2 days prior to conducting the experiments.

[0133] 2. Drugs. Morphine, 13e and 3b were dissolved in water. Drugs were injected at a volume of 0.1 ml.

[0134] 3. Test for Nociception. Nociception was assessed using the tail flick assay with an analgesia instrument (Stoelting) that uses radiant heat. This instrument is equipped with an automatic quantification of tail flick latency, and a 15-sec cutoff to prevent damage to the animal's tail. During testing, the focused beam of light was applied to the lower half of the animal's tail, and tail flick latency was recorded. Baseline values for tail flick latency were determined before drug administration in each animal. Basal tail flick latency was between 3.2-8.0-sec (average 5.86 ± 0.16 SEM). Immediately after testing, animals were injected subcutaneously with the test compound or saline as a vehicle control. Following injections, animals were tested for tail flick latencies at 30-, and 60-min post-injection.

[0135] 4. Data Analysis. Antinociception was quantified by the following formula:

$$\% \text{ Antinociception} = 100 * [(\text{test latency} - \text{baseline latency}) / (15 - \text{baseline latency})].$$

If the animal did not respond prior to the 15-s cutoff, the animal was assigned a score of 100%. Behavioral results were analyzed using ANOVAs with morphine, **13e**, and **3b** as between group variables and post-drug treatment time (30-, 60-min) as the repeated measure followed by Student Newman-Keuls post-hoc tests where appropriate. The level of significance was set at $p < 0.05$.

B. Results.

[0136] 1. **Effects of morphine on tail-flick latency.** As shown in Figure 5, morphine produced dose-dependent increases in tail-flick latency. The overall ANOVA indicated a significant effect of dose [$F(3,45)=25.52$, $P < 0.0001$]. Thus, regardless of post-injection time, morphine produced the same effect on tail flick latency. Averaged across post-injection time, the 3-30 mg/kg dose of morphine produced a significant increase in tail-flick latency relative to controls (Student Newman-Keuls, $p < 0.05$). An escalating dose response curve for %MPE was observed, where the 3 mg/kg dose of morphine produced analgesic effects to a lower degree relative to the 10 and 30 mg/kg doses (Student Newman-Keuls, $p < 0.05$).

[0137] 2. **Effects of 13e on tail-flick latency.** Administration of **13e** produced an increase in tail-flick latency that was evident at 30 min and continued to be present at 60min (*see* Figure 6). The overall ANOVA indicated a significant effect of dose [$F(5,72)=14.86$, $P < 0.0001$]. Averaged across post-injection time, the two highest doses of **13e** produced a significant increase in tail-flick latency relative to controls (Student Newman-Keuls, $p < 0.05$). The analgesic effects of 30 mg/kg dose of **13e** were 2-fold greater than that produced by the 10 mg/kg dose (Student Newman-Keuls, $P < 0.05$). Compound **13e** seemed to have a slower

onset of action than morphine, with significantly increased potency at 60 min over 30 min. Considering its very high affinity ($K_i = 0.23$ nM at μ receptors) and potent full agonist activity with respect to stimulation of [^{35} S]GTP γ S binding ($EC_{50} = 2.4$ nM at μ), this compound had relatively weak antinociceptive activity, with ED₅₀ values of 30.2 mg/kg and 12.6 mg/kg at 30 and 60 min respectively. This probably less short-term potency relative to morphine, which has an ED₅₀ of approximately 3 mg/kg.

[0138] 3. Effects of 3a on tail-flick latency. Administration of 3a produced a dose-dependent increase in tail-flick latency indicative of the strong analgesic effects of the compound (*see* Figure 7). The overall ANOVA indicated a significant effect of dose [$F(5,64)=37.26$, $P<0.0001$]. Averaged across post-injection time, the 3-30 mg/kg doses of 3a produced a significant increase in tail-flick latency relative to controls (Student Newman-Keuls, $p<0.05$). The two highest doses (10 and 30 mg/kg) of 3a produced a greater amount of analgesia relative to the 3 mg/kg dose (Student Newman-Keuls, $p<0.05$). Compound 3a was significantly more potent as an analgesic than 13e, with an ED₅₀ of approximately 2.5 mg/kg at both 30 and 60 min. This value also suggests that 3a is slightly more potent morphine (ED₅₀ of 3 mg/kg). Although 3a has slightly lower *in vitro* binding affinity than morphine, it has roughly similar [^{35} S]GTP γ S potency and percent stimulation (*see* tables 1 and 2), indicating that the bioavailability of 3a is also similar to that or greater than that of morphine. Because this compound is somewhat non-selective with respect to each of the opioid receptors, it is not certain at this point which receptor mediates the antinociceptive activity. The onset of action for 3a is apparently faster than that for morphine (the activity is greater for the 60-min rather than 30 min time point).

Example 32: Heroin Dependence and Withdrawal

[0139] A. Methods. Effects of M6G Analogs on Heroin Dependent Animals. Heroin self-administration was done using a dose of heroin that produced optimal measures of dependence. 0.06 mg/kg/0.1 ml infusion was estimated based upon previous work. After stable responding was established (approx. 40 days at 23 hour/day access), the effects of low doses of naloxone (0.05 to 0.2 mg/kg) as a positive control and M6G analogues (0, 0.01, 0.04, 0.1 mg/kg, s.c.) and other analogs on different behavioral measures of heroin intake were examined. Four doses were tested for each compound. An attempt was made to perform within-subjects dose-effect studies for each M6G analog, but studies also employed between-subjects dose-effect functions as needed. To explore the effects of naloxone and M6G analogs over a 12-hr period, a minipump connected to an on/off gating device

developed in the Koob lab can also be used. Once stable heroin intake was achieved, the rats can be implanted with an osmotic minipump (in a gated-off position) at 6 AM. Twelve hours later, the gating device is turned to the on position and the rats are allowed access to heroin self-administration during the usual 23-hr sessions. During these sessions the minipump was in the gated-on position for a duration of 12 hours during the dark period which is the active phase (6 PM on 6 PM off). After 2 days, the minipump was removed and replaced with another minipump containing a different dose of the test compound (*i.e.*, naloxone or M6G analog) in a Latin Square design. This cycle is repeated so that 3 doses and vehicle control are tested. The large number of drugs and doses required may force a between-subjects design of dose for naloxone and M6G analogs. The particular behaviors to be examined were determined from the results from tests of long term heroin exposure via self-administration that may reflect the transition from self-administration in a non-dependent pattern to self administration in a dependent pattern. Sophisticated statistical modeling was done by using a Hierarchical Linear Modeling approach where individual acquisition trajectories were fitted with a polynomial function while accounting for within-subject and between-subject variables.

[0140] **B. Results.** Heroin self-administration paradigms are now well-established in the rat. [See Walker *et al.*, *Eur. J. Pharmacol.*, **383**:115 (1999)]. Fewer studies have explored the change in behavior associated with unlimited access to heroin and the development of self-administration of heroin to the point of dependence. Preliminary results have established that rats will reliably self-administer heroin i.v. with unlimited access, under conditions of no food deprivation or restriction. The pattern of unlimited access self-administration changes over time and produces animals that exhibit measures of dependence. An animal model of the development of heroin dependence in humans was developed. Animals given extended access (23-hour access to heroin self administration at doses of 0.06 mg/kg/0.1 ml infusion) exhibited sustained intake of heroin for 50-60 days. During this period, the self-infusion pattern changed from one observed only in the "active/dark" phase to a pattern where self-administration occurred about every 15-20 mins. From weeks 2-3 to week 7 essentially uniform self-administration was observed. Each self-administration per day was recorded for about 50 days. These studies have provided full information about heroin doses, patterns of intake, and time of day for maximal drug intake. Heroin dependence can be measured as a manifestation of withdrawal from chronic heroin administration. [See Woolverton and Schuster (1983)]. Dependence can be expressed as overt withdrawal signs following the

removal of heroin or following administration of a heroin antagonist in dependent rats. Both produce somatic signs and motivational effects. [See Weeks and Collins (1964).] The ability of M6G analogs to decrease heroin self-administration was tested in the extended-access model during self-administration and after administration of M6G analogs.

[0141] The effect of M6G analogs **3a**, **13e**, **13g** and **13h** on self-administration of heroin was examined in dependent rats that are consistent with effects in humans dependent on heroin. The goal of these experiments was to identify M6G analogs that were efficacious at decreasing heroin self-administration. Examination of figures 8-12 reveals that M6G analogs **13e** (0.04 mg/kg), **13g** (0.2 mg/kg), M6G (0.04 mg/kg), **13h** (0.01, 0.04, 0.2 mg/kg) were effective at reducing heroin self-administration. The most effective compound was **13h** which reduced heroin intake by 1000 ug/kg at a dose of 0.01 mg/kg.

Example 33: Synthesis and biological evaluation of a C-glycoside analog of M6G

[0142] Morphine-6-glucuronide (M6G) is a phase II metabolic conjugate of morphine with approximately 100-fold the analgesic potency of morphine itself when injected intracerebroventricularly into rats. [Carrupt *et al.*, *J. Med. Chem.* **34**, 1272-1275 (1991)] M6G is currently in late stage clinical trials for the treatment of postoperative pain. [Gutman *et al.*, U. S. Patent 6,737,518 (2004)] The oral bioavailability of M6G is only 11% [Penson *et al.*, *Br. J. Clin. Pharmacol.*, **53**:347-354 (2002)] and improvement of the metabolic stability of M6G could possibly increase its effectiveness as a potential pain medication. A general strategy for improving the *in vivo* metabolic stability of glycoconjugates involves the replacement of the glycosidic oxygen atom with carbon, nitrogen or sulfur atoms. [Postema *et al.*, *Organic Lett.*, **5**:1721-1723 (2003); Kiefel *et al.*, *J. Carbohydr. Chem.*, **18**:937-959 (1999).] This strategy in designing a library of glucosyl and glucuronosyl analogues of M6G, in which the glycosidic oxygen atom was replaced with a sulfur atom, was previously employed. [MacDougall *et al.*, *J. Med. Chem.* **47**:5809-5815 (2004).] The 6- β sulfur analogues of M6G showed modest improvement in μ opioid receptor affinity and functional efficacy, but showed less selectivity for μ versus δ and κ opioid receptors. Reported herein is an extension of this work detailing the results of a 14-step synthetic route and biological evaluation of a novel, μ -selective, amide-linked carbon glycoside analogue of M6G.

[0143] The C- β -glycopyranosyl acyl chloride **9** was prepared by a five step procedure from commercially available 2,3,4,6-tetrabenzylglucopyranose **4**. Compound **4** was oxidized with DMSO/Ac₂O to provide the corresponding lactone **5** (94%). [Kuzuhara, H.; Fletcher, H.G.,

J. Org. Chem., **32**:2531-2534 (1967).] Addition of 5 to a -78°C THF solution of lithium ethyl acetate [Rathke, M. W., *J. Am. Chem. Soc.*, **92**:3222-3223 (1970)], followed by acidic aqueous workup afforded the hemiketal 6, that was formed by a stereoselective aldol reaction (91%). [Lewis *et al.*, *J. Am. Chem. Soc.*, **104**:4976-4978 (1982).] The reduction [Lewis *et al.*, *supra*; Tiedemann *et al.*, *J. Org. Chem.*, **64**:4030-4041 (1999)] of 6 with triethylsilane in the presence of BF₃·OEt₂ in acetonitrile at 0 °C gave the ethyl ester 7 (86%). Hydrolysis of the ethyl ester group of 7 with LiOH in 1:1 THF/H₂O at reflux and subsequent acidic aqueous workup gave the carboxylic acid 8 (87%). The conversion of 8 to the corresponding acyl chloride 9 was accomplished by stirring in neat thionyl chloride for 18 h. Addition of 1.5 equivalents of the crude acid chloride 9 to 3-triisopropylsilyl-6-β-aminomorphine [MacDougall *et al.*, *Bioorg. Med. Chem.*, **12**:5983-5990 (2004)] in CH₂Cl₂ in the presence of 2.0 equivalents of Et₃N gave the protected morphine glucose analogue 10 (93%). The triisopropylsilyl protecting group in 10 was removed by the addition of TBAF in THF to give the phenol 11 (90%). Subsequent catalytic hydrogenation of 11 with activated 10% Pd/C in acidic methanol gave the amide-linked C-β-glycopyranoside analogue of M6G, compound 3 (52%). Hydrogenolysis of 11 with Pd/C in the absence of HCl resulted in the reduction of the phenanthrene carbon double bond and afforded 12 in quantitative yield, but did not result in hydrogenolysis of the glucose benzyl ether groups. Under these conditions, the basic morphinan nitrogen atom in 11 likely inhibited *O*-debenzylation. [Czech, B. P.; Bartsch, R. A., *J. Org. Chem.* **49**:4076-4078 (1984).] It is known that both saturation of the 7,8-double bond and substitution of the glucuronic acid moiety with a glucose moiety provide analogues of M6G with increased analgesic potency. [Stachulski *et al.*, *Bioorg. Med. Chem. Lett.*, **13**:1207-1214 (2003).] Accordingly, compound 3 was evaluated directly rather than develop an alternate route to the corresponding dehydro analogue or the glucuronic acid analogue of 3. The spectral data for all the synthetic compounds was in full agreement with the assigned structures. [New compounds 10, 11, 12 and 3 were characterized by ¹H NMR, ¹³C NMR and MS. The purity of test compounds 3 and 11 was determined by HPLC and was found to be ≥ 98%.]

[0144] The IC₅₀ values obtained from competition binding assays with . μ, δ and κ opioid receptors for compounds 3 and 11 were converted into K_i values as described in the Experimental section. The K_i values for the test compounds and reference materials are listed in Table 5. In the binding assays the following radioligands were used: [³H]DAMGO (μ opioid receptor agonist); [³H]U69593 (κ opioid receptor agonist); [³H]DPDPE (δ opioid

receptor agonist). K_i values were determined from measuring the inhibition of binding of these radioligands to the receptor by the test compounds **3** and **11**. [Zaveri *et al.*, *Eur. J. Pharmacol.*, **428**:29-36 (2001)] The benzyl derivative **11** and the deprotected congener **3** were both μ receptor selective. Compared to M6G, compound **11** possessed 27-fold higher potency than M6G for the μ opioid receptor. The selectivity of compound **11** for the μ versus δ and μ versus κ receptors were 10-fold and 34-fold, respectively. Compared to M6G, compound **3** showed 3.7-fold greater potency for the μ opioid receptor. The selectivity of compound **3** for the μ versus δ and μ versus κ receptors was 77- and 166-fold, respectively. It is noteworthy that the μ versus δ but not μ versus κ receptor selectivity of compound **3** was considerably improved relative to the value for M6G (*i.e.*, 12.5- and 316-fold selectivity, respectively). Compound **3** showed slightly greater potency toward the μ receptor compared to thiosaccharides **2a** (2.5-fold) and **2b** (1.6-fold) and significantly improved δ/μ and κ/μ receptor selectivity ratios. The functional activity of compounds **3** and **11** was evaluated using the [^{35} S]GTP γ S assay. [Traynor, J.R. and Nahorski S.R. Modulation, *Mol. Pharmacol.* **47**:848-854 (1995)]. The [^{35} S]GTP γ S assay measures the ability of the test compound to activate the G protein associated with either the μ , δ or κ opioid receptor. Based on the $E_{\max}$ values for stimulating [^{35} S]GTP- γ -S binding, compound **3** was determined to be a full agonist at the μ and δ receptors and a partial agonist at the κ receptor. Compound **11** was determined to be a full agonist at the δ receptor and a partial agonist at the μ and κ receptors. The efficacy ($E_{\max}$) of compound **3** at the μ receptor (75%) was substantially higher than M6G (45%) and the thiosaccharide analogues **2a** (46.6%) and **2b** (36.0%), respectively.

[0145] In conclusion, the C-glycoside **3** was prepared by a 14-step convergent synthesis from 2,3,4,6-tetra-*O*-benzyl-D-glucose **4** and morphine sulfate. Compound **3** showed a 3.7-fold greater affinity for the μ opioid receptor compared to M6G. The selectivity ratios of compound **3** for the δ versus μ and κ versus μ receptors were 76.7 and 166, respectively. The δ/μ selectivity for compound **3** was significantly improved relative to the value for M6G which was 12.5. Further work is currently in progress to fully delineate the *in vivo* biological properties of these compounds. Increasing metabolic stability of M6G may provide a new class of longer-lived, potent opioids agonists.

Table 5. Competitive inhibition of μ , δ and κ opioid receptors by compounds 2a, 2b, 3 and 11.

	K_i (nM) $\pm$ SEM ^a				Receptor selectivity
entry	μ	δ	κ	δ/μ	κ/μ
M6G^b	12.9 $\pm$ 0.9	170 $\pm$ 1	4060 $\pm$ 230	12.5	316
2a^b	8.7 $\pm$ 0.9	31.4 $\pm$ 2.3	288 $\pm$ 12	3.6	33
2b^b	5.4 $\pm$ 0.8	56.2 $\pm$ 2.2	136 $\pm$ 17	10.4	25.4
3	3.47 $\pm$ 0.37	266.33 $\pm$ 47.27	574.9 $\pm$ 7.8	76.7	166
11	0.47 $\pm$ 0.15	7.18 $\pm$ 1.2	15.82 $\pm$ 0.44	10.3	33.7

^aSEM, standard error of the mean. Each value is the mean of at least three independent determinations $\pm$ SEM.

^bData taken from MacDougall *et al.*, *supra*.

Table 6. Stimulation of [³⁵S]-GTP- γ -S binding by compounds 2a, 2b, 3 and 11 mediated by the μ , δ and κ opioid receptors

	μ		δ		κ	
entry	EC ₅₀ ^a	E _{max} ^b	EC ₅₀	E _{max}	EC ₅₀	E _{max}
M6G^d	72.3 $\pm$ 26.7	45.0 $\pm$ 5.0	190 $\pm$ 20	80.0 $\pm$ 1.0	>10K	ND ^a
2a^d	90.6 $\pm$ 22.9	46.6 $\pm$ 10.1	50.1 $\pm$ 36.7	78.7 $\pm$ 0.9	NA ^a	ND ^a
2b_d	91.5 $\pm$ 23.4	64.5 $\pm$ 0.5	192 $\pm$ 15	51.5 $\pm$ 6.5	321 $\pm$ 93	42.5 $\pm$ 2.5
3	37.2 $\pm$ 0.5	75.2 $\pm$ 3.6	334.9 $\pm$ 123.2	73.95 $\pm$ 7.85	1717.5 $\pm$ 24.5	38.5 $\pm$ 5.5
11	622.6 $\pm$ 9.2	36.0 $\pm$ 11.2	2.17 $\pm$ 1.14	65.35 $\pm$ 1.85	1.81 $\pm$ 0.62	44.5 $\pm$ 16.3

^aEC₅₀: The EC₅₀ value represents the concentration of a compound that produced 50% stimulation of [³⁵S]GTP γ S binding.

^bE_{max}: Agonist efficacy is defined as the degree to which the compound maximally stimulates [³⁵S]GTP γ S binding relative to control.

^cND: No detectable activity.

^dData from reference 6.

[0146] General information. All reactions were run under a positive pressure of dry nitrogen with magnetic stirring at ambient temperature using oven-dried glassware unless otherwise indicated. Air- and moisture-sensitive liquids were transferred via syringe through rubber septa. The term brine refers to a saturated solution of sodium chloride. Silica gel (230-400 mesh) was used for column chromatography. DMF was dried through a column of neutral alumina and stored over activated 4 Å molecular sieves under nitrogen prior to use. CH₂Cl₂ and THF were distilled from CaH₂ immediately prior to use. All other solvents and reagents were used as received. ¹H NMR spectra were recorded at 18 °C with a 300 MHz Varian NMR. Chemical shifts were reported in ppm (δ) relative to CDCl₃ at 7.26 ppm unless indicated otherwise. High-resolution mass spectra was done on a VG 7070 spectrometer with Opus V3.1 and DEC 3000 Alpha Station data system at the University of California at Riverside. Low resolution mass spectroscopy (LRMS) was done on a Hitachi M-8000 3DQMS (ion trap) mass spectrometer using ESI. Melting points were reported uncorrected. Analytical purity was determined by straight phase HPLC using a Hitachi L74 liquid chromatograph with a D7500 integrator and a Hamilton PRP-I stainless steel column (250 mm x 4.6 mm, i.d.). For determination of analytical purities a mobile phase A = 60/40/0.02 MeOH/2-propanol/HClO₄ (v:v) or mobile phase B = 55/45/0.018 MeOH/2-propanol/HClO₄ (v:v) was used.

[0147] 3-O-Triisopropylsilyl-6-β-(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)acetamidomorphine 10. SOCl₂ (2.0 mL) was added to the carboxylic acid **8** (389 mg, 0.67 mmol) and the solution was stirred at rt for 18 h. The excess SOCl₂ was removed under high vacuum with the aid of a water bath (60 °C) and the yellow oil that resulted was dissolved in CH₂Cl₂ (5 mL) and added to 3-O-triisopropylsilyl-6-β-aminomorphine (196 mg, 0.445 mmol) and Et₃N (0.12 mL, 0.89 mmol) in CH₂Cl₂ (5 mL). The solution was stirred at rt for 1 h, concentrated and purified by flash chromatography (SiO₂, 30:1 to 10:1 EtOAc/MeOH), providing **10** as a white solid (417 mg, 93%): R_f = 0.46 (10:1 CH₂Cl₂/MeOH); mp = 56.6 °C; ¹H NMR (CDCl₃) δ 7.35-7.10 (20H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 6.22 (d, *J* = 6.9 Hz, 1H), 5.71 (ddd, *J* = 3.0, 6.0, 9.5 Hz, 1H), 5.41 (dd, *J* = 1.9, 9.5 Hz, 1H), 4.89-4.48 (9H), 4.36 (t, *J* = 6.3 Hz, 1H), 3.72-3.46 (5H), 3.29 (t, *J* = 9.0 Hz, 1H), 3.17 (dd, *J* = 3.0, 5.2 Hz, 1H), 2.96 (d, *J* = 18.7 Hz, 1H), 2.88 (bs, 1H), 2.72 (dd, *J* = 2.7, 15.2 Hz, 1H), 2.50-1.72 (10H), 1.30-1.05 (21H). ¹³C NMR (CDCl₃) δ 170.0, 147.9, 143.6, 138.2, 137.8, 137.6, 132.9, 130.4, 128.7, 128.4, 128.34, 128.32, 128.0, 127.8, 127.76, 127.6, 127.0, 120.8, 118.4, 92.0, 86.8, 80.9, 78.7, 78.1, 77.4, 76.1, 75.7, 75.2, 75.0,

73.3, 68.7, 59.0, 49.3, 46.8, 44.1, 43.1, 40.3, 39.0, 36.4, 20.3, 18.0, 17.99, 12.8, 11.3; MS (EI) m/z 1006 $[M + H]^+$.

[0148] 6- β -(2,2,4,6-Tetra-O-benzyl- β -D-glucopyranosyl)acetamidomorphine 11. The silyl ether **10** (270 mg, 0.27 mmol) was dissolved in THF (4 mL). Water (0.05 mL) and TBAF (0.4 mL, 0.4 mmol, 1.0 M solution in THF) were added. After 2.5 h, 1% concentrated HCl (4 mL) was added and the mixture was stirred for 2 min, diluted with water (10 mL) and made basic with solid NaHCO_3 . The mixture was extracted with CH_2Cl_2 (5 x 30 mL), dried (Na_2SO_4), filtered and concentrated. Flash chromatography (24:1 to 12:1 EtOAc/MeOH) provided **11** as a white solid (205 mg, 90%): R_f = 0.15 (12:1 EtOAc/MeOH); mp = 103.8 °C; ^1H NMR δ 7.34-7.10 (20H), 6.64 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 6.34 (d, J = 6.3 Hz, 1H), 5.68 (ddd, J = 2.5, 5.8, 9.5 Hz, 1H), 5.39 (d, J = 9.5 Hz, 1H), 4.89-4.46 (10H), 4.34 (t, J = 6.3 Hz, 1H), 3.72-3.46 (6H), 3.30 (t, J = 9.1 Hz, 1H), 3.18 (bs, 1H), 2.97 (d, J = 18.1 Hz, 1H), 2.94 (bs, 1H), 2.74 (dd, J = 2.5, 15.7 Hz, 1H), 2.55-2.16 (7H), 1.95 (dt, J = 8.0, 12.6 Hz, 1H), 1.76 (d, J = 11.3 Hz, 1H); ^{13}C δ 170.4, 144.2, 143.6, 138.1, 138.0, 137.8, 137.7, 137.6, 132.6, 129.8, 128.38, 128.37, 128.33, 128.3, 128.2, 128.0, 127.8, 127.7, 127.7, 127.65, 127.6, 125.9, 119.1, 116.3, 93.0, 86.8, 80.8, 78.7, 78.1, 77.4, 76.0, 75.7, 75.3, 75.0, 73.3, 68.7, 59.0, 50.0, 47.0, 44.0, 43.0, 39.9, 38.8, 35.9, 20.2; MS (EI) m/z 850 $[M + H]^+$; HRMS (ESI) calcd for $\text{C}_{53}\text{H}_{57}\text{N}_2\text{O}_8$ 849.4115, found 849.4099; the average purity of **11** was found to be $\geq 99\%$ by analytical HPLC giving t_R = 3.24 min (mobile phase A) and t_R = 4.66 min (mobile phase B).

