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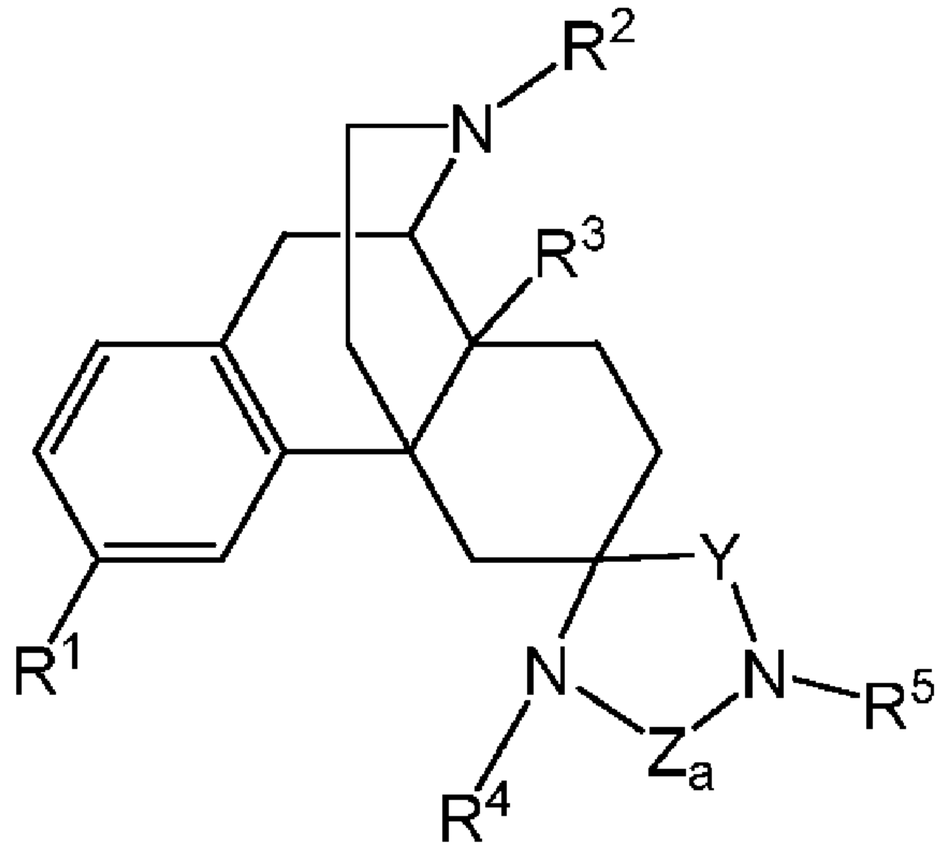
(54) **Titre : MORPHINANES SPIROCYCLIQUES ET UTILISATION ASSOCIEE**
(54) **Title: SPIROCYCLIC MORPHINANS AND USE THEREOF**



(I)

(57) **Abrégé/Abstract:**
In one aspect, the invention provides compounds of Formula I: (I) and pharmaceutically acceptable salts and solvates thereof, wherein R^1, R^2, R^3, R^4, R^5, Y, Z_a are defined as set forth in the disclosure. The invention also provides compounds of any one of Formulae II to VII, IA to IC, and IIA to IIC, and pharmaceutically acceptable salts and solvates thereof. Other aspects of the invention include the use of compounds of Formulae I to VII, IA to IC, and IIA to IIC, and pharmaceutically acceptable salts and solvates thereof for the treatment of disorders responsive to modulation of one or more opioid receptors. In certain embodiments, the Compounds of the Invention are useful for treating pain.

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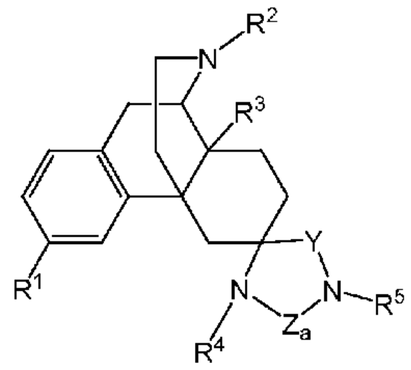
(54) Title: SPIROCYCLIC MORPHINANS AND USE THEREOF



(I)

(57) Abstract: In one aspect, the invention provides compounds of Formula I: (I) and pharmaceutically acceptable salts and solvates thereof, wherein R^1, R^2, R^3, R^4, R^5, Y, Z_a are defined as set forth in the disclosure. The invention also provides compounds of any one of Formulae II to VII, IA to IC, and IIA to IIC, and pharmaceutically acceptable salts and solvates thereof. Other aspects of the invention include the use of compounds of Formulae I to VII, IA to IC, and IIA to IIC, and pharmaceutically acceptable salts and solvates thereof for the treatment of disorders responsive to modulation of one or more opioid receptors. In certain embodiments, the Compounds of the Invention are useful for treating pain.

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SPIROCYCLIC MORPHINANS AND USE THEREOF

BACKGROUND OF THE INVENTION

Pain is the most common symptom for which patients seek medical advice and treatment. While acute pain is usually self-limited, chronic pain can persist for 3 months or longer and lead to significant changes in a patient's personality, lifestyle, functional ability and overall quality of life (K.M. Foley, Pain, in *Cecil Textbook of Medicine* 100-107, J.C. Bennett and F. Plum eds., 20th ed. 1996).

Pain has traditionally been managed by administering either a non-opioid analgesic (such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