[0149] 6- β -(2,3,4,6-Tetra-O-benzyl- β -D-glucopyranosyl)acetamido-7,8-dihydromorphine 12. The tetrabenzyl ether **12** (35.4 mg, 0.042 mmol) was dissolved in MeOH and 10% Pd-C (15 mg) was added. The mixture was stirred under an atmosphere of hydrogen for 24 h and then filtered through Celite. The Celite was washed with MeOH (10 mL) and CH_2Cl_2 (2 mL) and the filtrates were concentrated to provide **12** as a white solid (35 mg, 100%): R_f = 0.66 (200:80:5:0.05 CH_2Cl_2 /MeOH/ H_2O /13% NH_4OH); mp = 94.3 °C; ^1H NMR (CDCl_3) δ 7.33-7.10 (20H), 6.92 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 4.88-4.29 (9H), 3.73-3.32 (8H), 3.05 (bs, 1H), 2.96 (d, J = 18.4 Hz, 1H), 2.72 (dd, J = 2.7, 15.7 Hz, 1H), 2.49-0.95 (15H); MS (EI) m/z 852 $[M + H]^+$.

[0150] Dihydromorphine-6- β -acetamidoglucose, 3. The tetrabenzyl derivative **11** (41 mg, 0.05 mmol) was dissolved in MeOH (2 mL). Concentrated HCl (13 μL) and then 10% Pd-C (40 mg) was added. The mixture was stirred under an atmosphere of hydrogen for 24 h.

The solution was neutralized with Bio Rad RG 501-X8 mixed bed resin (1 g) and the mixture was filtered through Celite. The solids were washed with MeOH (30 mL) and the filtrate was concentrated. The residue was triturated with ethyl ether (3 x 2 mL) and dried under high vacuum, providing 3 as a white powder (12 mg, 52%): $R_f = 0.4$ (SiO₂, 5:4:0.5:0.5 CHCl₃/MeOH/H₂O/concentrated NH₄OH); mp = 266.4 °C (decomposed); ¹H NMR δ 6.62 (s, 2H), 4.47 (d, $J = 7.8$ Hz, 2H), 3.81-3.77 (m, 2H), 3.55-3.43 (m, 4H), 3.00 (t, $J = 9.3$ Hz, 1H), 2.90 (d, $J = 5.4$ Hz, 1H), 2.84 (s, 3H), 2.79-2.69 (m, 1H), 2.63 (dd, $J = 12.9, 14.4$ Hz, 1H), 2.45 (d, $J = 11.7$ Hz, 1H), 2.30-2.05 (m, 3H), 1.77-1.57 (m, 4H), 1.34-1.24 (2H), 1.00-0.92 (2H); ¹³C NMR (CD₃OD) δ 173.9, 143.9, 142.6, 128.5, 122.3, 121.1, 119.4, 92.7, 81.6, 79.5, 77.9, 75.1, 72.0, 63.1, 52.7, 43.1, 41.9, 41.7, 40.3, 34.6, 29.2, 24.6, 21.7; MS (EI) m/z 491 [M + H]⁺; HRMS (ESI) calcd for C₂₅H₃₅N₂O₈ 491.2393, found 491.2375; the average purity of 3 was found to be $\geq 98\%$ by analytical HPLC giving $t_R = 3.41$ min (mobile phase A) and $t_R = 3.74$ min (mobile phase B).

[0151] Receptor Binding. Binding to membranes from cells transfected with human μ , δ and κ opioid receptor was done in a 96-well format, as described previously (New compounds 10, 11, 12 and 3 were characterized by ¹H NMR, ¹³C NMR and MS. The purity of test compounds 3 and 11 was determined by HPLC and was found to be $> 98\%$) Cells were removed from the plates by scraping with a rubber policeman, homogenized in Tris buffer using a Polytron homogenizer, then centrifuged once and washed by an additional centrifugation at 27,000 x g for 15 min. The pellet was resuspended in 50 mM Tris, pH 7.5, and the suspension incubated with [³H]DAMGO, [³H]DPDPE, or [³H]U69593, for binding to μ , δ or κ opioid receptors, respectively. The total incubation volume was 1.0 mL and samples were incubated for 60-120 min at 25 °C. The amount of protein in the binding reaction varied from approximately 15 μ g to 30 μ g. The reaction was terminated by filtration using a Tomtec 96 harvester (Orange, CT) with glass fiber filters. Bound radioactivity was determined by counting with a Pharmacia Biotech beta-plate liquid scintillation counter (Piscataway, NJ) and data expressed in counts per minute. IC₅₀ values were determined using at least six concentrations of test compound, and calculated using Graphpad/Prism (ISI, San Diego, CA). K_i values were determined by the method of Cheng and Prusoff [Traynor, J. R. *Mol. Pharmacol.*, **47**:848-854 (1995)].

[0152] [³⁵S]GTP γ -S binding. [³⁵S]GTP γ -S binding was done essentially as described by Traynor and Nahorski [Zaveri, N. *et al.*, *Eur. J. Pharmacol.*, **428**:29-36 2001]. Cells transfected with μ , δ and κ opiate receptors were scraped from tissue culture dishes into 20

mM Hepes, 1 mM EDTA, then centrifuged at 500 x g for 10 min. Cells were resuspended in this buffer and homogenized using a Polytron homogenizer. The homogenate was centrifuged at 27,000 x g for 15 min and the pellet resuspended in Buffer A, containing 20 mM Hepes, 10 mM MgCl₂, 100 mM NaCl, pH 7.4. The suspension was recentrifuged at 27,000 x g and suspended once more in Buffer A. For the binding assay, membranes (8-15 µg protein) were incubated with [³⁵S]GTPγ-S (50 pM), GDP (10 µM), and the test compound, in a total volume of 1.0 mL, for 60 min at 25 °C. Samples were filtered over glass fiber filters and counted as described for the binding assays. Statistical analysis was done using the program GraphPad Prism. In this assay, a compound's potency or affinity for the receptor was defined by its EC₅₀ for stimulating [³⁵S]GTPγS binding. Agonist efficacy was defined as the degree to which the compound maximally stimulated [³⁵S]GTPγS binding relative to control. The EC₅₀ value represents the concentration of a compound that produced 50% maximal stimulation of [³⁵S]GTPγS binding.

Example 34: 6-Naltrexamides for Alcohol and Nicotine Addiction

[0153] In the United States, alcoholism, nicotine addiction, and gambling addiction are serious psychiatric disorders with significant social and economic consequences. Epidemiological studies show that alcoholism will affect approximately 14% of the American population at some time in their lives [Regier, *et al.*, *Arch. Gen. Psychiatry*, **50**:85-94 (1993)]. An estimated 100,000 US citizens will die of alcoholism each year from direct and indirect causes [McKinnis and Foege, *JAMA*, **270**:2207-2212 (1993)] and the economic costs including health and social costs are staggering at \$166 billion per year (NIDA and NIAAA, 1998). Smoking is directly linked to lung cancer and stopping smoking is the major means of preventing lung cancer. Use of medications to treat withdrawal from alcoholism or nicotine and a role in rehabilitation of alcoholic patients or smokers is limited. A number of medications have been tested to reduce or prevent the consumption of alcohol in addicted individuals. Some of these include disulfiram, lithium, selective serotonin reuptake inhibitors, and acamprosate. Disulfiram has been shown to have limited effectiveness [Garbutt *et al.*, *JAMA*, **281**:1318-1325 (1999)]. There are several ways that medications have been used to treat withdrawal from alcoholism. Several approaches to stopping smoking have been developed but the relapse rate is great. For alcoholism, deterrent drugs such as disulfiram make the ingestion of alcohol unpleasant. In contrast, medications attempt to decrease alcohol intake by reducing the reinforcing effects of alcohol or by reducing the urge or craving to ingest alcohol. Pharmacological agents appear to influence several

neurotransmitter systems that underlie reinforcing or discrimination stimulus effects of ethanol or nicotine including endogenous opioids, catecholamines (especially dopamine, serotonin) and excitatory amino acids such as glutamate [Kranzler, *Am. J. Psychiat.*, **152**:391-397 (1995)]. Despite the fact that a number of medications have been shown to be of value in the treatment of alcohol or nicotine dependence, pharmacotherapies have not had a large effect. There is some evidence that subgroups of alcoholics or smokers may respond well to certain medications, suggesting that treatment matching may increase the efficacy of medications. However, considerable basic information about strategic approaches, dosing and duration of treatment is just becoming available and much more information needs to be established. New approaches and new medications development are clearly needed to address these important issues.

[0154] In 1994, naltrexone was approved by the US FDA for treatment of alcoholism. Naltrexone is a pure opioid mu receptor antagonist with no agonist activity and no abuse potential. In a laboratory study of non-problem drinkers, naltrexone was found to decrease the reinforcing (*i.e.*, stimulant) effects and increase the unpleasant (*i.e.*, sedative) properties of initial alcohol consumption [Swift *et al.*, *Am. J. Psychiat.*, **151**:1463-1467 (1994)]. Studies using rodent and monkey have shown that the opioid antagonists naloxone and naltrexone reduce the voluntary consumption and stress-induced increase in alcohol consumption, suggesting that these agents may prevent the reinforcing effects of alcohol consumption [O'Brian *et al.*, *Alcohol*, **13**:35-39 (1996)]. Naltrexone may be most beneficial among alcoholics with higher levels of craving and poorer cognitive functioning [Jaffe *et al.*, *J. Consult. Clin. Psychol.*, **64**:1044-1053 (1996)]. However, in one study, 15% of patients undergoing treatment terminated treatment early due to adverse effects including intolerable nausea [Croop *et al.*, *Arch. Gen. Psychiat.*, **54**:1130-1135 (1997)]. Naltrexone is also associated with dose-dependent hepatotoxic side effects that complicate use and confound treatment of alcoholic patients with liver disease [Mason *et al.*, *Arch. Gen. Psychiat.*, **56**:719-724 (1999)]. Additional shortcomings include less than desirable duration of action and relatively low bioavailability [Wall *et al.*, *Drug Metab. Dispos.*, **9**:369-375 (1981)] and possibly, a relatively low affinity for delta and kappa receptors thought to be involved in diminishing the reinforcing effects of drinking alcohol. Beneficial effects of naltrexone diminish gradually over time. In addition, compliance with naltrexone treatment was variable and only among highly-compliant subjects was the active medication significantly better than placebo [Volpicelli *et al.*, *Arch. Gen. Psychiat.*, **54**:737-742 (1997)]. In summary, naltrexone

appears to produce a modest effect on drinking behavior among alcoholics. In some cases, the effects of naltrexone have been quite robust but evidence of its efficacy has been less consistent. However, nalmefene, an opioid antagonist with superior pharmaceutical properties to naltrexone, may hold more promise as an alcohol treatment medication. Naltrexone has been reported to be useful for smoking cessation [O'Malley *et al.*, US Patent No. 6,541,478].

[0155] Opioid receptor antagonists apparently have direct effects on alcohol-seeking behavior. For example, direct perfusion of naloxone via microdialysis into the nucleus accumbens neurons inhibited alcohol-mediated dopamine release [Benjamin *et al.*, *Brain Res.*, **621**:137-140 (1993)]. The decrease in alcohol consumption by blockade of opioid receptors suggests direct effects of naloxone in this reinforcement system. Animal studies have provided evidence that μ -, δ - and κ -opioid receptors contribute to alcohol-induced reinforcement [Herz (1997); Ulm *et al.*, *J. Clin. Psychiat.*, **56**:5-14 (1995)]. Considerable work has been done related to the norbinaltorphimine (norBNI, Figure 1) that is selective for the κ -opioid receptor [Portoghese *et al.*, *J. Med. Chem.*, **31**:1344-1347 (1987)]. The SAR of norBNI has been extensively investigated and is a bivalent ligand containing two naltrexone-derived pharmacophores. It is believed that only one of the norBNI pharmacophores is required for kappa antagonist activity and the basic group (at N-17') in the second pharmacophore of the receptor-bound ligand acts as an "address" to confer selectivity. In view of the apparent requirement of a rigid scaffold for orienting the molecule to the receptor, alternate structures have been developed including naltrindole (NTI, *see* Figure 15). This indolomorphinan structures related to NTI is simpler than norBNI and has provided considerable evidence that κ antagonists interact with a Glu297 address subsite [Stevens *et al.*, *J. Med. Chem.*, **43**:2759-2769 (2000)].

[0156] The requirement of a positively charged amino functionality in the address group necessary for κ antagonist activity was further evidenced in a recent report that described a nonopiate-derived compound as a potent and selective opioid κ antagonist. The compound, JD₁Tic (*see* Figure 16) illustrates the importance of two basic amine groups: one each in both the address and message group. Further work showed the importance of a phenol group in κ selectivity that was not observed for the nor-BNI series [Thomas *et al.*, *J. Med. Chem.*, **47**:1070-1073 (2004)]. Based on chimeric kappa-mu opioid receptors, it is apparent that a negatively charged residue (*i.e.*, Glu 297) is important in κ -selective binding and functional activity. Highly active κ -selective or non- κ -selective receptor selective antagonists would

be useful for the treatment of addictions, particularly addictions to substances such as, *e.g.*, nicotine or alcohol.

[0157] The chemical structures of nalmefene **1** and naltrexone **2** are shown in Figure 17. These compounds are used for the treatment of opioid overdose, addiction and alcoholism. The medicinal chemistry objective of the present study was to develop metabolically stable analogues of these compounds by replacing the metabolically labile 6-methylene or 6-keto groups in **1** and **2**, respectively, with an amide moiety. Various substitution patterns in the aromatic ring of the amide group were explored in order to increase mu and kappa opioid receptor selectivity and potency. A novel four step synthesis of either 6- α - or 6- β -naltrexamides was developed in order to meet this objective. The condensation of naltrexone **2** with hydroxylamine hydrochloride in the presence of NaOAc in refluxing aqueous ethanol provided the corresponding oxime **3** (*see* Figure 18). Subsequent reduction of the oxime functional group in **3** to the corresponding amine **4** was accomplished by heating with BH_3/THF for 48 hours and subsequent aqueous workup giving the amines **4** as a 9:1 (β/α) mixture of diastereomers. The diastereomeric amines were separated by chromatography on silica gel. The amines **4** were coupled with carboxylic acids (RCOOH) in the presence of benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphonium hexa-fluorophosphate (BOP) and diisopropylethylamine in CH_2Cl_2 . Alternatively, the amides could be formed by the reaction of an acid chloride, triethylamine and **4** in CH_2Cl_2 . In both cases, the product was treated with K_2CO_3 in methanol to deesterify the side-product resulting from esterification of the 3-position hydroxyl group. While the BOP coupling procedure resulted in less esterification at the 3-position than the acid chloride method, some esterification at the 3-position could not be avoided. Thus, it was found to be more convenient to run the reaction with an excess of the acid derivative to aid in the purification of the intermediate amide ester. These methods allowed us to conveniently prepare the amides **5** and **6a-h**. The benzyl groups in compound **5** were removed by hydrogenolysis in the presence of Pd-C and HCl to give the glucose conjugate **6a**.

Table 7. K_i , K_e and pA_2 binding values of mu, delta and kappa opioid binding to CHO membranes.

compound	K_i (nM)			K_e (mu)	K_e (other)	pA_2 (mu)
	mu	delta	kappa			
morphine	1.1 ± 0.1	140 ± 2	46.9 ± 14	NA		

compound	Ki (nM)			Ke (mu)	Ke(other)	pA2 (mu)
naltrexone	0.2±0.03	11± 1.1	0.3 ± 0.03	NA		
5	2.5 ± 0.6	140 ± 13.9	39 ± 6.3	0.16 + 0.02	10.35 +2.01 (delta)	2.5 ± 0.6
6a	1.8 ± 0.5	91.3 ± 3.8	10.4 ± 2.8	0.37 + 0.03	1 3.39 + 1.51 (kappa)	9.33 + 0.05
6b	NA	NA	NA	NA	NA	NA
6c	2.9 ± 0.1	6.2 ± 0.6	7.1 ± 0.8	0.41+ 0.02	-	9.34 + 0.02
6d	0.6±0.1	10.6±1.2	0.6±0.01	0.17 + .009	-	9.78 + 0.04
6e	2.9 ± 0.1	6.2 ± 0.6	7.1 ± 0.8	0.41+ 0.02	-	9.34 + 0.02
6d	NA	NA	NA	NA	NA	NA
6e	NA	NA	NA	NA	NA	NA
6f	NA	NA	NA	NA	NA	NA

NA, Not available.

[0158] The potency and selectivity observed for the corresponding agonists [MacDougall *et al.*, *J. Med. Chem.*, **47**:5809-5815 (2004); MacDougall *et al.*, *Bioorganic Med. Chem.*, **12**:5983-5990 (2004); MacDougall *et al.*, *Bioorganic Med. Chem.*, **15**:583-1586 (2005)] was generally retained in the antagonists. The amides **6d**, **6e** and **6c** all possessed high affinity for the opioid receptors and partial or full or partial agonism at delta and kappa receptors (Table 8). All the compounds were strong antagonists at the mu receptor, based on GTPγS binding to cell membranes. Compound **6a** had high affinity for mu and moderate affinity for delta and kappa receptors. **6a** is a strong antagonist at mu and kappa and a partial agonist at delta receptors. In summary, the data shows potent leads are present with the functional consequences of antagonizing mu- alone or mu- and kappa-receptors.

Table 8. Stimulation of ^{35} S-GTP-gamma-S binding by HBRI Compounds.

Entry	mu		delta		kappa	
	EC ₅₀	% stimulation	EC ₅₀	% stimulation	EC ₅₀	% stimulation
morphine	15.6 ± 0.5	93 ± 3	ND	ND	ND	ND
M6G	72.3±26.7	45.0±5.0	190.4±22.9	80.0 ± 1.0	>10,000	-
5	9.7±0.5	21.4±0.5	106.8	20.5	10.8	45.5
6a	42.3±5.4	15.8±1.6	90.9	43.1	11.2	11.01
6b	NA	NA	NA	NA	NA	NA
6c	4.6±0.9	19.3±0.1	7.3	100	1.1	126.5
6d	1.2±0.6	20.6± 1.5	11.1	98.7	1.7	109.1
6e	5.2±1.6	16.1± 1.9	24.5	88.5	100.1	53.6.1

[0159] To investigate metabolic stability, HPLC and LCMS assays were developed to study the metabolic and chemical stability and found that generally, the compounds in these series were remarkably stable to metabolism and to degradation. The analogs were designed to be stable in hepatic preparations due to blockade of the C-6 position and this is what was observed. Preliminary results showed that **6d** and **6a** hold promise as potent opioid antagonists (Tables 7 and 8). Because the tetra-*O*-benzyl- β -D-glucopyranosyl protected compound **5** had been synthesized, its *in vitro* binding and functional properties were investigated. Compound **5** had high affinity for mu and moderate affinity for kappa and low affinity for delta receptors. The studies point to the glucose analogs themselves as promising development candidates.

[0160] The data show the feasibility that metabolically stable opioid antagonists can be synthesized and tested *in vitro*. Metabolically stable C-6 substituted opioid antagonists will retain favorable side effect profiles. *In vitro* results show that potent mu antagonists with either agonistic or antagonistic kappa properties can be synthesized. To examine whether kappa antagonism or agonism is more efficacious in decreasing alcohol consumption, leads were studied in an animal model of alcoholism and nicotine addiction. Highly active κ - selective or non- κ -selective receptor selective antagonists would be useful for the treatment of addictions, particularly addictions to substances such as, *e.g.*, nicotine or alcohol.

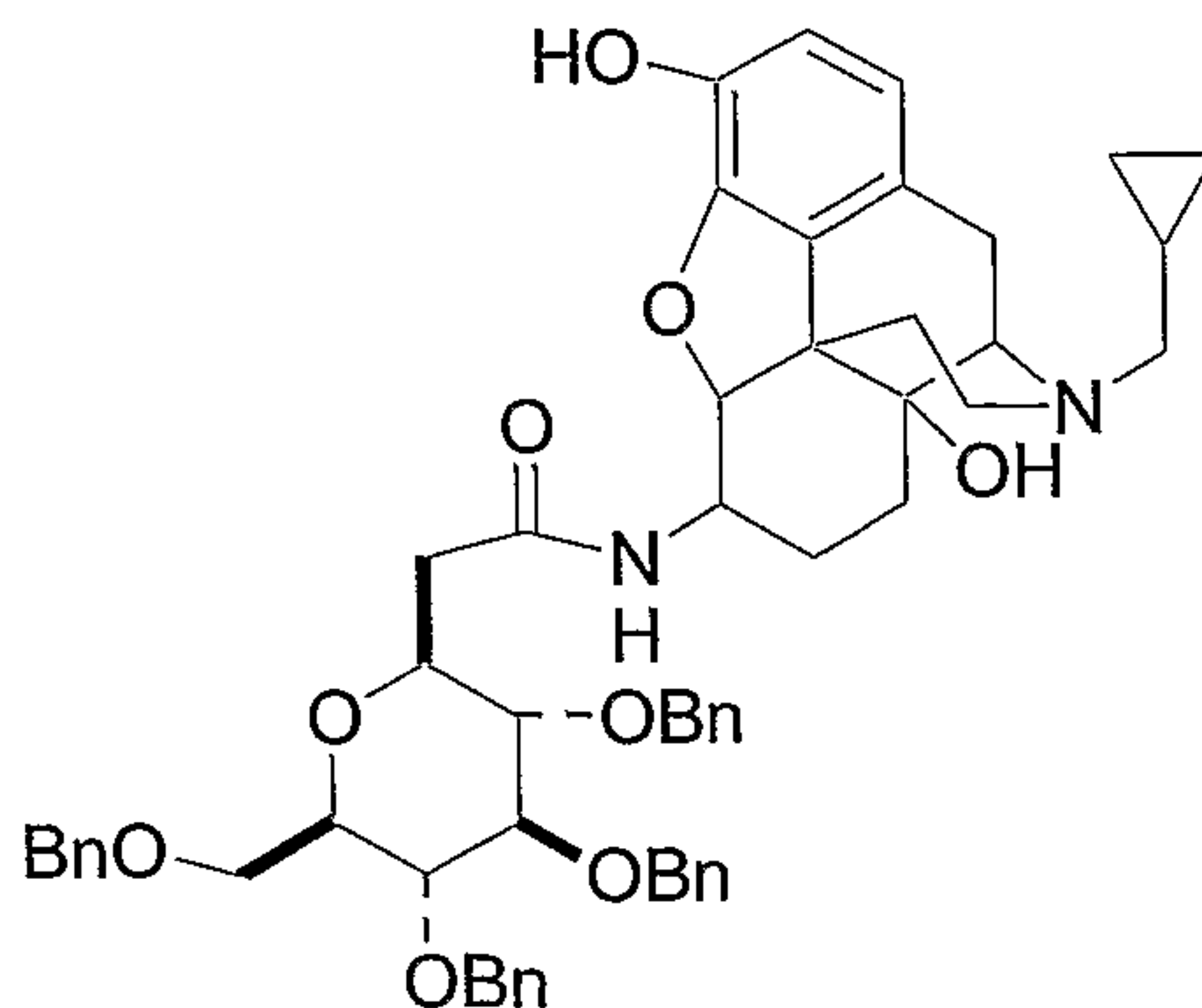
[0161] In the following examples (Examples 35-43), all reactions were run under a positive pressure of nitrogen with magnetic stirring at ambient temperature using oven-dried glassware unless otherwise indicated. Air- and moisture-sensitive liquids were transferred *via* syringe through rubber septa. Silica gel (230-400 mesh) was used for column

chromatography. DMF was dried by filtration through a column of neutral alumina and stored over activated 4 Å molecular sieves under nitrogen prior to use. All other solvents and reagents were used as received. ^1H NMR spectra were recorded at 300 MHz using a Varian NMR. Chemical shifts were reported in ppm (δ) relative to CDCl_3 at 7.26 ppm. ^1H NMR spectra were recorded in CDCl_3 unless stated otherwise. Melting points were reported uncorrected. High-resolution mass spectra was done on a VG 7070 spectrometer with an Opus V3.1 and DEC 3000 Alpha Station data system at the University of California Riverside. Where combustion analyses was not specified, analytical purities were determined by straight phase HPLC using a Hitachi L74 liquid chromatograph with a L-7400 uv detector, a D7500 integrator and a Hamilton PRP-I stainless steel column (250 mm x 4.6 mm i.d.).

Naltrexone oxime, 3 was prepared according to the following method. Naltrexone (6.2 g, 1.46 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.5 g) and NaOAc (2.9 g) were dissolved in absolute EtOH (80 mL) and water (5 mL). The mixture was heated at reflux for 2.5 h and then concentrated. Water (20 mL) was added and the mixture was made basic with K_2CO_3 and extracted with CHCl_3 . The CHCl_3 extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated to a white solid (5.83 g, 90%); $R_f = 0.65$ (5:1:0.2 EtOAc/MeOH/ NH_4OH); MS (EI) $m/z = 357$ $[\text{MH}]^+$.

6- β -Naltrexamine and 6- α -naltrexamine, 4b, 4a were prepared according to the following method. Naltrexone oxime (5.83 g, 16.3 mmol) was dissolved in THF (40 mL) and transferred by cannula to a 10 °C solution of BH_3 :THF (300 mL, 300 mmol, 1 M solution in THF) over 10 min. A white precipitate formed and then slowly dissolved as the reaction was heated at reflux for 2 d. The solution was cooled to rt and water (10 mL) and 1 N KOH (200 mL) were added slowly with caution. The solution was heated at reflux for 2 h. The pH was then reduced to 2.5 with 10% HCl (225 mL). The solution was heated at reflux for 2 h, concentrated to remove the THF and then made basic (pH 8-9) with K_2CO_3 . The mixture was extracted with CHCl_3 (4 X 150 mL) and the extract was dried over Na_2SO_4 , filtered and concentrated. The resulting oil was purified by chromatography on SiO_2 (26 x 60 cm, elution with $\text{CH}_3\text{CN}/\text{MeOH}/\text{NH}_4\text{OH}$, 25:5:1) providing **4b** (2.14 g, 38%) as a white-yellow solid: $R_f = 0.20$; ^1H NMR (300 MHz, CDCl_3 with 2 drops of CD_3OD) δ 6.61 (d, $J = 8.1$ Hz, 1H), 6.49 (d, $J = 8.1$ Hz, 1H), 4.17 (d, $J = 7.5$ Hz, 1H), 3.39-0.45 (20 H); MS $m/z = 343$ $[\text{MH}]^+$. An additional 0.64 g (12%) of material consisting of a mixture of the α - and β -diastereomers was isolated. Preparative chromatography (SiO_2 , $\text{CH}_3\text{CN}/\text{MeOH}/\text{NH}_4\text{OH}$, 25:5:1) of the tailing fractions of this material gave an analytical sample of **4a**: $R_f = 0.16$; ^1H NMR δ 6.65 (d, $J =$

8.1 Hz, 1H), 6.46 (d, 8.1 Hz, 1H), 4.50 (d, $J = 3.0$ Hz, 1H), 3.34 (dt, $J = 3.9, 12.6$ Hz, 1H), 3.04 (t, $J = 6.6$ Hz, 1H), 2.95 (s, 1H), 2.63-0.29 (17H); MS m/z 343 $[MH]^+$.



Example 35: 6-acetamido-2,3,4,6-tetra-O-benzyl-D-glucopyranosyl-14-Hydroxy-17-(cyclopropylmethyl)nordesmorphine, 5

[0162] 6-Naltrexamine (100 mg, 0.292 mmol), carboxylic acid (RCOOH, Scheme 1) (187 mg, 0.321 mmol) and BOP (142 mg, 0.321 mmol) were dissolved in CH_2Cl_2 (3 mL) and NPr_2Et (0.16 mL, 0.92 mmol) was added. The colorless solution was stirred at rt for 90 min and concentrated. The residue was filtered through SiO_2 (20:1 EtOAc/MeOH) providing a white solid. This material (240 mg) was dissolved in MeOH (10 mL) and K_2CO_3 (36 mg, 0.26 mmol) was added. The mixture was stirred for 115 min and saturated NH_4Cl (10 drops) was added. The mixture was concentrated and adsorbed onto SiO_2 and purified by SiO_2 chromatography (20:1 $CHCl_3/MeOH$) providing 7 as a white solid (200 mg, 75% from 6-naltrexaminenaltrexamine, 2-steps): $R_f = 0.11$ (20:1 $CHCl_3/MeOH$); MS (EI) $m/z = 907$ $[M]^+$; ^1H NMR ($CDCl_3$, key resonances) δ 7.31-7.06 (m); 6.76 (d), 6.71 (d); 6.55 (d); 6.54 (d) 4.94-4.38 (m); 3.86-3.79 (m); ^{13}C NMR ($CDCl_3$) δ 170.4, 143.6, 138.1, 137.6, 128.4, 128.4, 128.3, 128.1, 127.9127.8, 127.78, 127.7, 127.69, 127.64, 118.9, 93.8, 86.8, 81.0, 78.4, 75.8, 75.7, 75.2, 75.0, 73.2, 70.1, 59.2, 50.9, 30.2, 4.1, 3.9.

Example 36: 14-Hydroxy-17-(cyclopropylmethyl)nordesmorphine-6-acetamidoglucose, 6a

[0163] Anhydrous MeOH (8 mL) was added to benzylated derivative 5 (180 mg, 0.198 mmol) and 10% activated Pd-C (180 mg). Concentrated HCl (0.015 mL) was added by syringe. The flask was purged with nitrogen and then stirred under a balloon of hydrogen for

21 h, filtered through Celite (eluting with MeOH) and concentrated. The resulting white solid was triturated with ethyl ether (anhyd, 3 x 2 mL) to provide **6a** as a white solid (92 mg, 85%): $R_f = (5:4:0.5:0.5 \text{ CHCl}_3/\text{MeOH}/\text{H}_2\text{O}/\text{NH}_4\text{OH})$; $^1\text{H NMR}$ (CD_3OD , key resonances) δ 6.72 (s), 4.67 (d); 4.60-4.52 (m); 3.99 (d); 3.90-3.48 (m); MS $m/z = 547$ $[\text{M} + \text{H}]^+$.

Example 37: General procedure for the amidation of 6-naltrexamines with an acid chloride. 6-(Pyridine-3'-yl)carboxamido-14-hydroxy-17-(cyclopropylmethyl)nordes-morphine, 6b

[0164] 6-Aminonaltrexamine (53 mg, 0.155 mmol) was dissolved in CH_2Cl_2 (2 mL) and nicotinyl chloride-HCl (40 mg, 0.226 mmol) and NEt_3 (0.085 mL, 0.465 mmol) were added. The solution was stirred for 1.5 h and concentrated. The residue was purified by chromatography on SiO_2 (10:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) providing the amide ester as a yellow-white solid (63 mg, 74%): $R_f = 0.11$ (10:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$); MS $m/z = 552$. The amide ester (53 mg, 0.096 mmol) was dissolved in MeOH (2 mL) and K_2CO_3 (46 mg, 0.33 mmol) was added. The mixture was stirred at rt for 1 h and NH_4Cl (sat. aq. 10 drops) and SiO_2 (2 g) were added. The mixture was concentrated and purified by SiO_2 chromatography (10:1 $\text{CHCl}_3/\text{MeOH}$) providing the title compound as an off-white solid (27 mg, 63%): $R_f = 0.31$ (10:1 $\text{CHCl}_3/\text{MeOH}$); MS $m/z = 447$.

Example 38: General procedure for the amidation of 6-naltrexamines with the BOP reagent and a carboxylic acid. 6-(3'-dimethylamino)benzamido-14-hydroxy-17-(cyclopropylmethyl)nordesmorphine, 6c

[0165] CH_2Cl_2 (1.5 mL) was added to naltrexamine (50 mg, 0.146 mmol), 3-dimethylaminobenzoic acid (24 mg, 0.14 mmol), BOP reagent (64 mg, 0.14 mmol) and Pr_2EtN (0.081 mL, 0.47 mmol). The yellow solution was stirred at rt for 80 min and concentrated. The residue was chromatographed on SiO_2 (10:1 EtOAc/MeOH) providing a white solid (70 mg). This material was dissolved in MeOH (4 mL) and K_2CO_3 (30 mg, 0.22 mmol) was added. After 90 min the mixture was concentrated. The residue was purified by chromatography on SiO_2 (10:1 $\text{CHCl}_3/\text{MeOH}$) to provide the title compound as a white solid (17.4 mg, 24% from naltrexamine): $R_f = 0.16$ (10:1 $\text{CHCl}_3/\text{MeOH}$); MS $m/z = 490$ $[\text{MH}]^+$.

Example 39: 6-(3'-Methoxy)benzamido-14-hydroxy-17-(cyclopropylmethyl)nordes-morphine, 6d

[0166] Reference JMM-VIII-42. Employing the general procedure described for compound **6b**, 6-naltrexamine (90 mg, 0.263 mmol), 3-anisoylchloride (0.09 mL, 0.69 mmol), NEt₃ (0.11 mL, 0.83 mmol) and CH₂Cl₂ (2 mL) gave the intermediate amide ester as a white foam (96 mg); MS *m/z* = 611. Hydrolysis of this material with K₂CO₃ (43 mg, 0.31 mmol) in MeOH (3 mL), followed by SiO₂ chromatography (10:1 CH₂Cl₂/MeOH) gave **6d** as a white solid: 57 mg (78%); MS *m/z* = 477.

Example 40: 6-(Thiophen-2'-yl)acetamidomido-14-hydroxy-17-(cyclopropylmethyl)nordesmorphine, 6e

[0167] Employing the general procedure described for compound **6b**, 6-naltrexamine (19 mg, 0.055 mmol), 2-thiophene acetylchloride (0.014 mL, 0.11 mmol), NEt₃ (0.019 mL, 0.14 mmol) and CH₂Cl₂ (2 mL) gave the intermediate amide ester as a white foam (15 mg, 46%); R_f = 0.12 (30:1 CH₂Cl₂/MeOH); MS *m/z* = 591 [MH⁺]. Hydrolysis of this material (13 mg, 0.022 mmol) with K₂CO₃ (2.5 mg, 0.018 mmol) in MeOH (2 mL), followed by SiO₂ chromatography (15:1 CH₂Cl₂/MeOH) gave **6e** as a white solid (10 mg, 100%): R_f = 0.17 (15:1 CH₂Cl₂/MeOH); MS *m/z* = 467.

Example 41: 6-(3',5'-Dimethoxy)benzamido-14-hydroxy-17-(cyclopropylmethyl)nordesmorphine, 6f

[0168] According to the general procedure described for compound **6c**, **4** (90 mg, 0.263 mmol), 3,5-dimethoxybenzoic acid (72 mg, 0.395 mmol), BOP (174 mg, 0.394 mmol), NPr₂Et (0.15 mL, 0.84 mmol) and CH₂Cl₂ (3 mL) provided the intermediate amide ester as a white-orange solid (186 mg). MS analysis of this material indicated that it consisted of a mixture of the amide ester (*m/z* = 671) and the amide (*m/z* = 507). Deesterification of this material with K₂CO₃ (150 mg, 1.1 mmol) in MeOH (4 mL) and SiO₂ chromatography (20:1 CH₂Cl₂/MeOH) provided **6f** as a white solid: MS *m/z* = 507.

Example 42: 6-(4'-Chloro)benzamido-14-hydroxy-17-(cyclopropylmethyl)nordesmorphine, 6g

[0169] Reference VIII-58. According to the general procedure described for compound **6c**, **4** (90 mg, 0.26 mmol), 4-chlorobenzoic acid (62 mg, 0.39 mmol), BOP (174 mg, 0.394 mmol) and NEtPr₂ (0.15 mL, 0.842 mmol), followed by SiO₂ chromatography (20:1 EtOAc/MeOH) afforded the intermediate amide ester as a white solid: R_f = 0.5 (20:1 EtOAc/MeOH); MS *m/z* = 620. Deesterification of this material with K₂CO₃ (72 mg, 0.53

mmol) in MeOH (4 mL), followed by SiO₂ chromatography (20:1 CH₂Cl₂/MeOH) provided **6g** as a white solid (76 mg, 60%): R_f = 0.41 (20:1 CH₂Cl₂/MeOH); MS *m/z* = 480.

Example 43: 6-(3'-Hydroxy)benzamido-14-hydroxy-17-(cyclopropylmethyl)nordes-morphine, 6h

[0170] Reference JMM-VIII-59, VIII-64. According to the general procedure described for compound **8b**, **4** (90 mg, 0.26 mmol), 3-acetoxybenzoic acid (71 mg, 0.39 mmol), NEtPr₂ (0.15 mL, 0.84 mmol), BOP (174 mg, 0.39 mmol) and CH₂Cl₂ (2 mL) and SiO₂ chromatography (20:1 EtOAc/MeOH) gave the intermediate amide ester as a white foam (180 mg): R_f = 0.28 (10:1 CHCl₃/MeOH); MS *m/z* = 667. Deesterification of this material with K₂CO₃ (72 mg, 0.53 mmol) in MeOH (2 mL) and SiO₂ chromatography (20:1 CH₂Cl₂/MeOH) gave **8h** as a white solid (76 mg, 60%), R_f = 0.41 (20:1 CH₂Cl₂/MeOH); MS *m/z* = 480.

Example 44: *In Vitro* Metabolic Stability

[0171] The metabolic stability of a compound in an *in vitro* study can provide significant information about the potential for metabolic stability in an *in vivo* experiment. Because a prominent route of metabolism in the opioid class of compound is for metabolism at the C-6 position, metabolic stability was designed into the compounds to increase half life, to increase bioavailability, and to improve the pharmacokinetic profile and the side effect profile of the synthetic compounds. By overcoming ADMET liabilities in the early stage of drug design and development, more drug-like compounds were produced.

[0172] *In vitro* metabolic stability studies of selected compounds were studied in the presence of pooled human liver S9, rat liver microsomes and mouse liver microsomes. The studies were done to mimic the human metabolic situation and the animal liver metabolism studies were done as a model study of *in vivo* animal studies (see below). The assay buffer contained 3.2 mg/mL human liver pooled S9 or 1.2 mg/mL rat or mouse liver microsomes, 0.1 M potassium phosphate buffer (pH 7.4), 0.1 mM compounds, 0.5 mM NADP⁺, 0.5 mM glucose-6-phosphate, 5 IU/mL glucose-6-phosphate dehydrogenase, 1 mg/mL DETAPAC, 7 mM MgCl₂ for a final incubation volume of 0.25 mL. After 0, 10, 25, 45 or 60 min the reactions were stopped by the addition of 1 mL CH₂Cl₂/IPA (3:1 v:v) and mixed thoroughly. After centrifuged, the organic phase was evaporated to dryness with a stream of nitrogen, taken up into 200 µL methanol, vortexed, and centrifuged. HPLC was used to analyze the organic extract with an Axxi-Chrom Silica 5 micron column purchased from Richard

Scientific (Novato, Ca) on a Hitachi HPLC. The mobile phase consisted of: 55/45/0.018 (MeOH/IPA/HClO₄) and a flow rate of 1.5 mL/min with UV detection at 254 nm. The retention time of naltrexone, nalmeferene and compound 6d was 2.7 min, 2.1 min, and 2.6 min, respectively.

[0173] As shown in Table 9, naltrexone and nalmeferene possessed considerable metabolic instability in the presence of the liver preparations examined. In contrast, in the presence of human liver S-9 and mouse liver microsomes, compound 6d was not detectably metabolized. In the presence of rat liver microsomes, a minor amount of metabolism was observed, but it was 6- or 22-fold more stable than naltrexone or nalmeferene, respectively. In summary, considerable metabolic stability was observed for compound 6d and the prediction is that the bioavailability of compound 6d and congeners will be considerable.

Table 9. Metabolic stability of C-6-substituted Opiate Antagonists.

Compound	Half life in various liver preparations (mins)		
	Human liver S-9 ^a	Rat liver microsomes	Mouse liver microsomes
Naltrexone	47	93.5	430
Nalmeferene	217.5	25	34
Compound 6d	ND	> 545	ND

^aHuman liver S-9 is the post-mitochondria supernatant from the 9000 x g centrifugation.

^bND, No Detectable change

Example 45: In vivo Activity

[0174] The observation of an acute dependence state as defined by antagonist-precipitation of somatic withdrawal signs following acute pretreatment with opiates has been reported in humans, monkeys, dogs, hamsters, mice and rats. In both humans and rats, opiates precipitate signs of opiate withdrawal after a single exposure to morphine. The paradigm in rats resembled the condition in humans. Thus, naloxone (0.03-3.0 mg/kg) precipitated somatic signs of withdrawal following a single treatment with morphine (5.0 mg/kg) 4 hr prior to injection of naloxone [Schulteis *et al.*, *Psychopharmacology*, **129**:56-65 (1997)]. The

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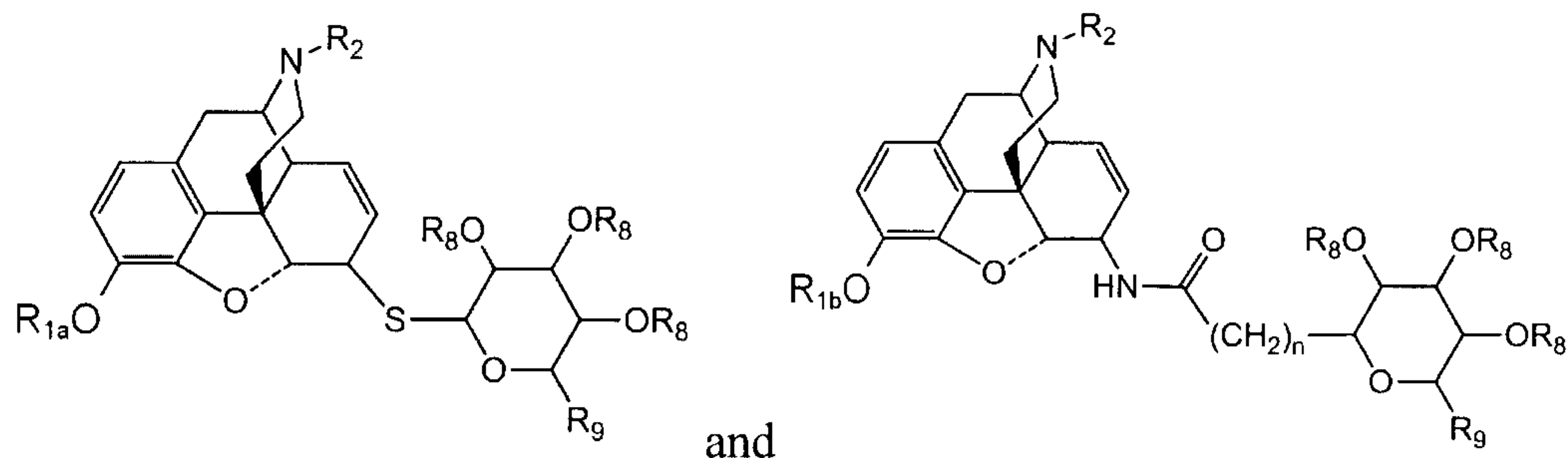
overall index of withdrawal intensity used the weighted scale of Gellert and Holtzman [*J. Pharmacol. Exper. Ther.*, **205**:536-546 (1978)]. The scale consists of graded signs of weight loss, number of escape attempts, rearings, number of wet dog shakes, instances of abdominal constrictions, and checked signs (present or absent) including diarrhea, facial fasciculations/teeth chattering, swallowing-movements, profuse salivation, chromodacryorrhea, ptosis, abnormal posture, penile grooming/erection/ejaculation and irritability upon handling. For our studies, the Global somatic sign (SS) rating included all the above individual signs based on the weighted scale of Gellert and Holtzman (1978). Four hr after a single dose of morphine (5.0 mg/kg), a single dose of compound 6a or 6d was administered to groups of rats. One min after s.c injection, somatic signs of withdrawal were observed for 10 mins. The results are summarized in Figures 19 and 20.

[0175] In summary, compounds 6a and 6d administered by subcutaneous route of administration precipitated somatic signs of withdrawal in adult male rats 4 hr after administration of 5.0 mg/kg of morphine. Compound 6d caused a dose-dependent increase in somatic signs of withdrawal that peaked at 0.3 mg/kg. An approximate EC_{50} value of less than 0.1 mg/kg was observed. At higher doses, the effect was decreased. For compound 6a, an approximate EC_{50} of approximately 1 mg/kg was observed for precipitation of somatic signs of withdrawal. For comparison, nalmeferene caused a dose-dependent (albeit noisy) increase in somatic signs of withdrawal that gave an approximate EC_{50} value of 0.6-1 mg/kg. For a literature standard, the minimum effective dose of naloxone to precipitate somatic signs of withdrawal was calculated to be 0.1-0.3 mg/kg [Schulteis *et al.*, *Psychopharmacology*, **129**:56-65 (1997)]. In conclusion, the data supports the *in vivo* efficacy of compounds 6a, 6d and congeners as potent antagonists of the opiate receptor. The compounds get into the central nervous system relatively rapidly (within 10 minutes) and exert a potent effect on the opiate receptor. Because this receptor system is prominent in controlling addiction susceptibility to alcohol and nicotine, opiate antagonists such as 6 should be effective at decreasing nicotine and alcohol addiction.

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CLAIMS:

1. A compound selected from the group consisting of:



wherein

- 5 R_{1a} is selected from the group consisting of H, $(C_1-C_5)alkylC(O)$, $(C_7-C_{10})aralkylC(O)$, $(C_6-C_{12})arylC(O)$, and silyl;

R_{1b} is selected from the group consisting of H, $(C_1-C_5)alkyl$, $(C_1-C_5)alkylC(O)$, $(C_7-C_{10})aralkylC(O)$, $(C_6-C_{12})arylC(O)$, and silyl;

R_2 is selected from the group consisting of $(C_1-C_5)alkyl$,

- 10 $C_3-C_6(cycloalkyl)alkyl$, $C_5-C_7(cycloalkenyl)alkyl$, $(C_6-C_{12})aryl$, $(C_7-C_{12})aralkyl$, $trans(C_4-C_5)alkenyl$, allyl, and furan-2-ylalkyl;

each R_8 is independently selected from the group consisting of H, $(C_1-C_5)alkylC(O)$, $(C_7-C_{10})aralkylC(O)$, $(C_7-C_{10})aralkyl$, and $(C_1-C_5)alkyl$;

- 15 R_9 is selected from the group consisting of CH_2OH , $CH_2O_2C(C_1-C_5)alkyl$, $CH_2O(C_7-C_{10})aralkyl$, CO_2H , $CO_2(C_1-C_5)alkyl$, and $CO_2(C_7-C_{10})aralkyl$;

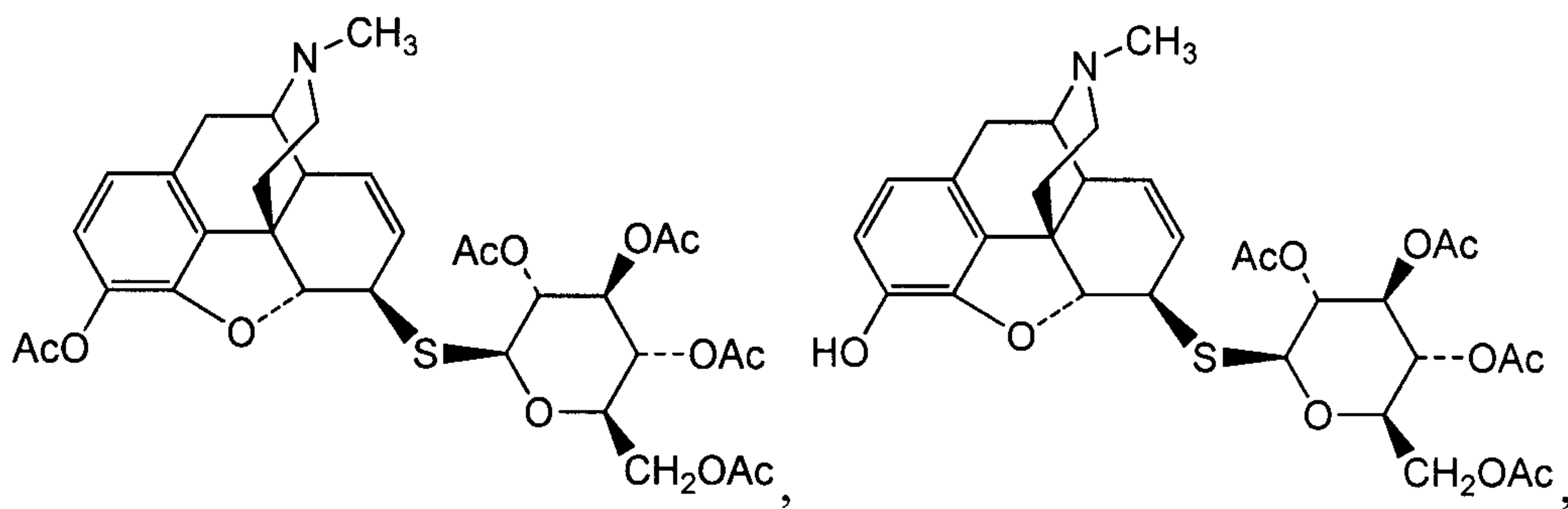
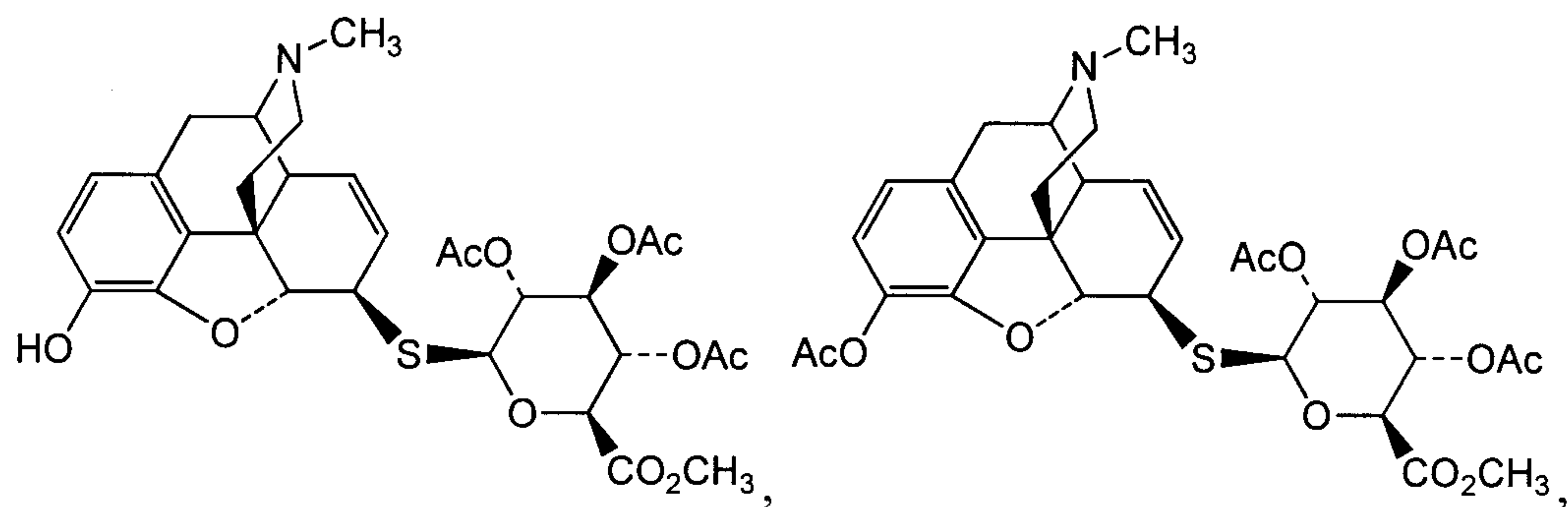
n is an integer of from 0 to 5; and

wherein alkyl is a straight chain, branched chain or cyclic saturated aliphatic group.

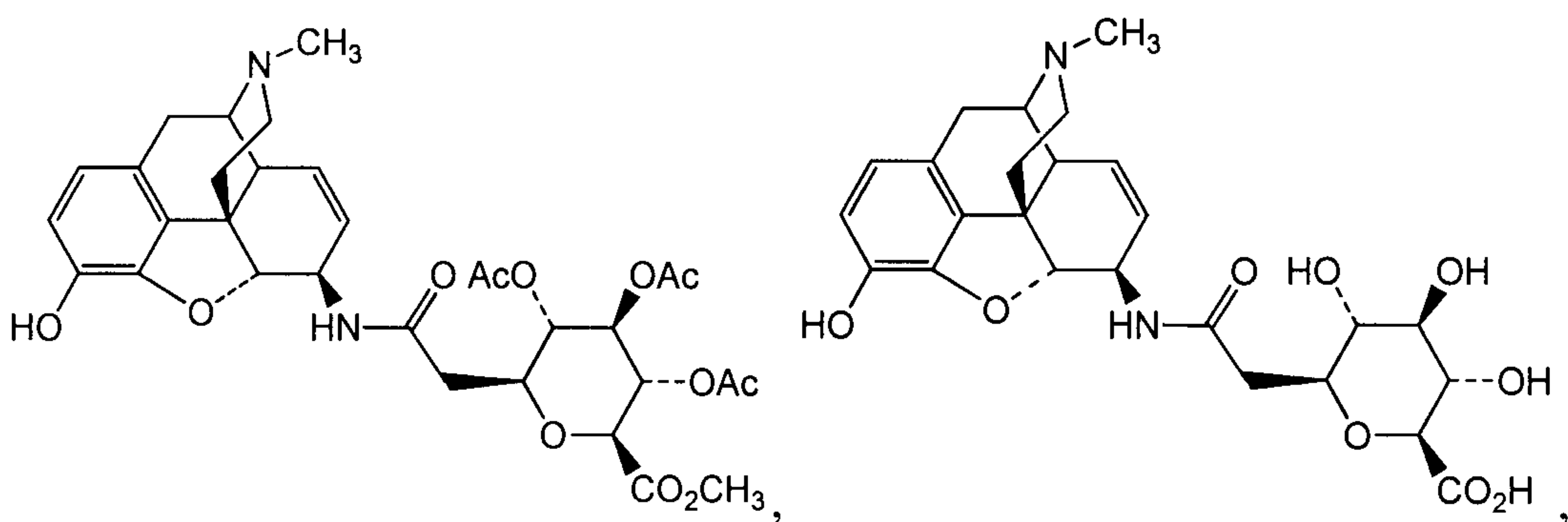
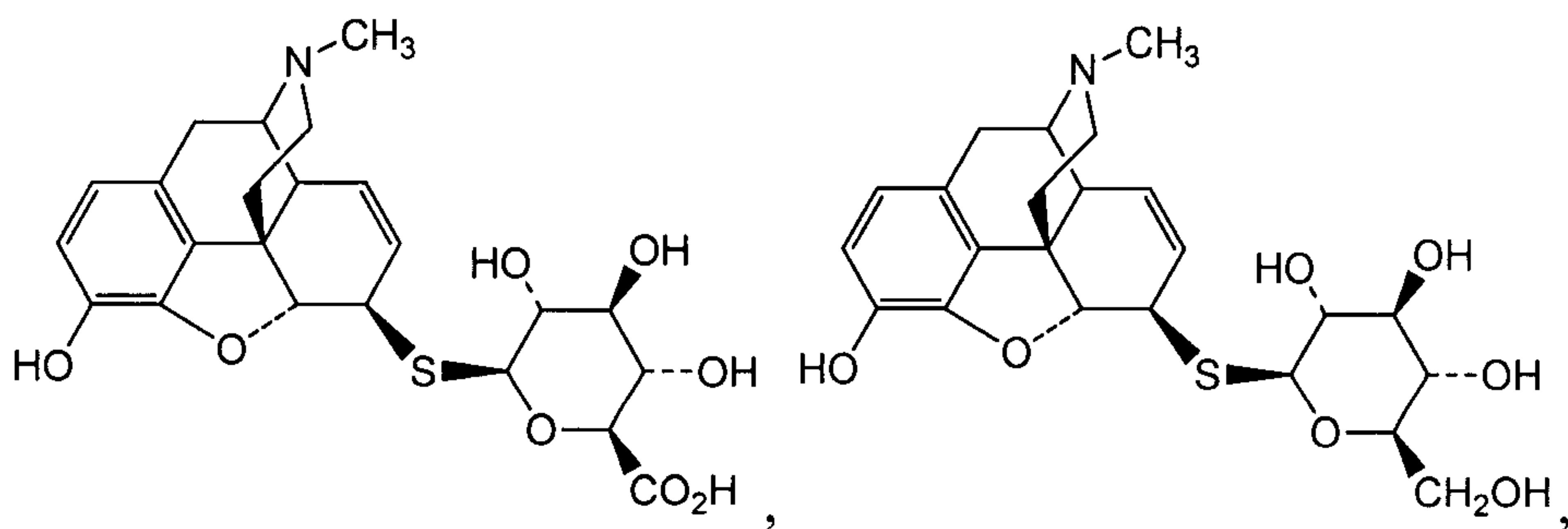
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2. The compound of claim 1, wherein R_2 is selected from the group consisting of cyclopropylmethyl, cyclobutylmethyl and allyl.

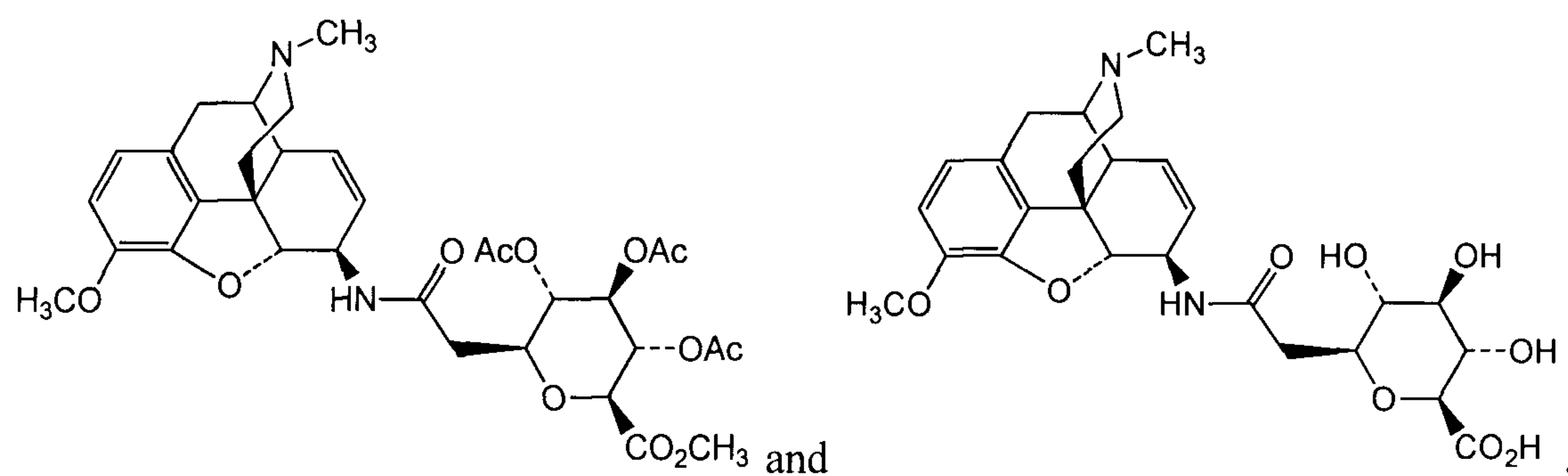
3. The compound of claim 1 having a formula selected from the group consisting of:



5



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4. A pharmaceutical composition comprising a compound as in any one of claims 1 to 3, and a pharmaceutically acceptable carrier.

5. A compound according to any one of claims 1 to 3 for use in the treatment

5 of pain.

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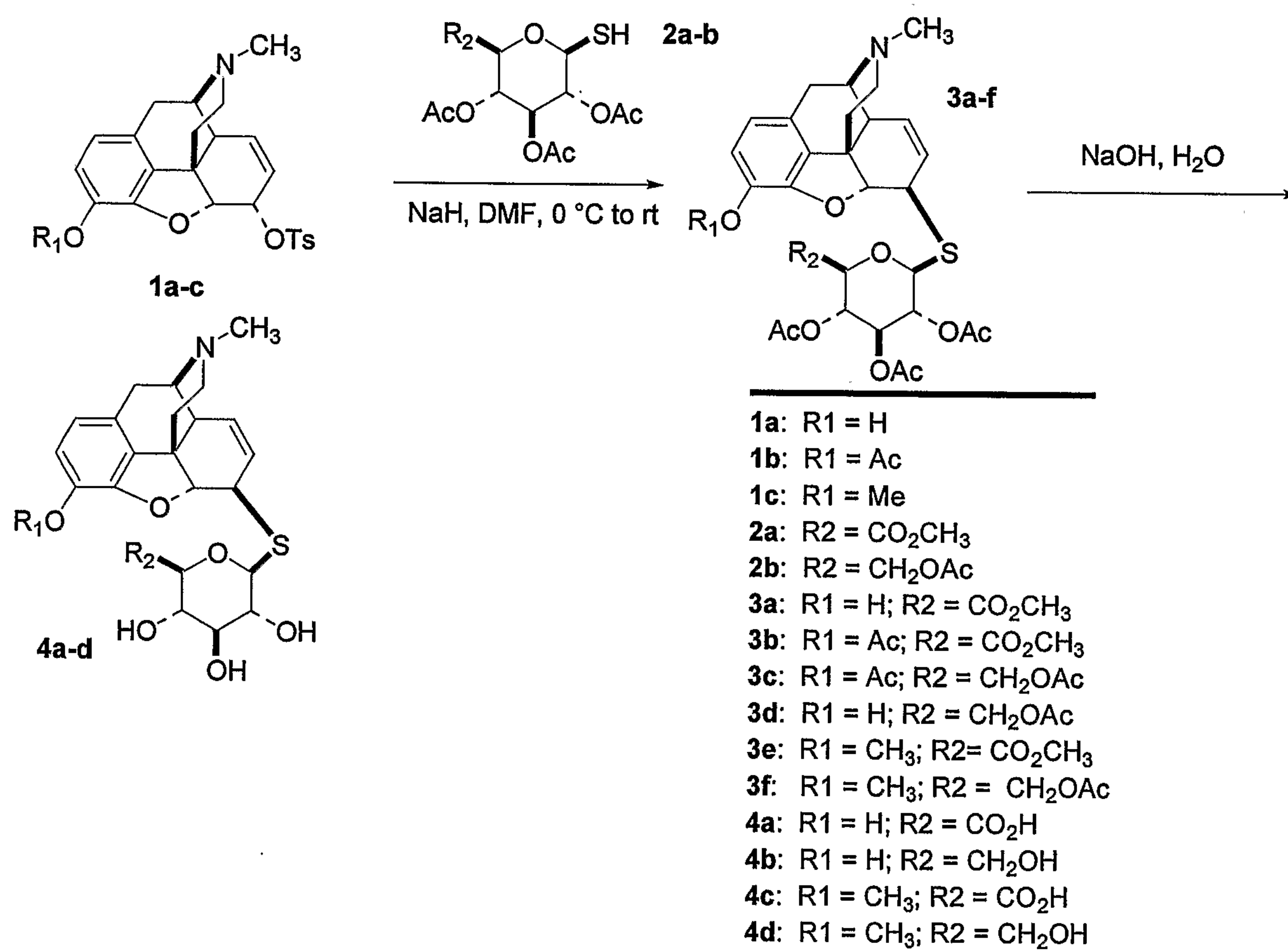
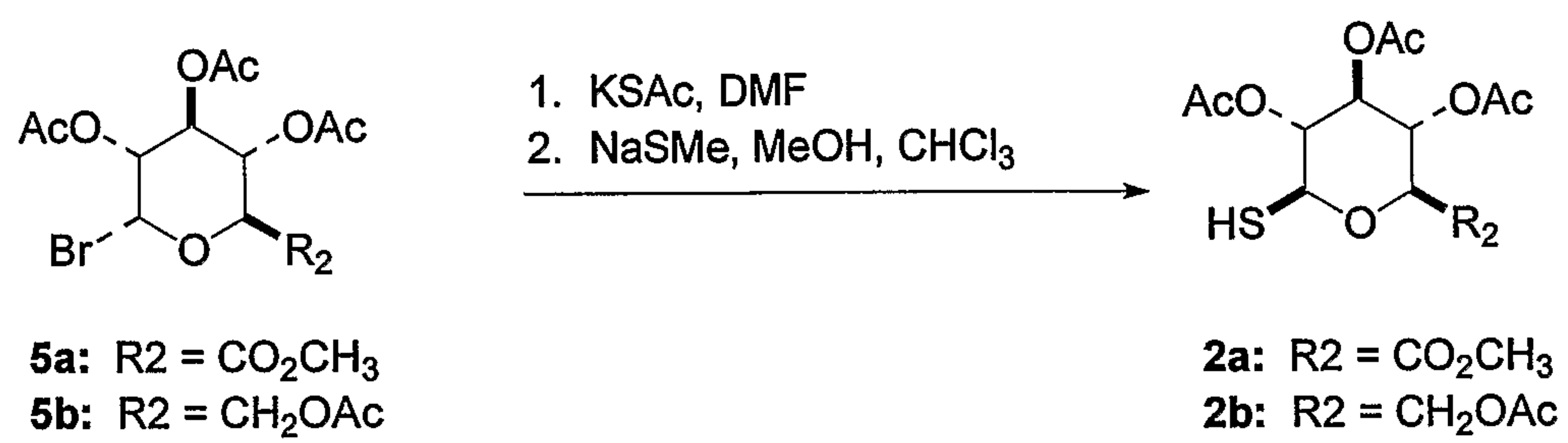


FIG. 1

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**FIG. 2**

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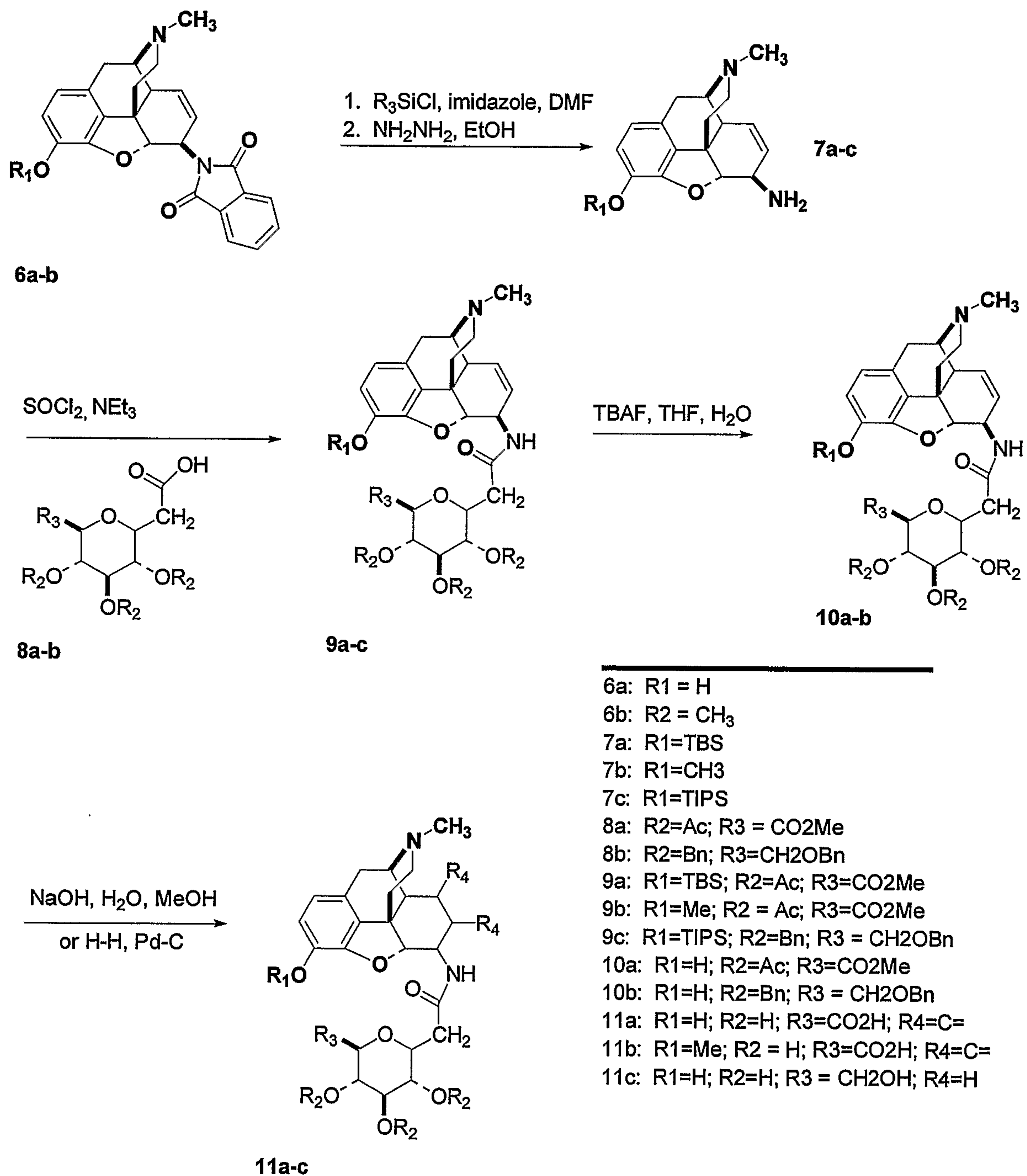
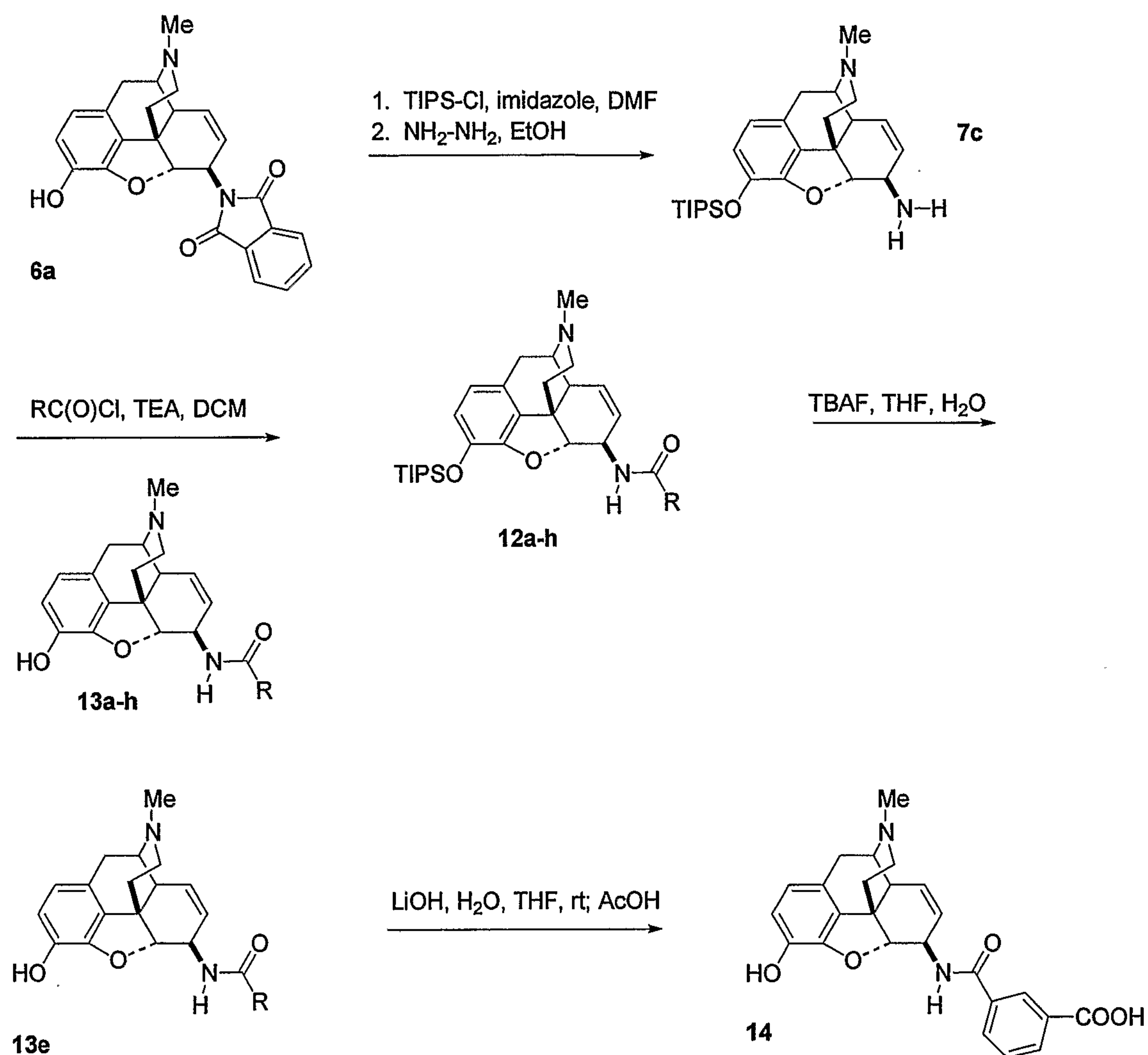


FIG. 3

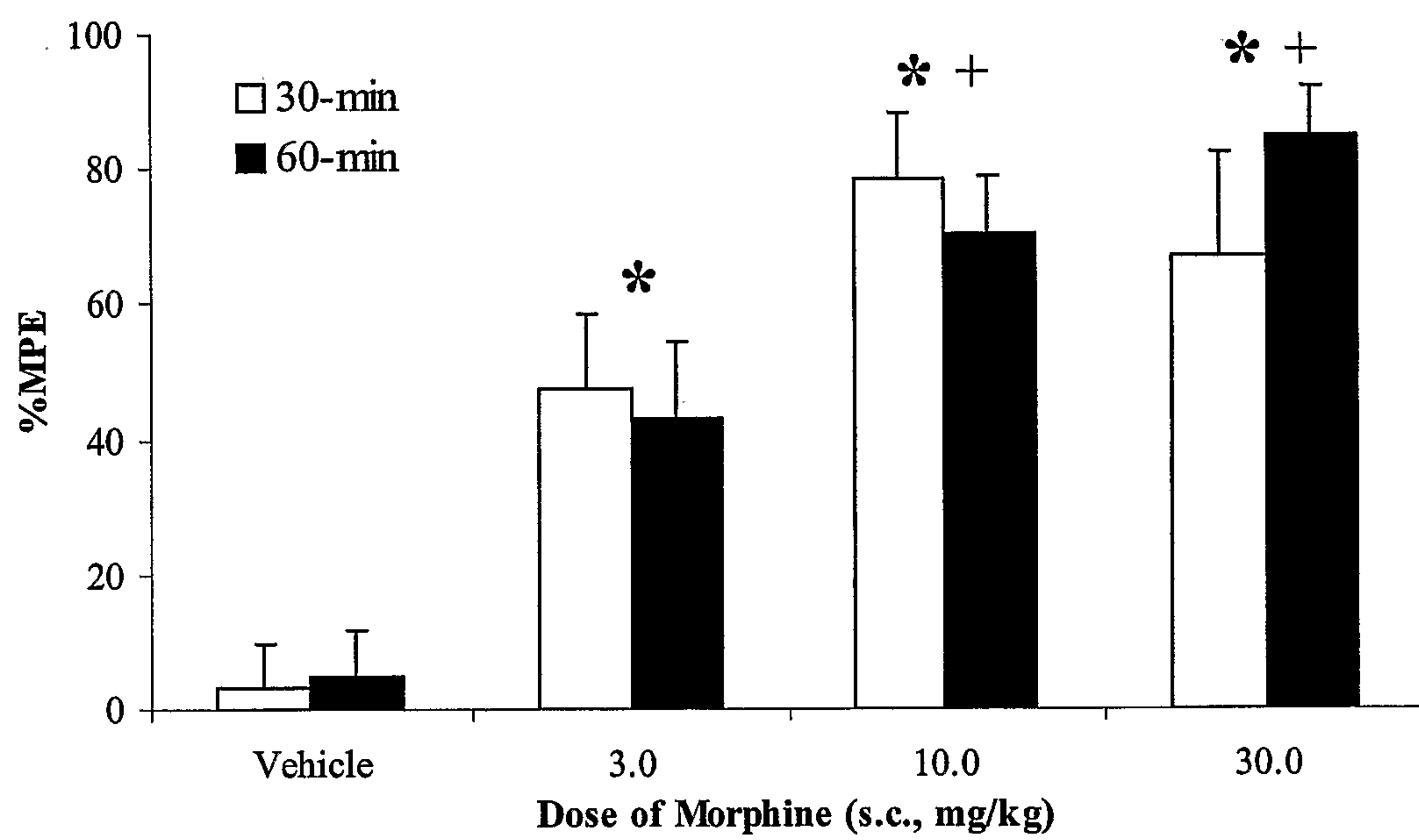
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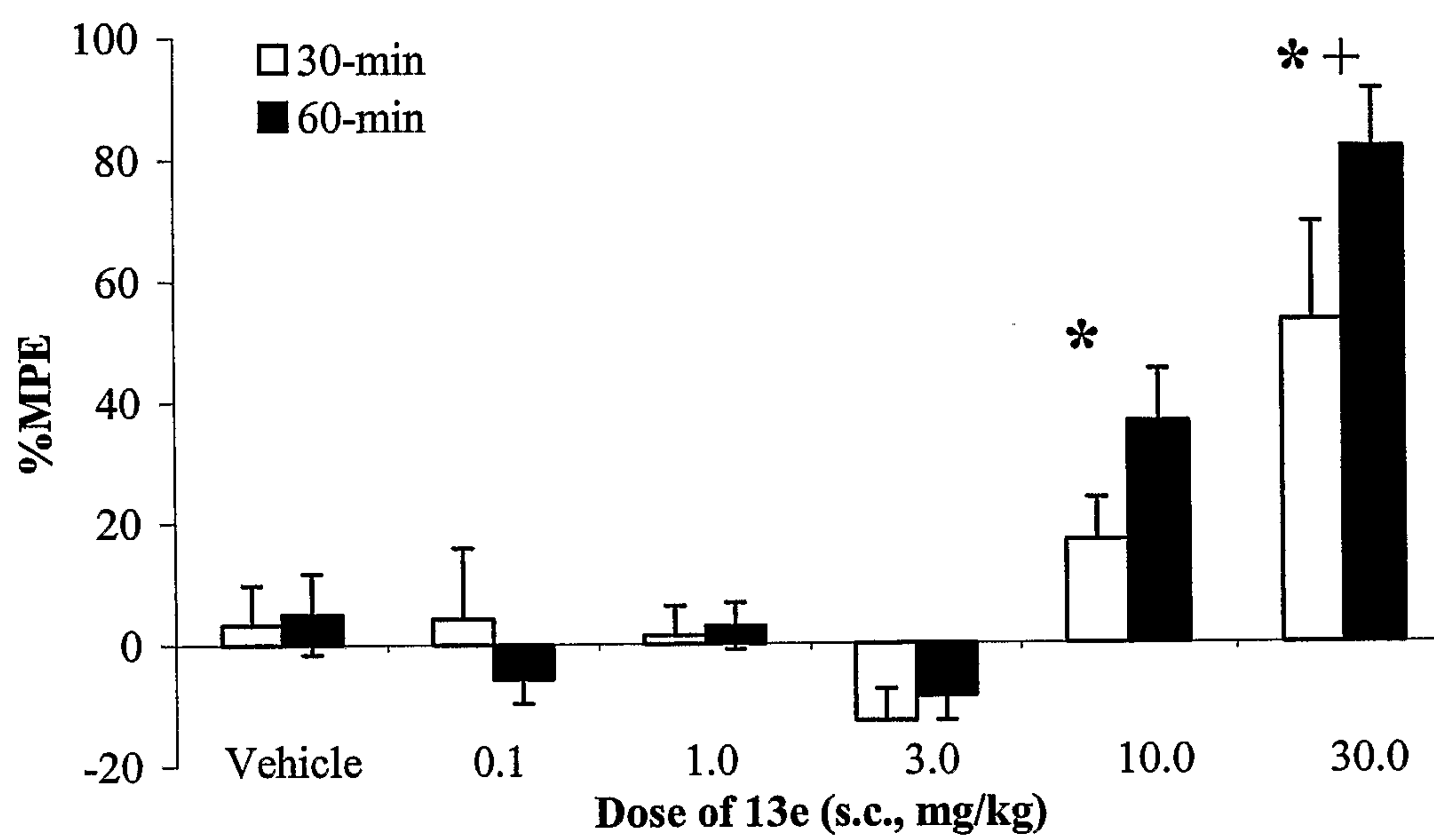
-
- R
 a: $\text{CH}_2\text{-3-(MeO)Ph}$
 b: $\text{CH}_2\text{-4-(MeO)Ph}$
 c: 3-(MeO)Ph
 d: Ph
 e: $\text{3-(CO}_2\text{Me)Ph}$
 f: $\text{3-(NO}_2\text{)Ph}$
 g: 3,4-(dichloro)Ph
 h: $\text{CH}_2\text{-2-thiophene}$

FIG. 4

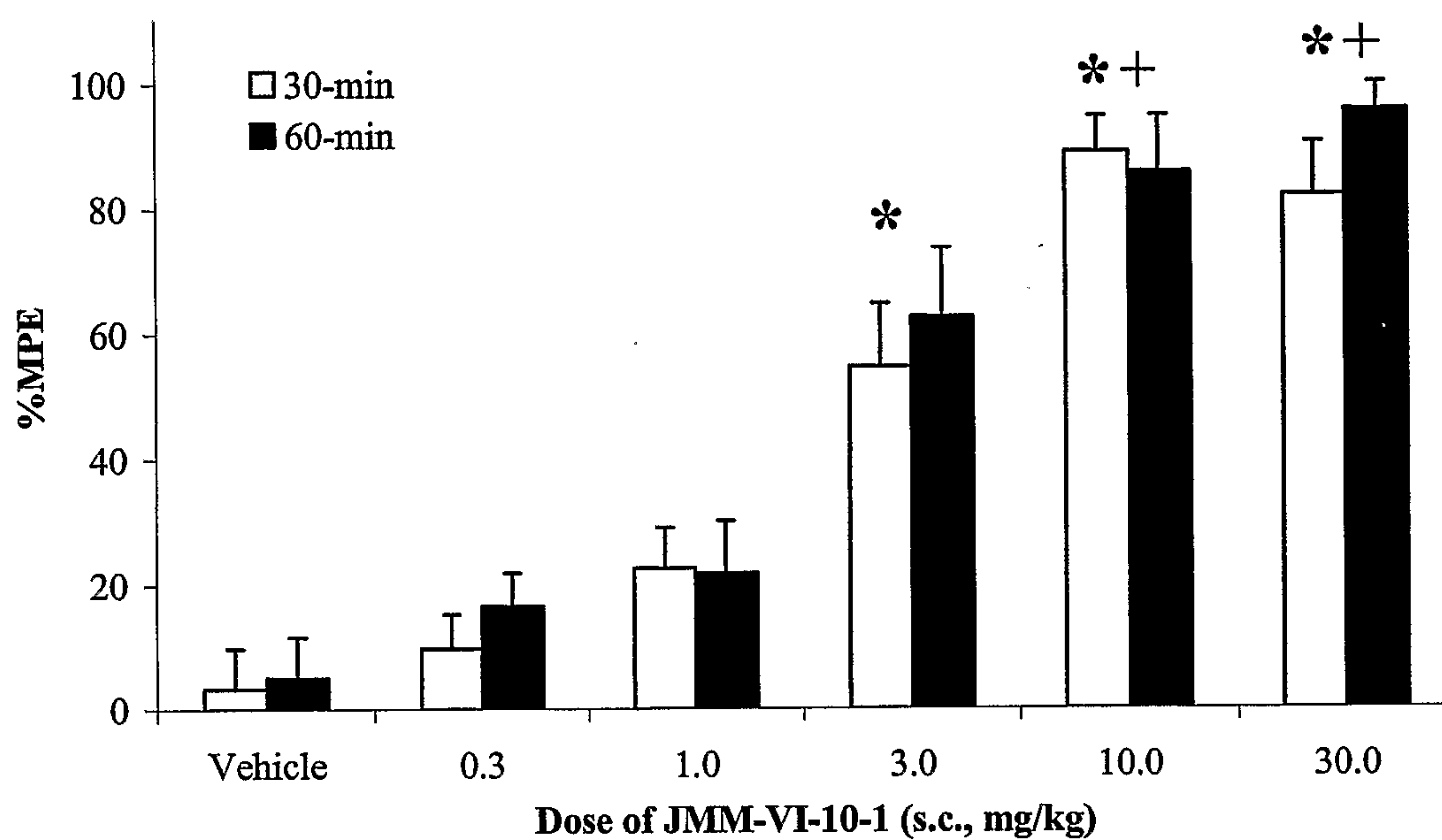
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**FIG. 5**

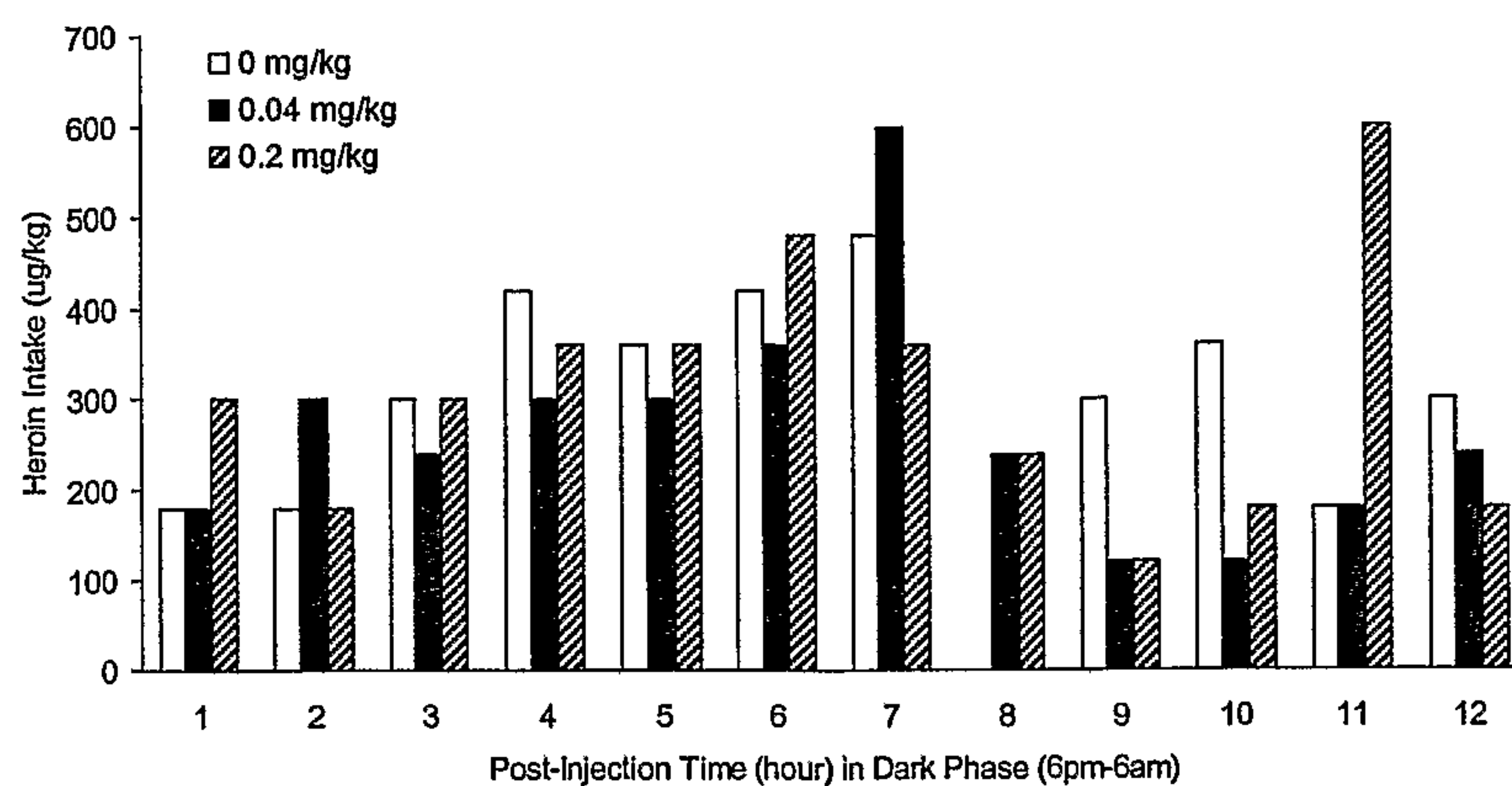
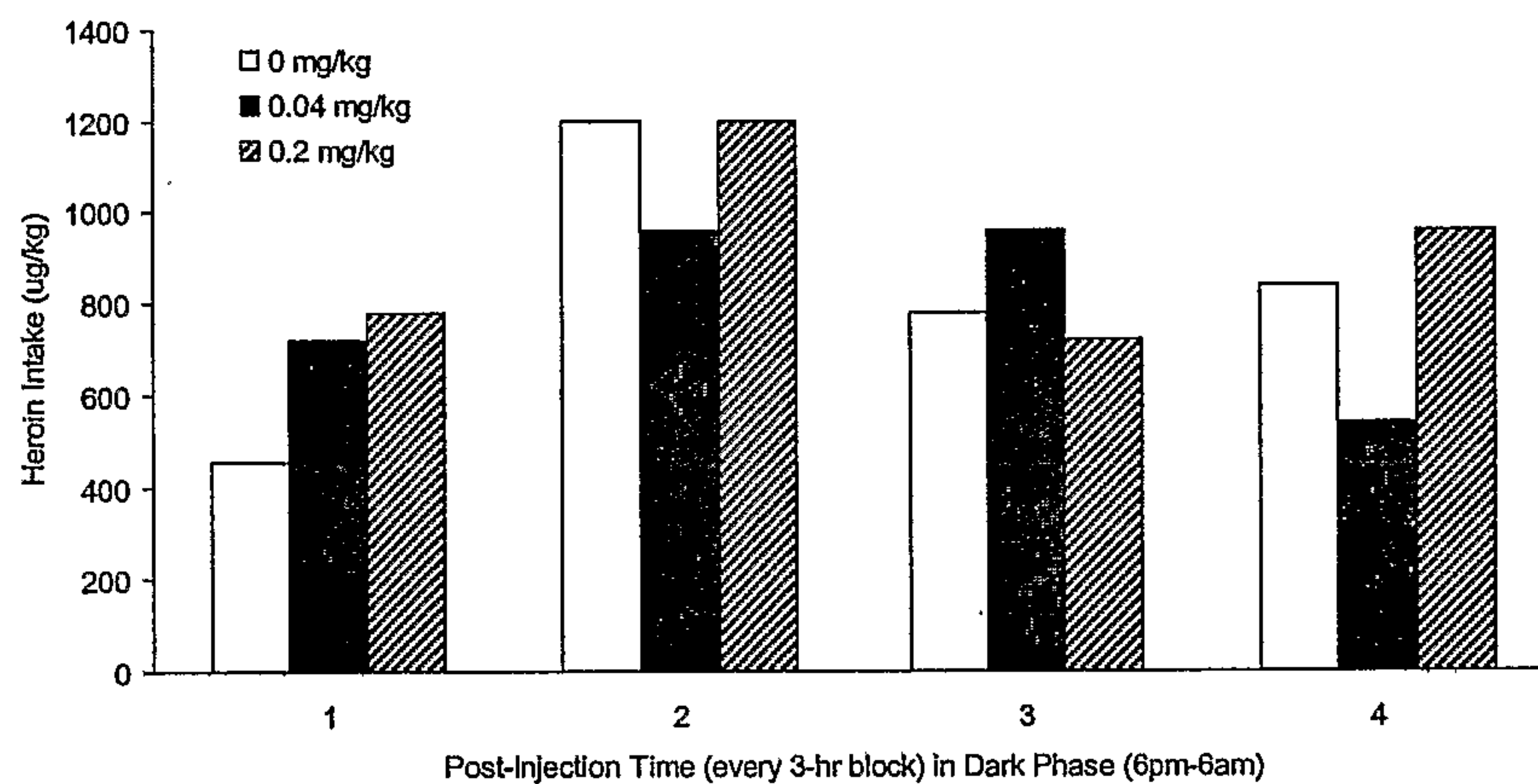
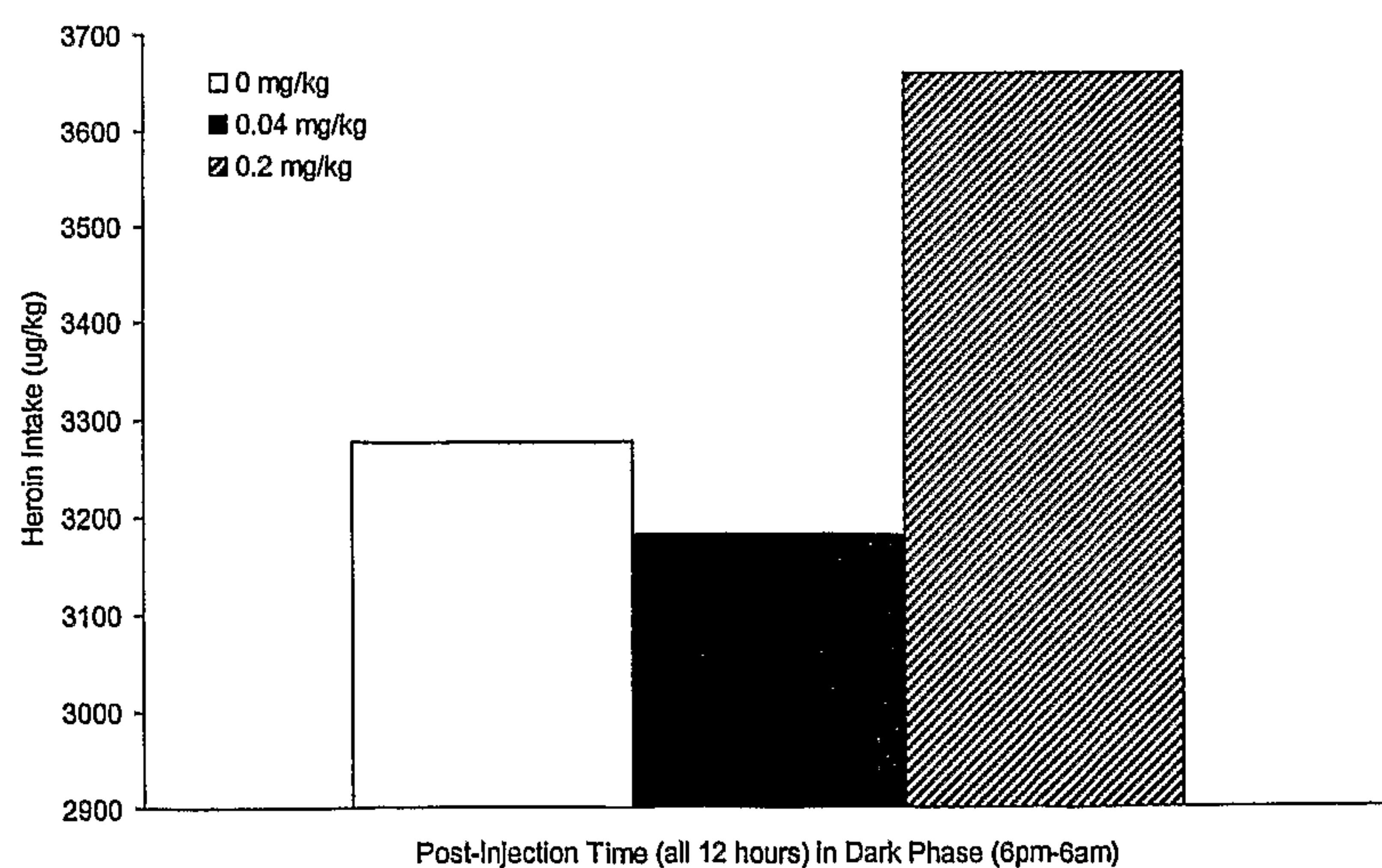
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**FIG. 6**

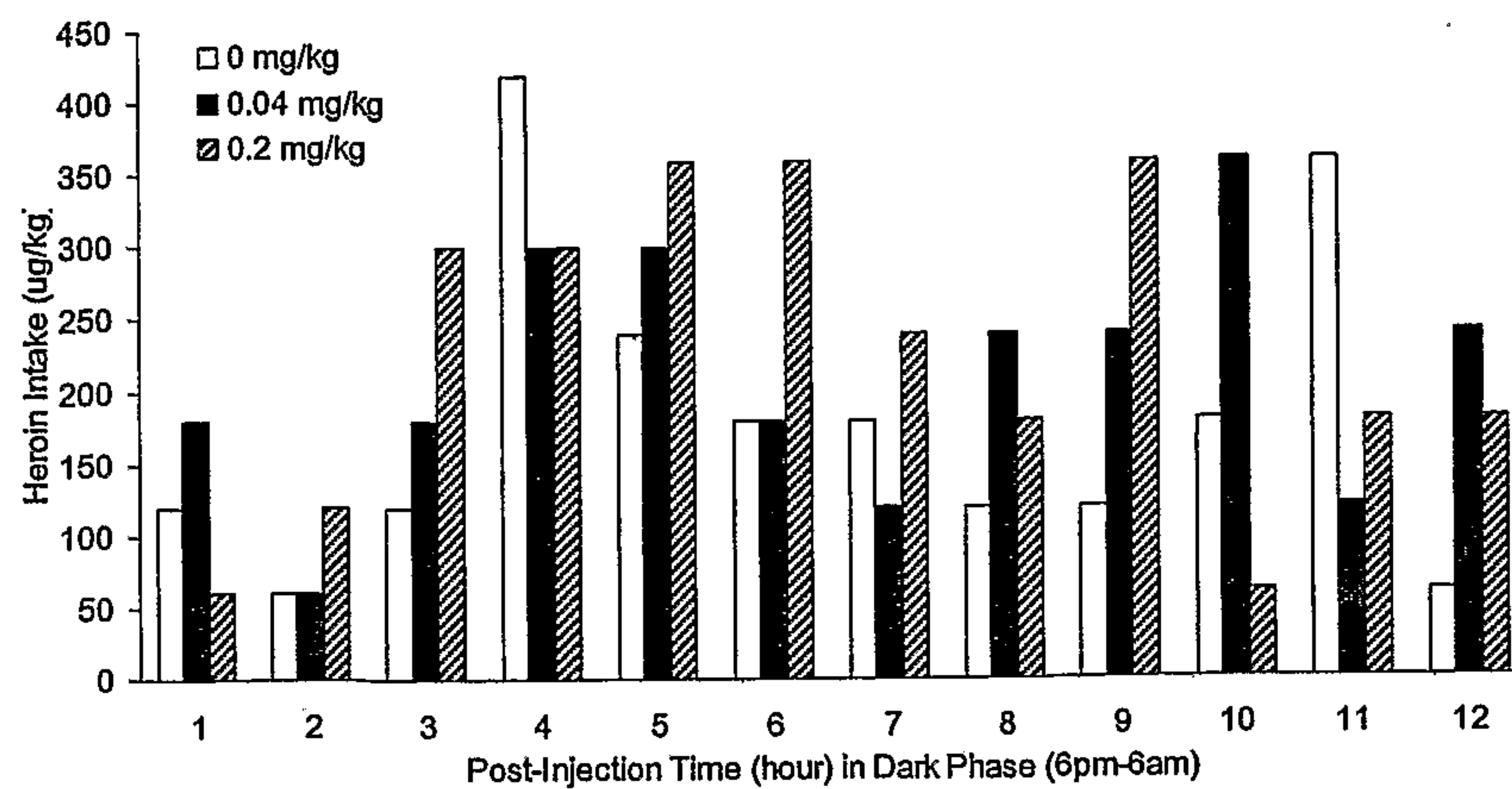
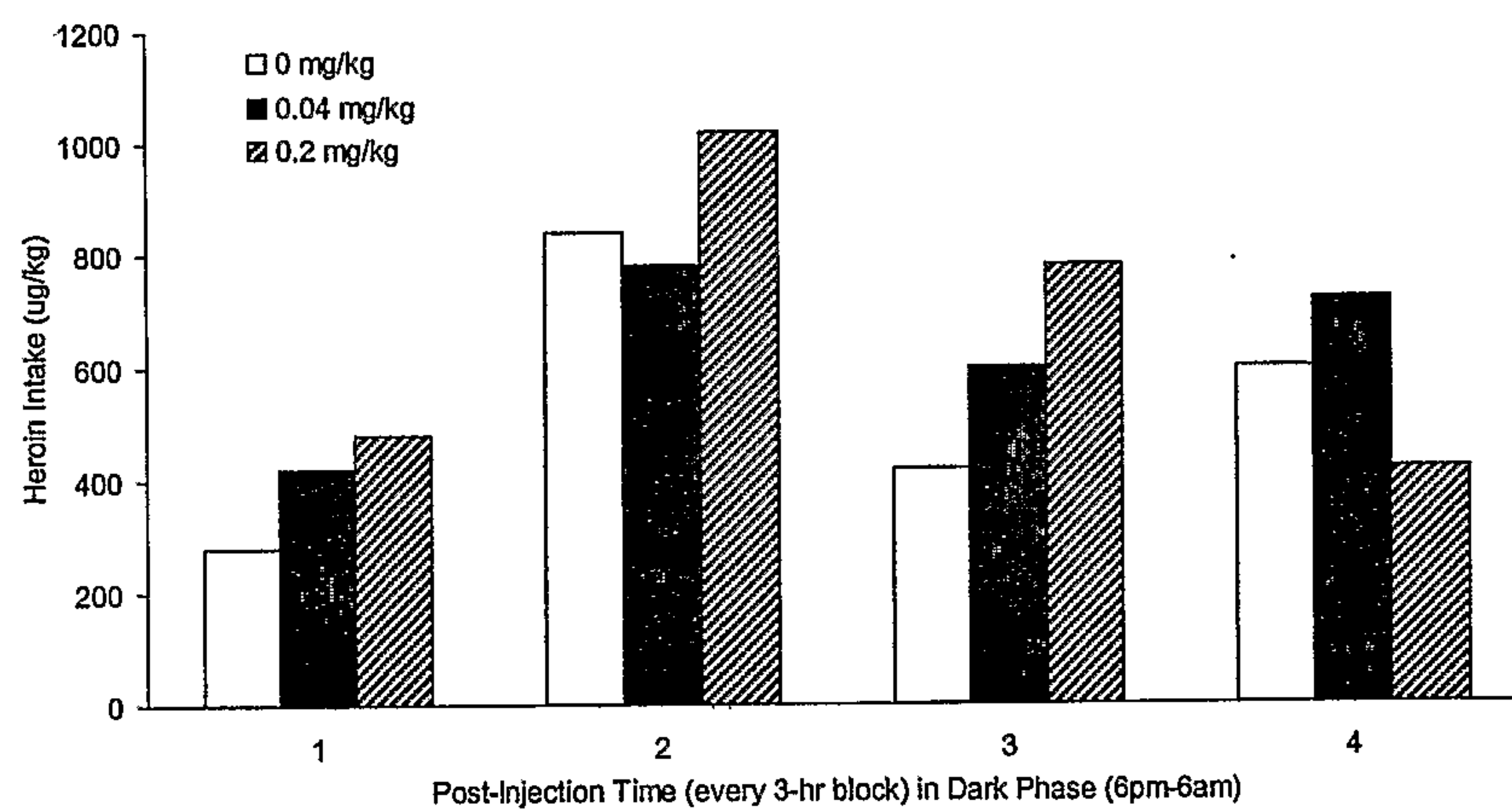
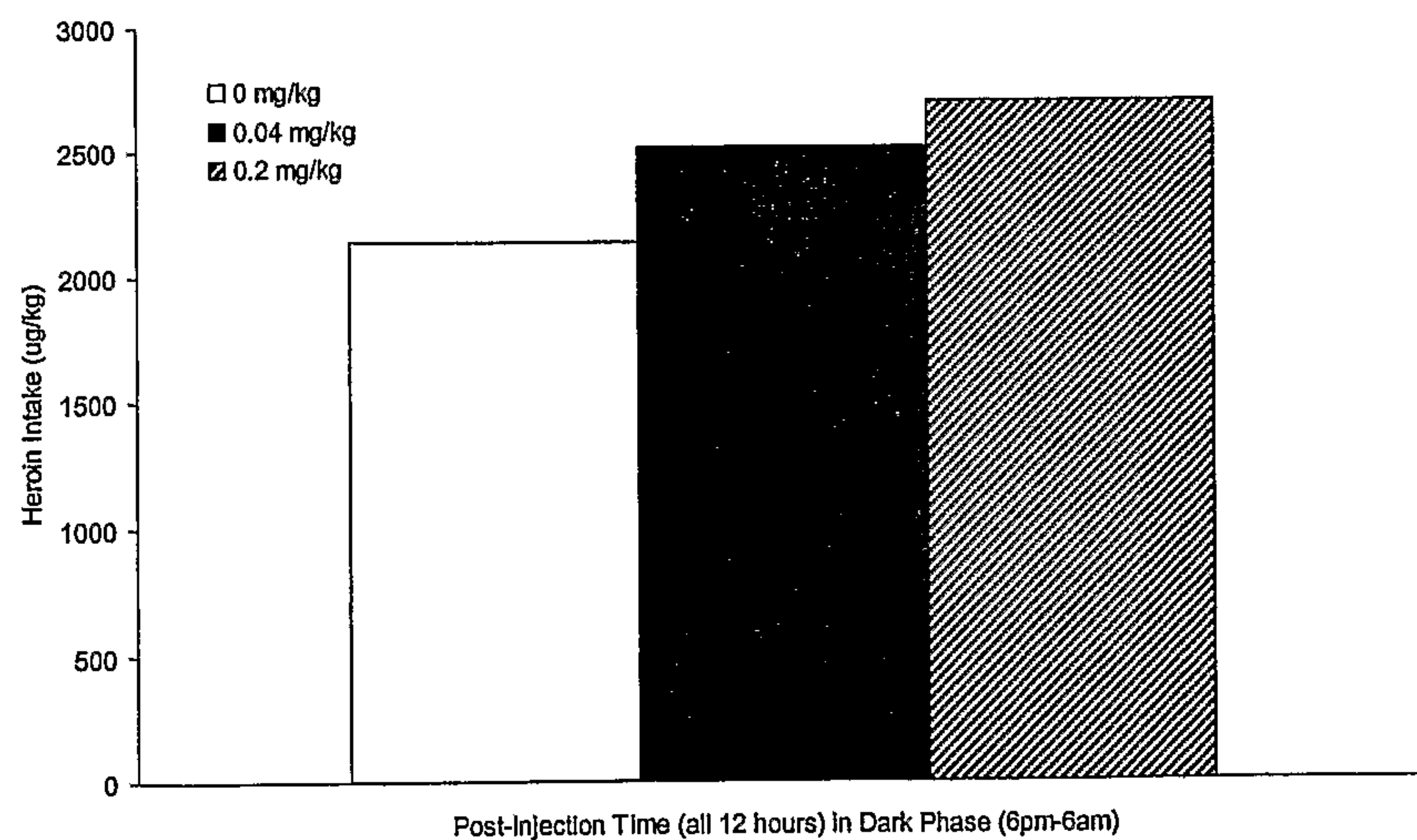
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**FIG. 7**

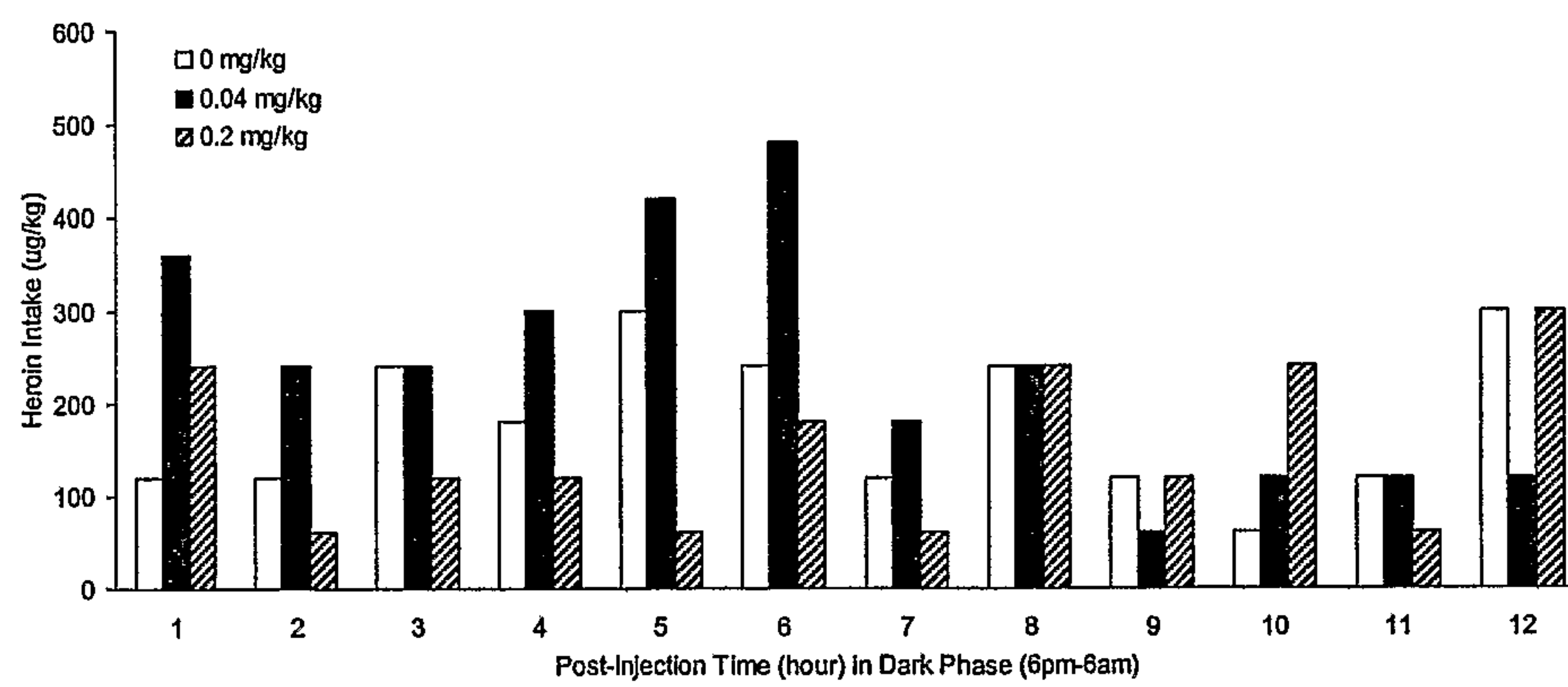
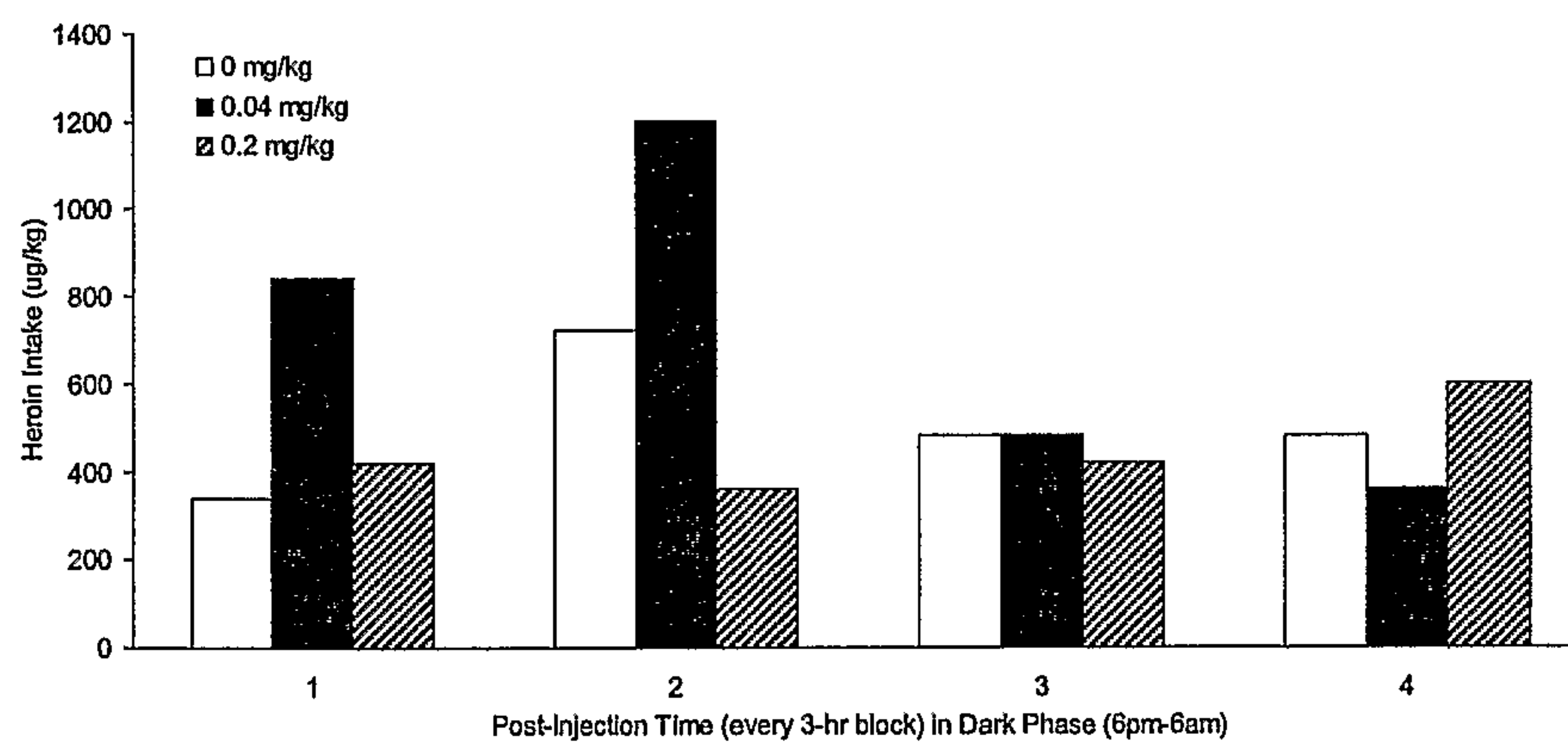
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**FIG. 8A****FIG. 8B****FIG. 8C**

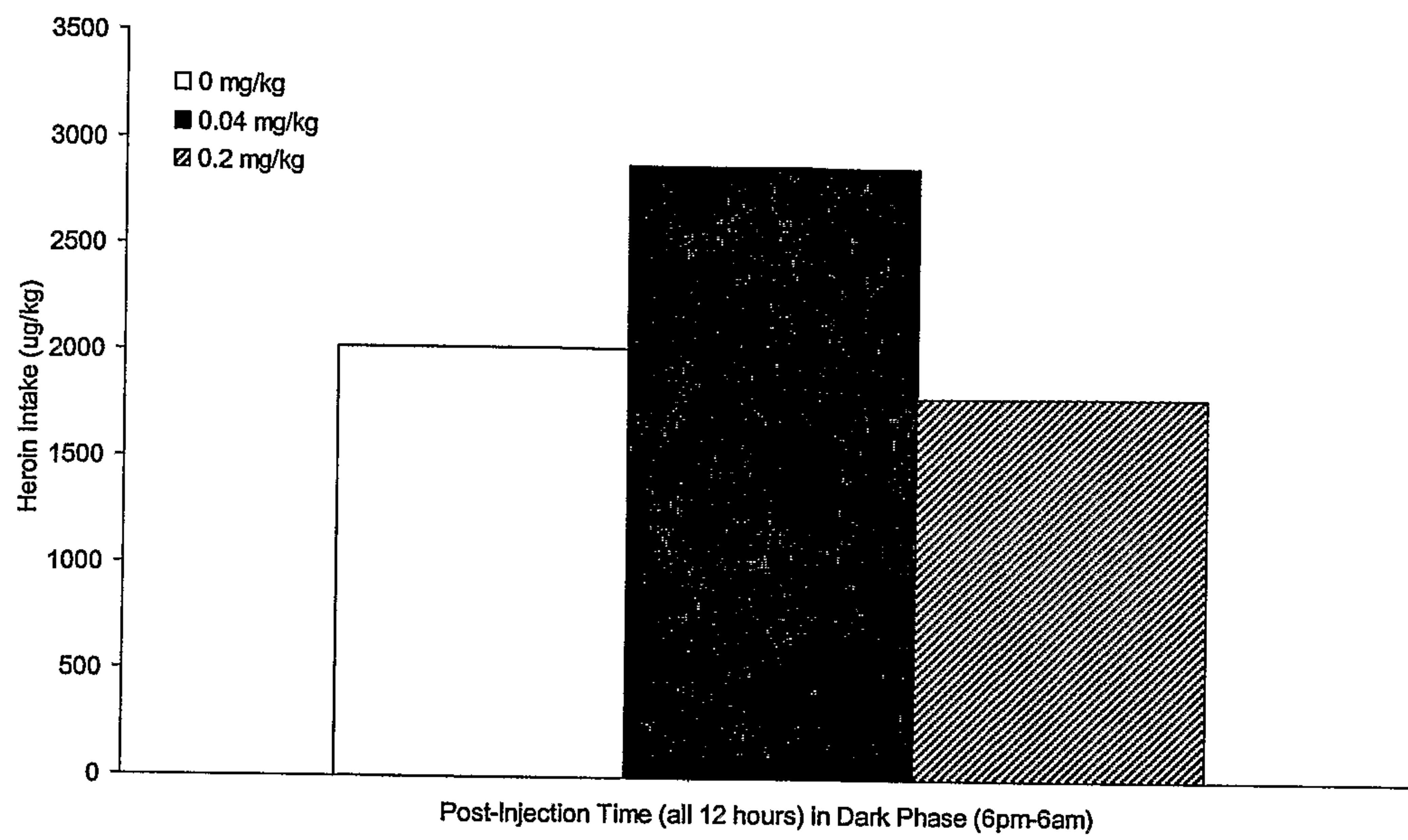
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**FIG. 9A****FIG. 9B****FIG. 9C**

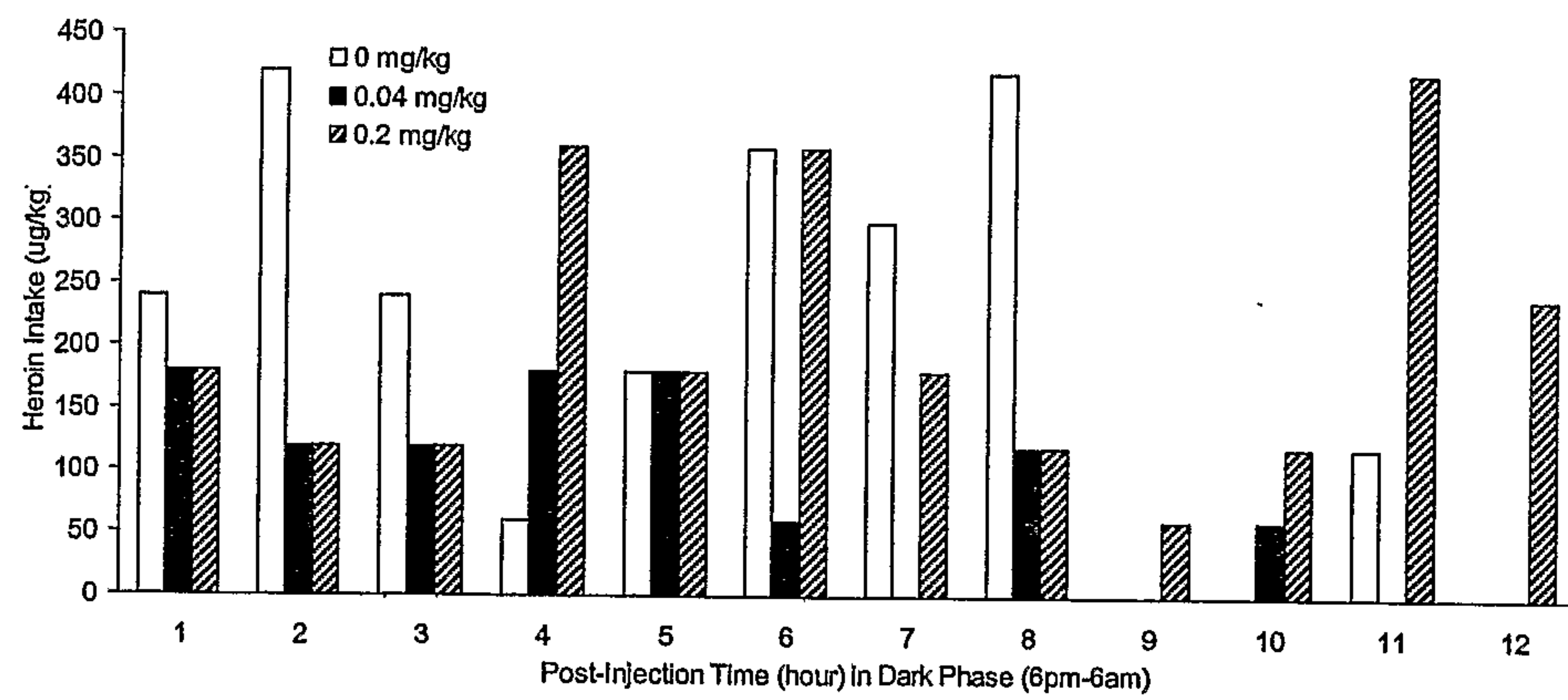
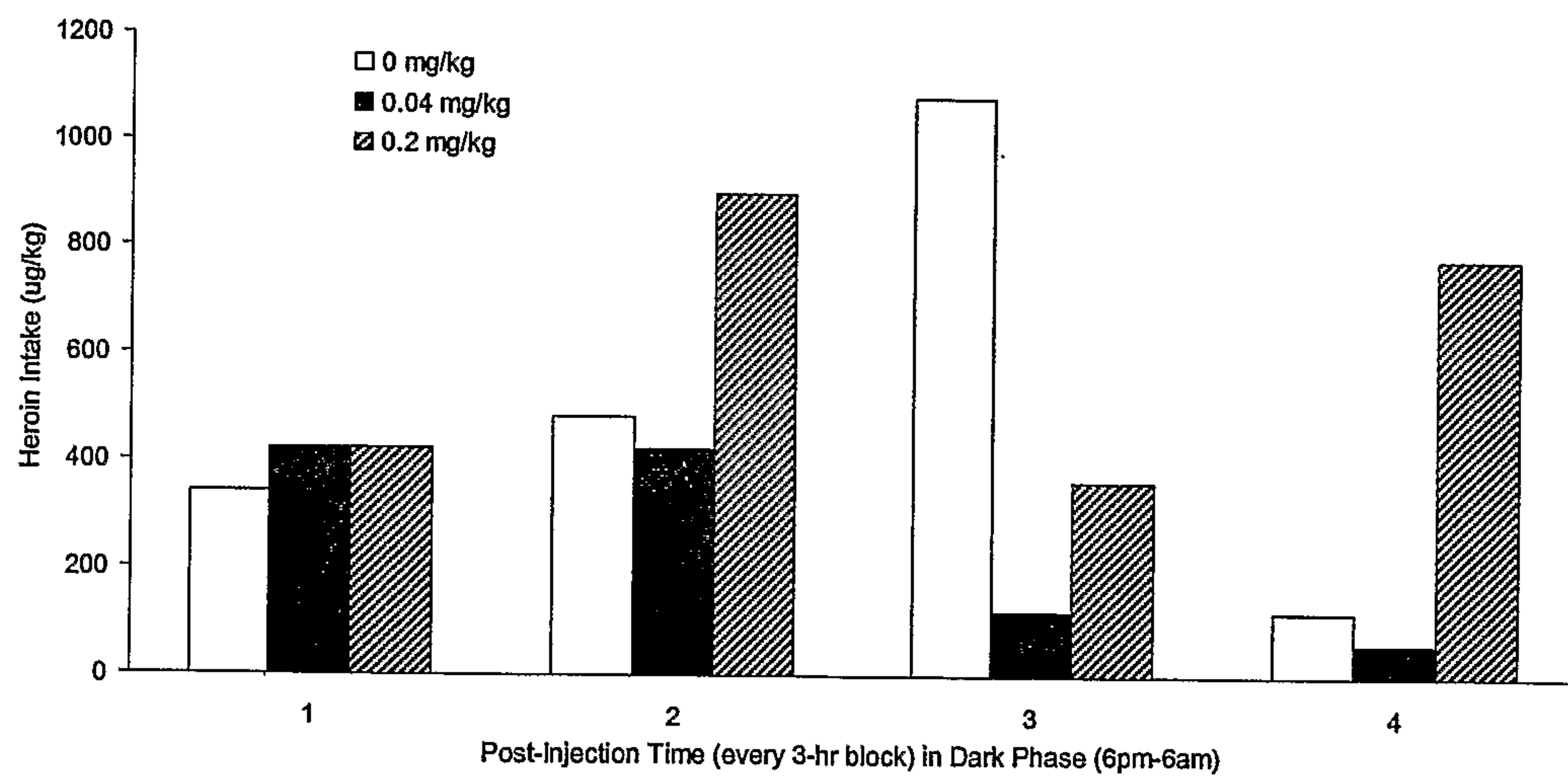
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**FIG. 10A****FIG. 10B**

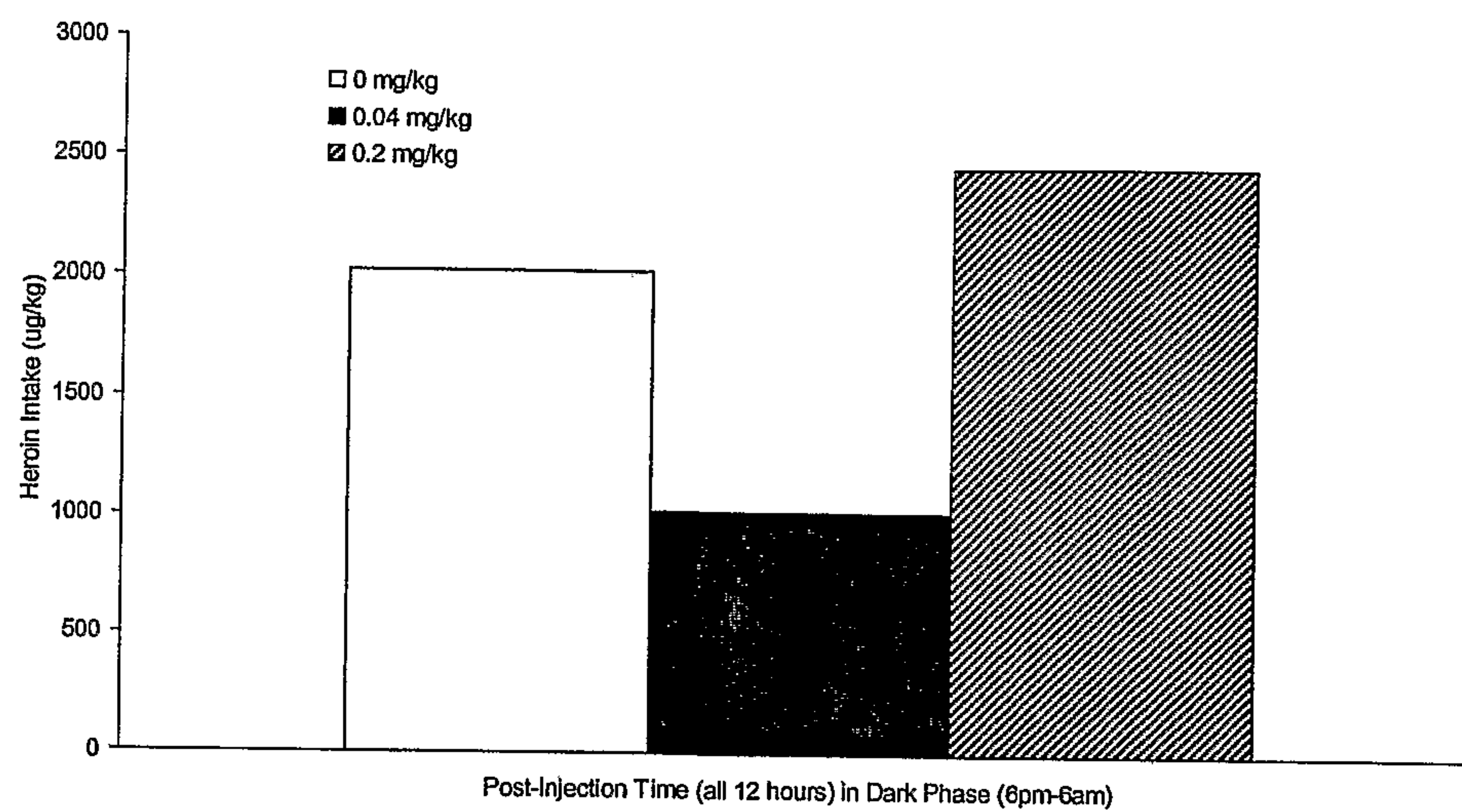
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**FIG. 10C**

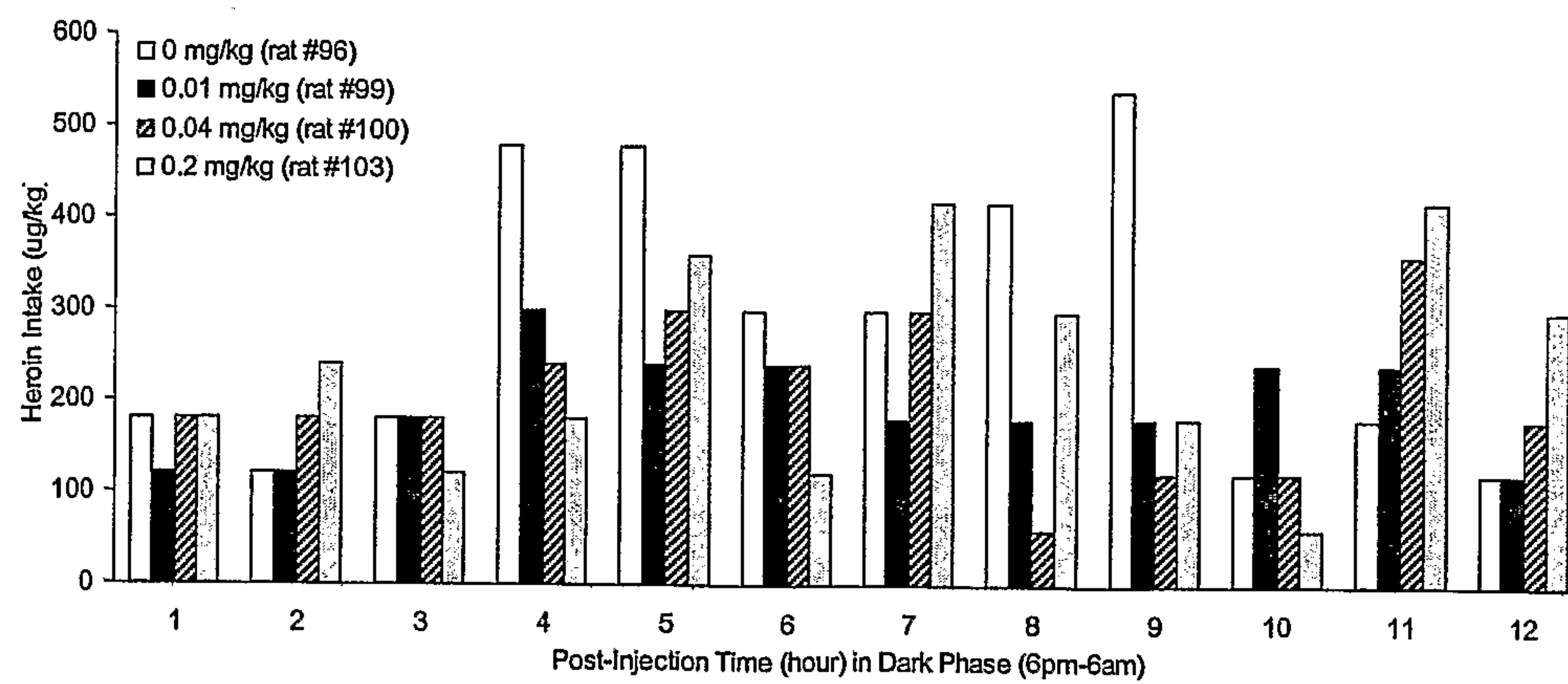
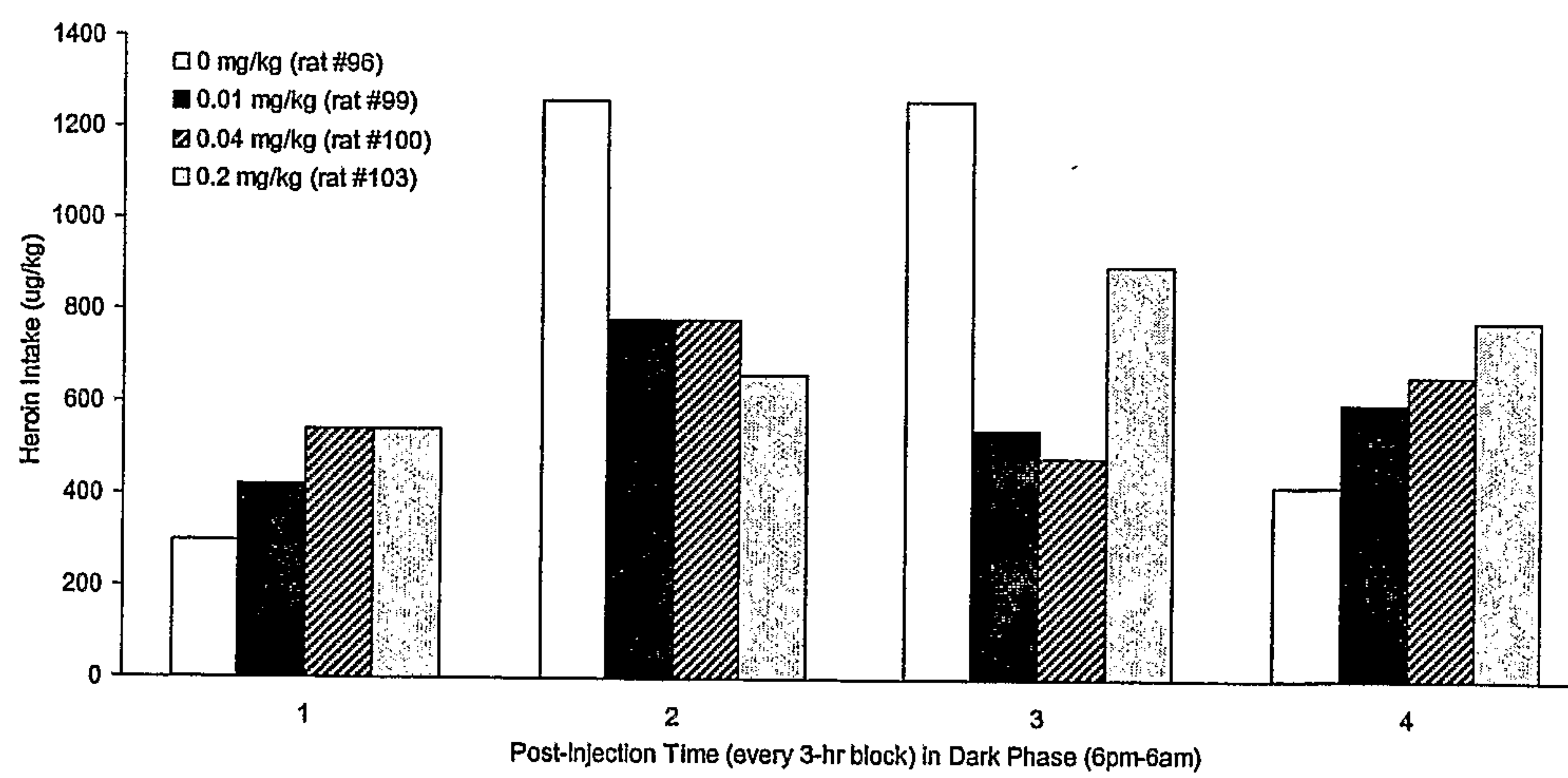
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**FIG. 11A****FIG. 11B**

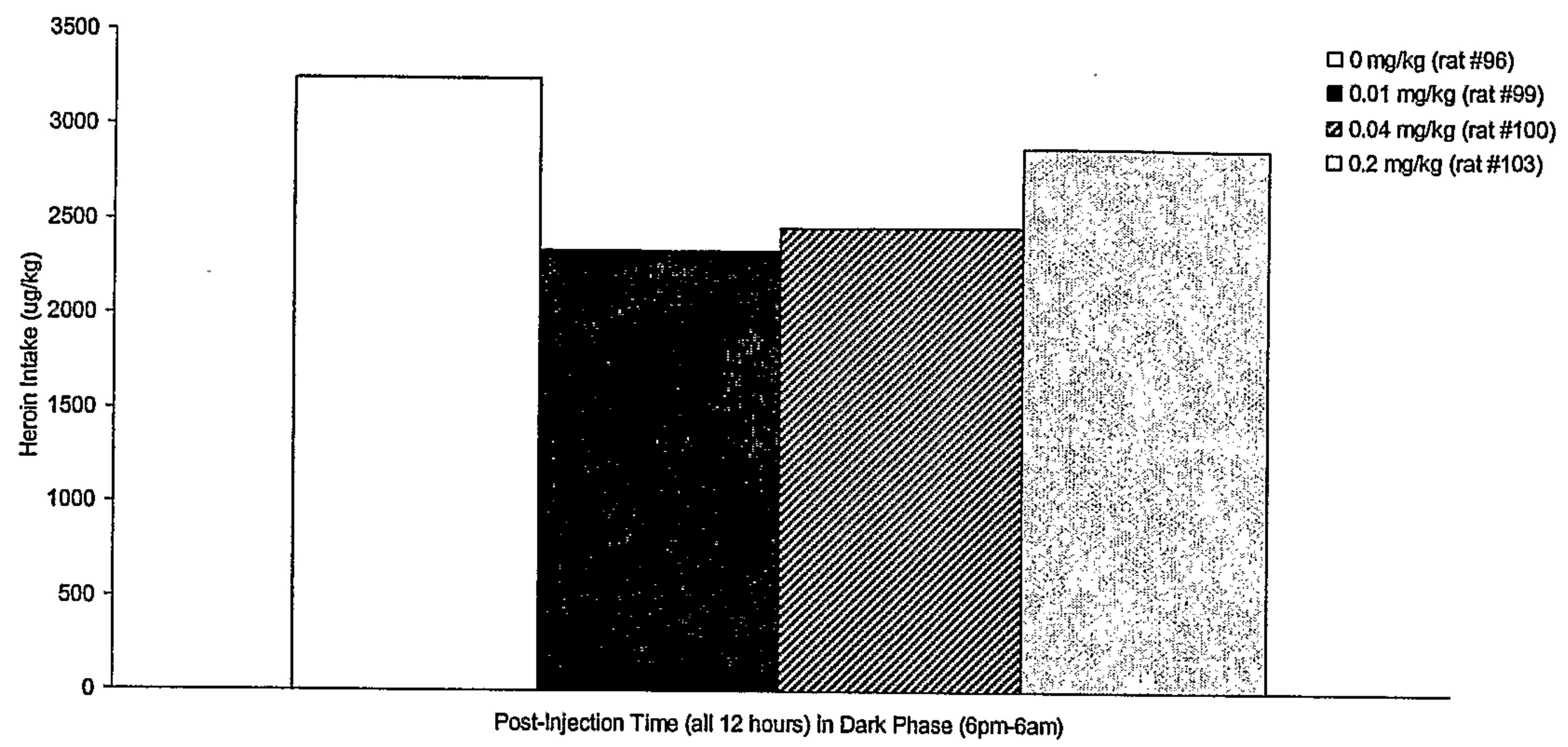
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**FIG. 11C**

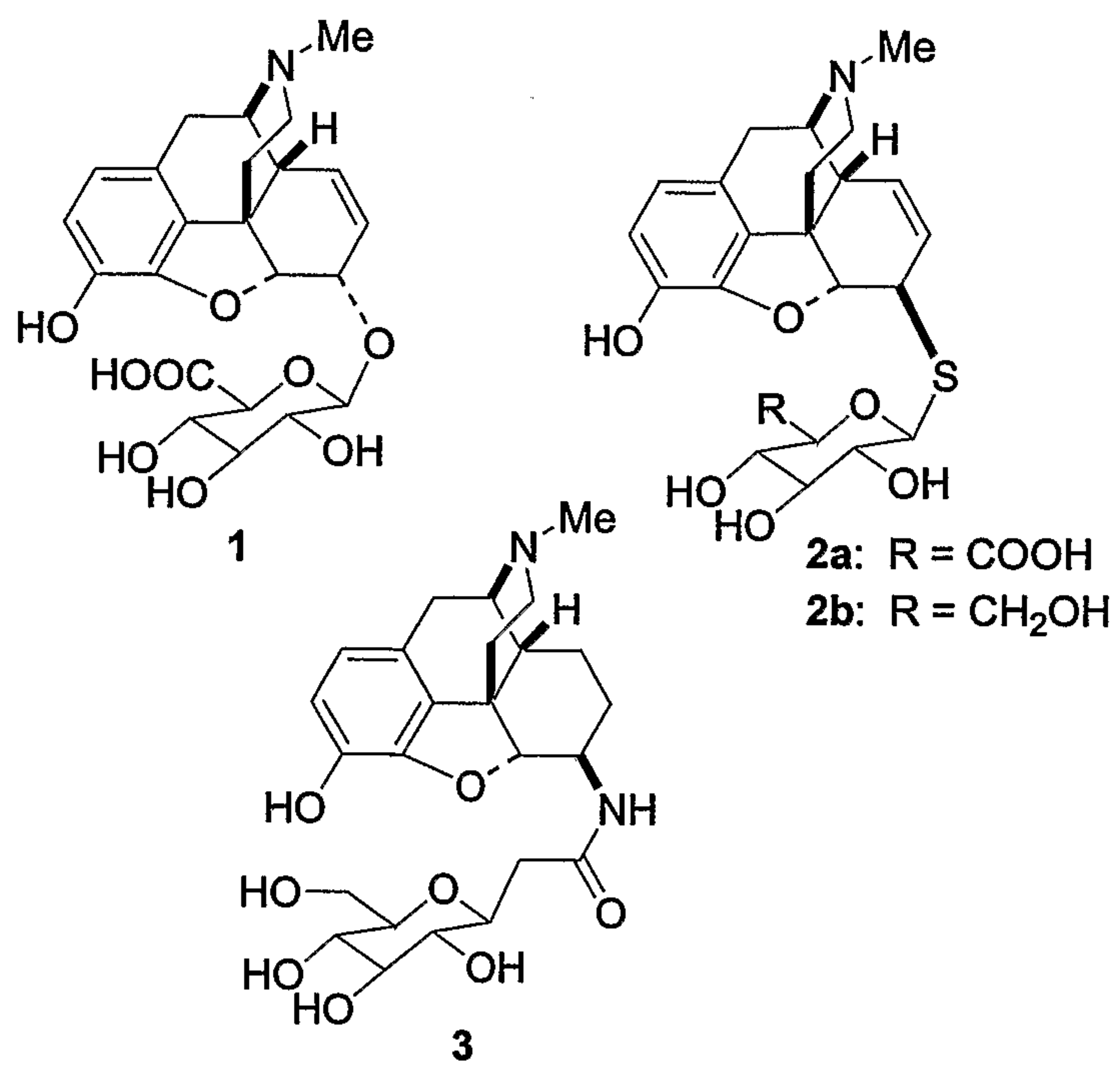
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**FIG. 12A****FIG. 12B**

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*FIG. 12C*

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**FIG. 13**

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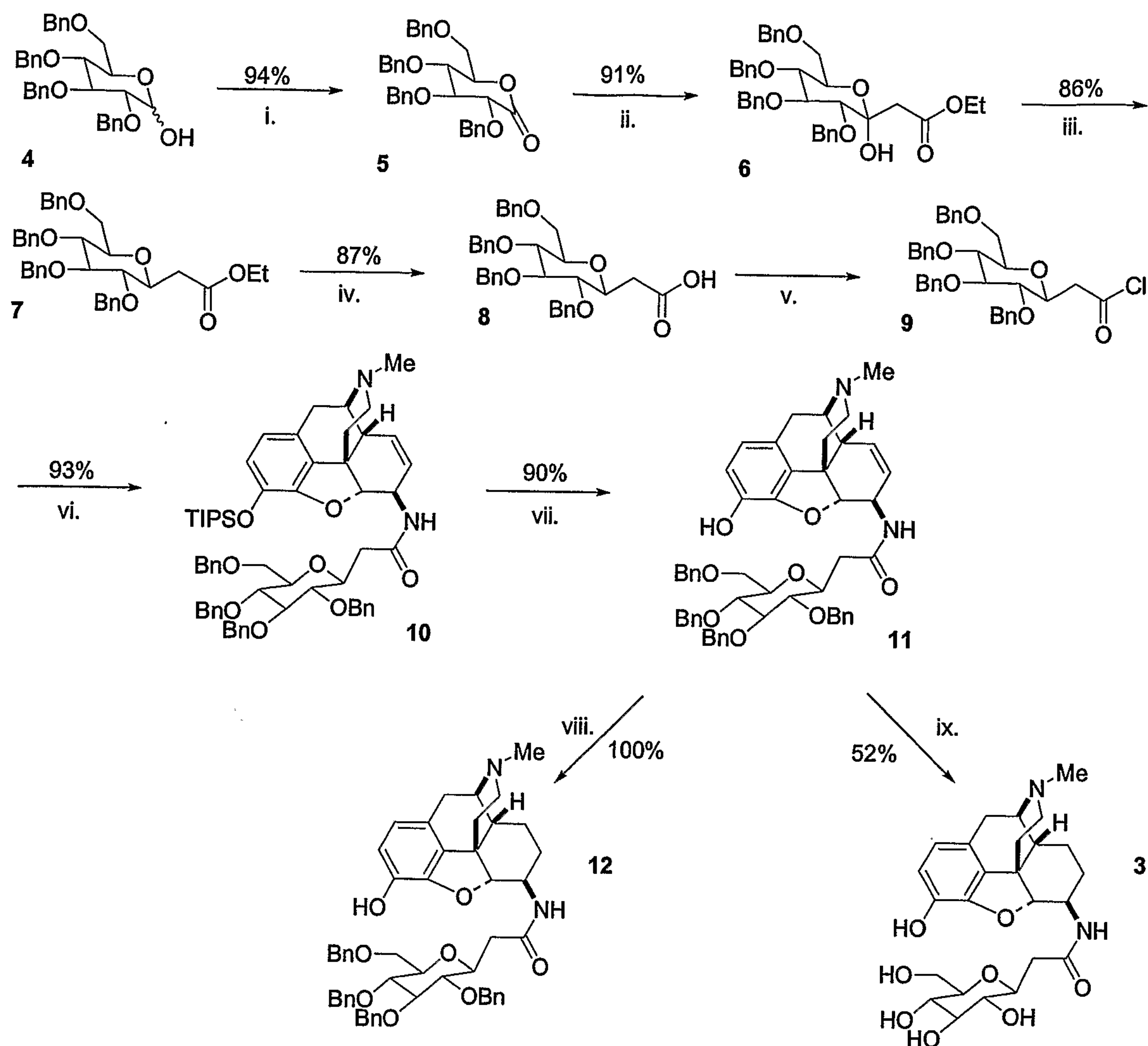
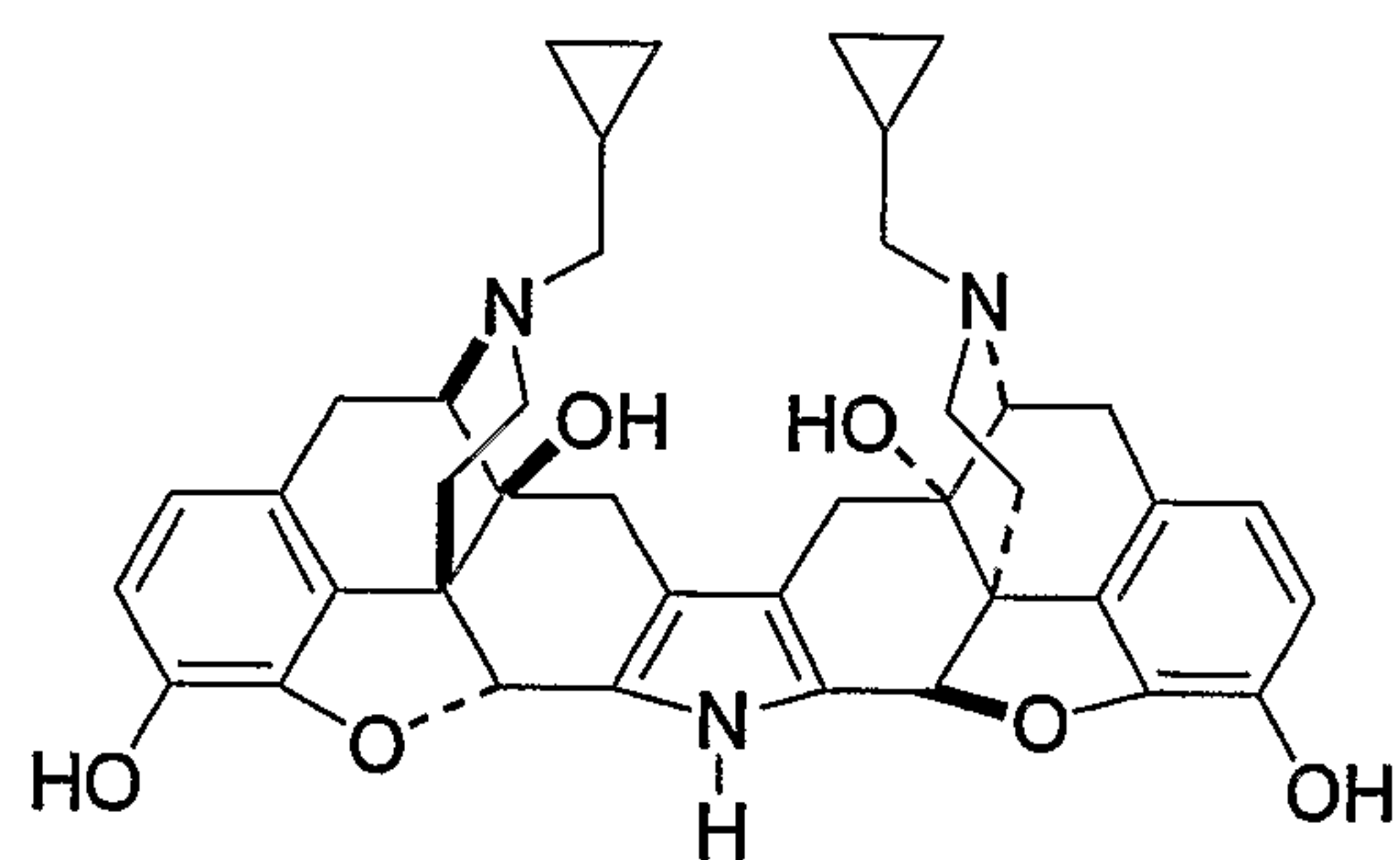
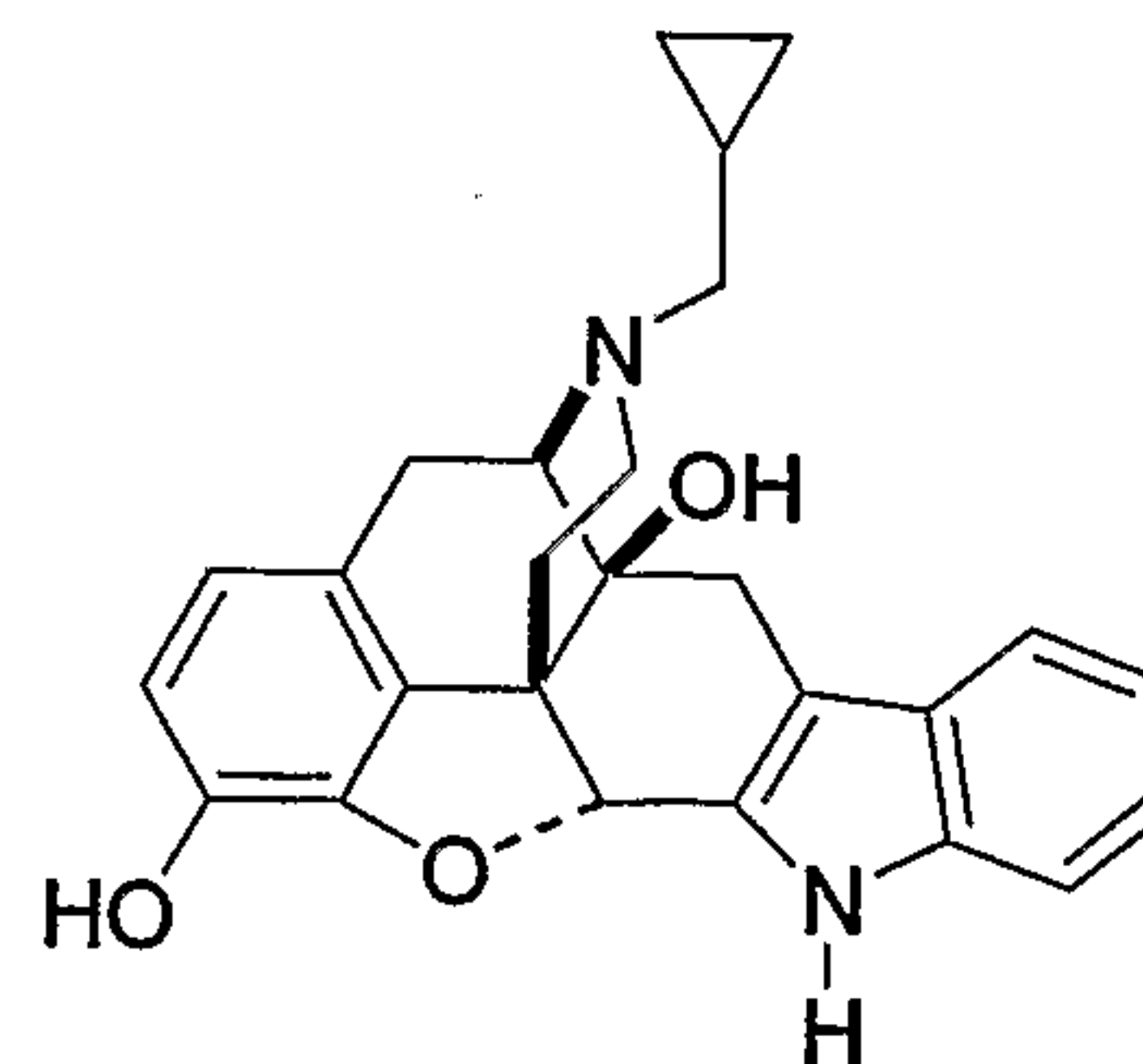


FIG. 14

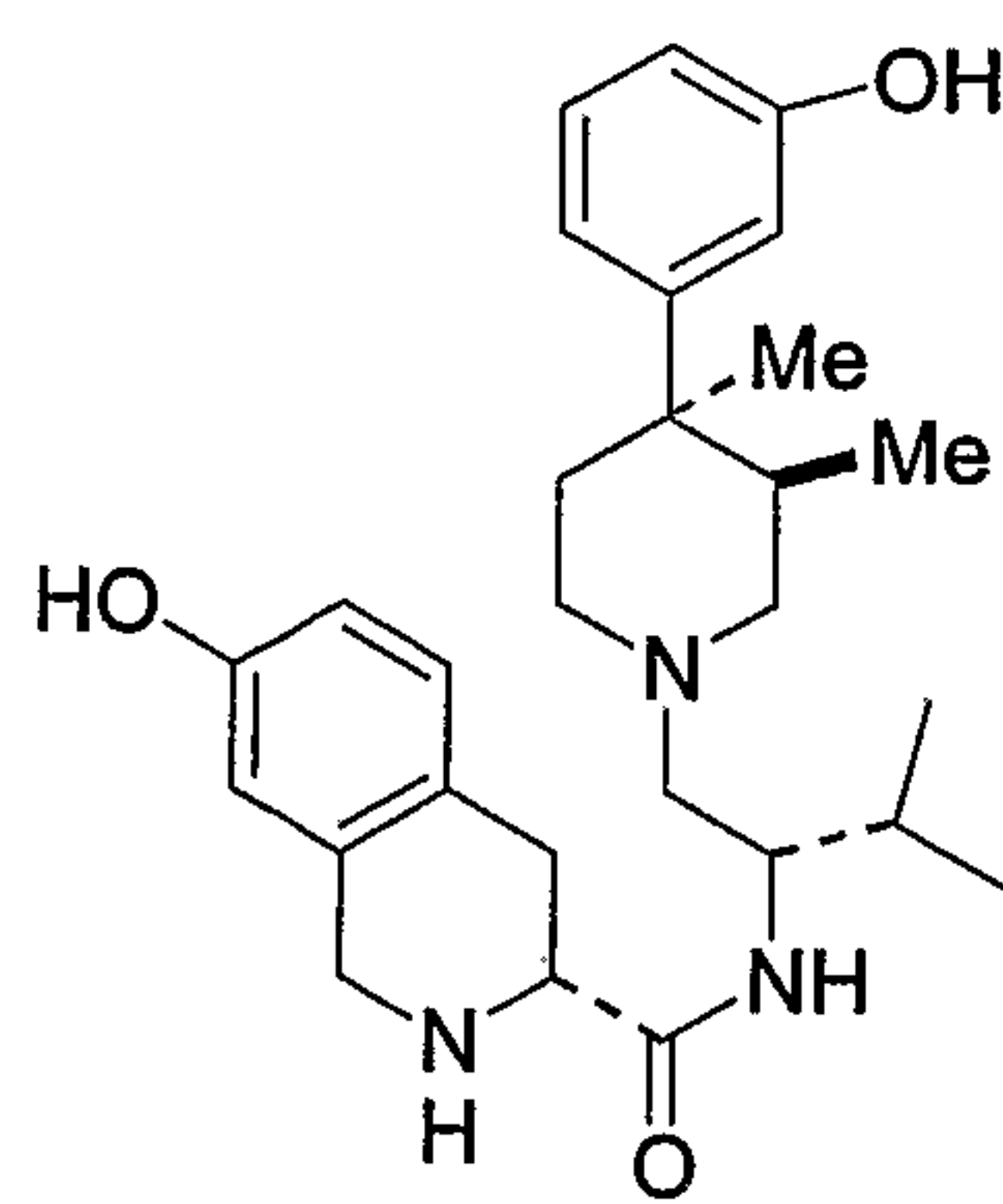
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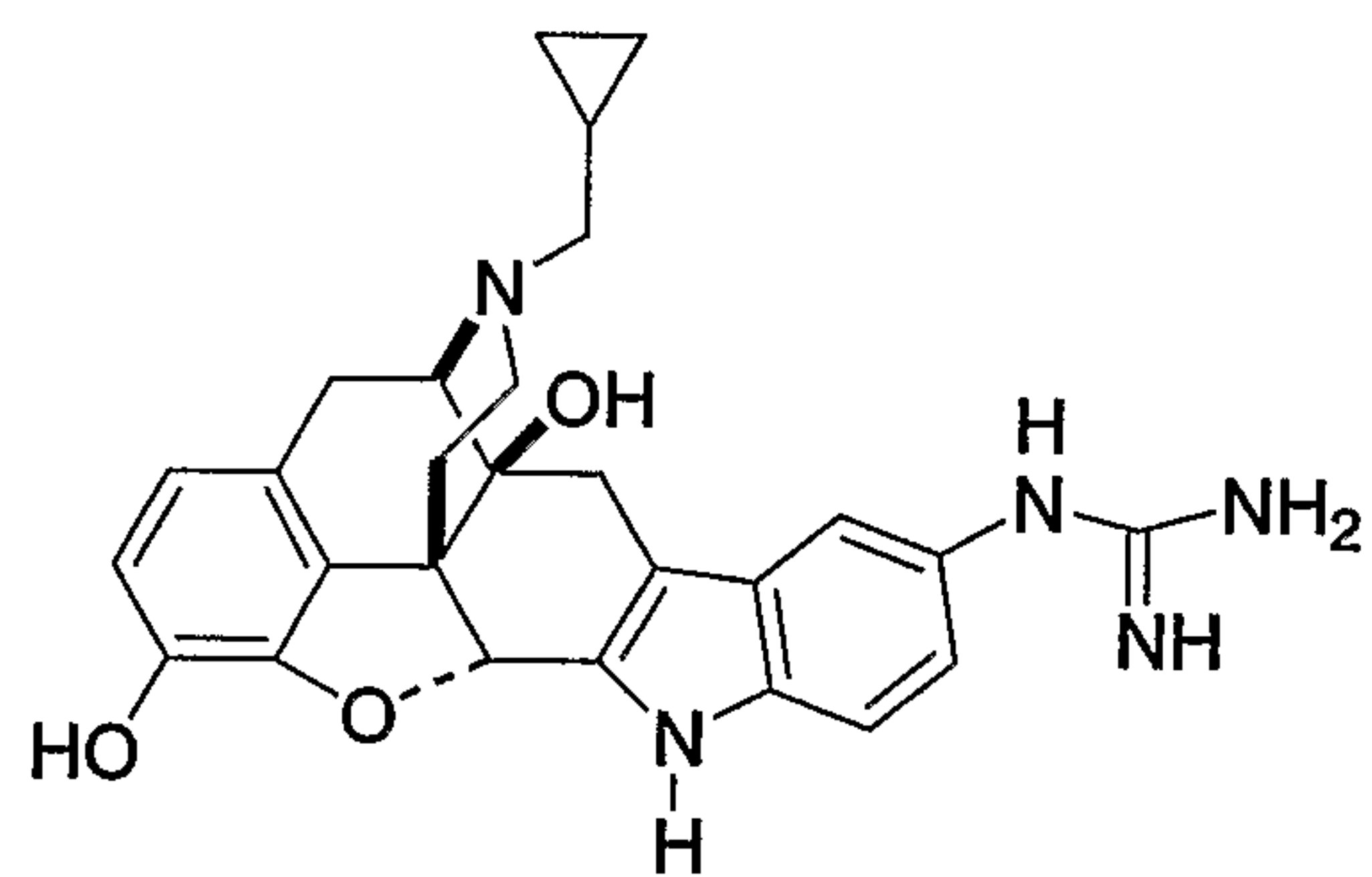
Norbinaltorphine (norBNI)



Naltrindole (NTI)

FIG. 15

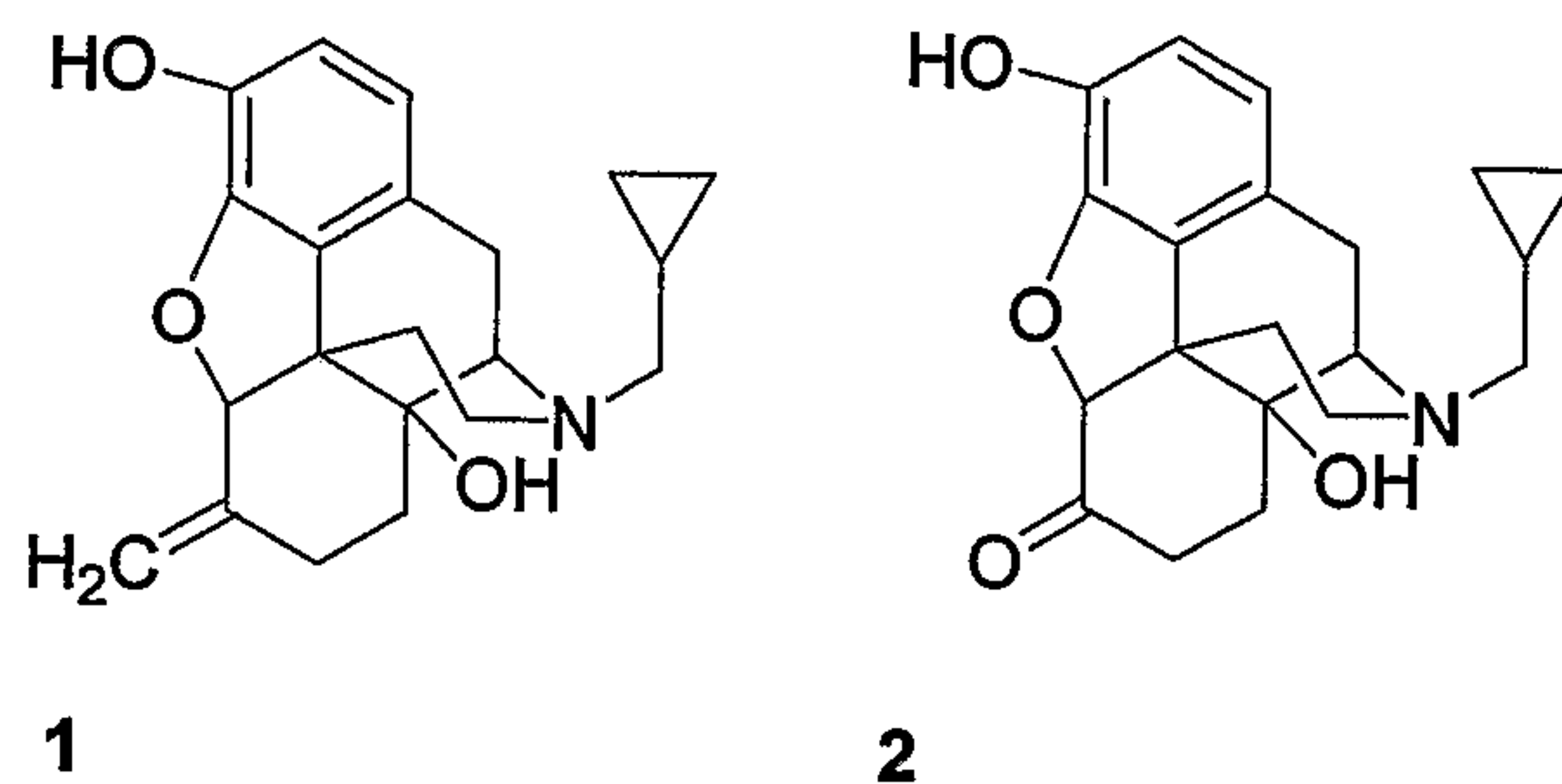
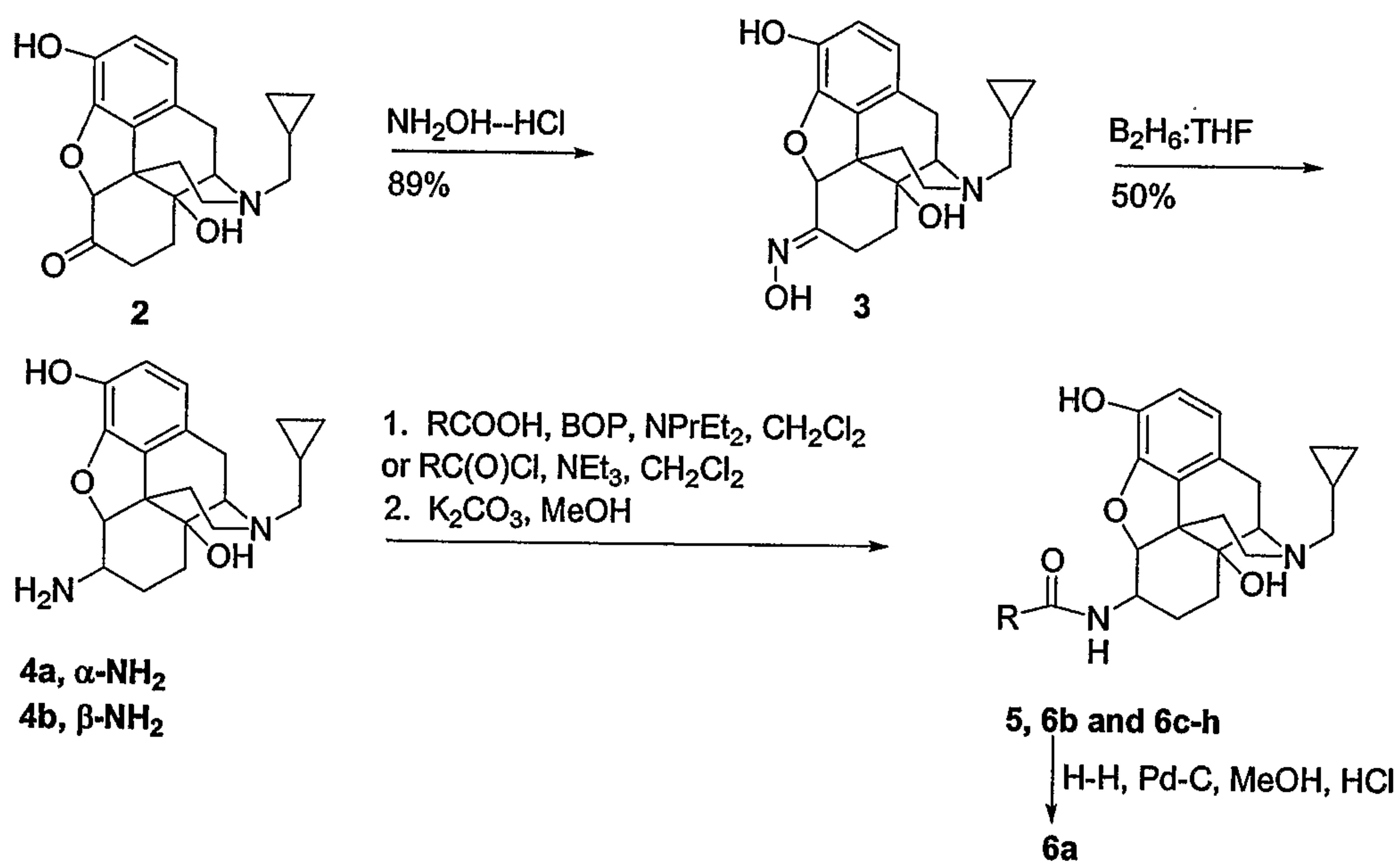
JDtic



GNTI

FIG. 16

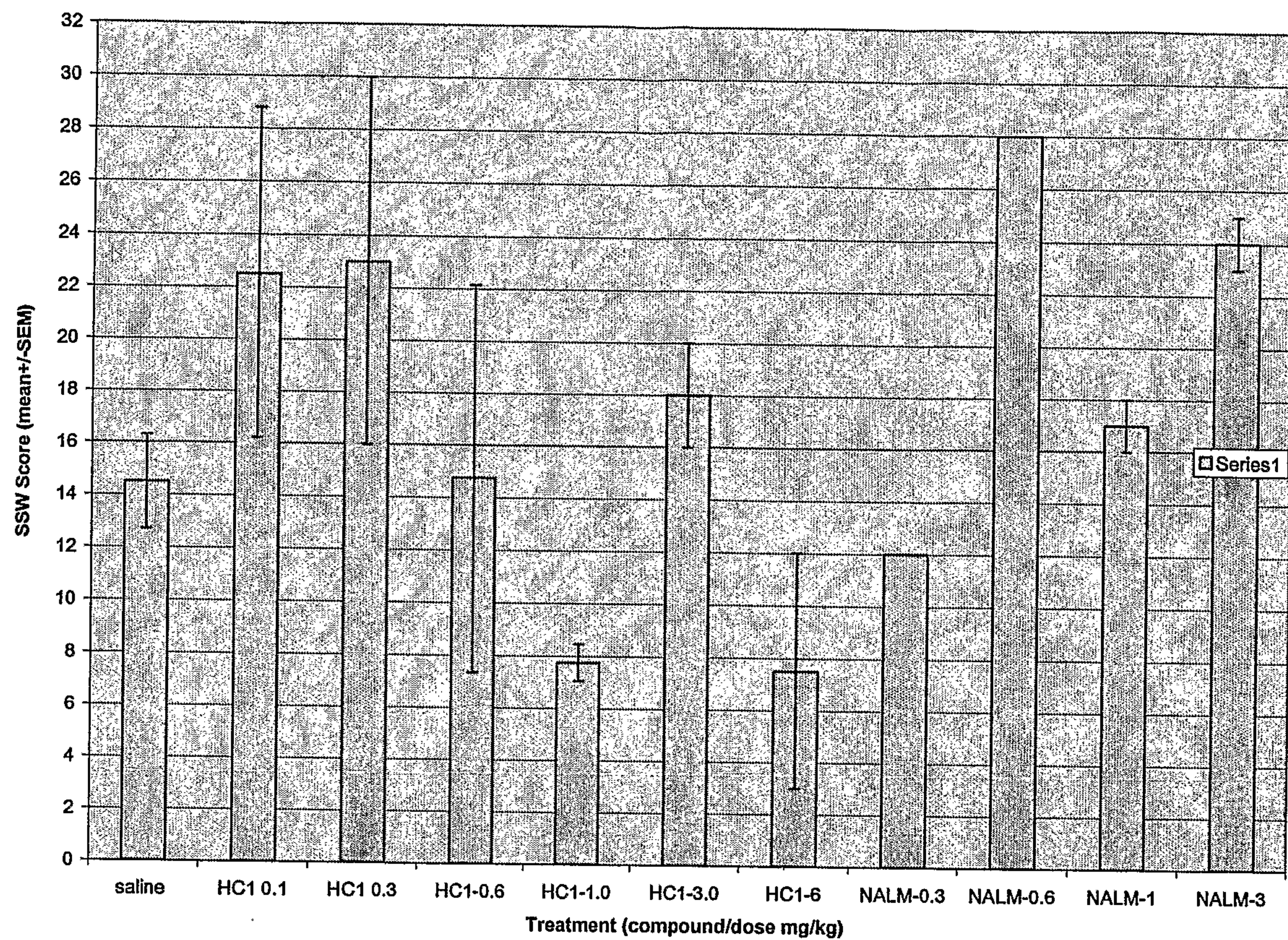
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**FIG. 17**

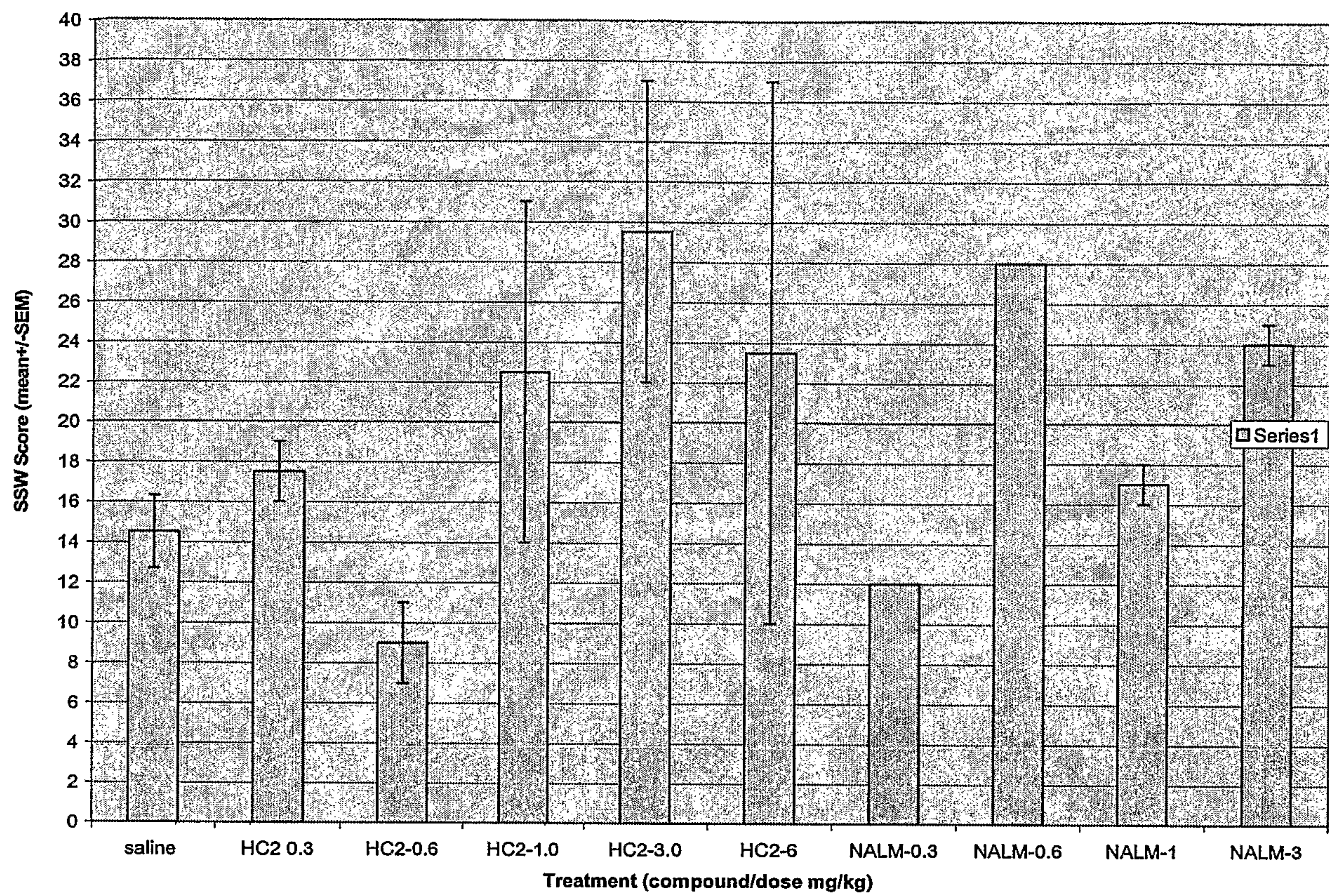
-
- 5:** CH₂-2,3,4,6-tetra-O-benzyl-D-glucose
6a: CH₂-D-glucose
6b: pyridine-3-yl
6c: 3-dimethylaminophenyl
6d: 3-methoxyphenyl
6e: CH₂-thiophene-3-yl
6f: 3,5-dimethoxyphenyl
6g: 4-chlorophenyl
6h: 3-hydroxyphenyl

FIG. 18

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**FIG. 19**

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**FIG. 20**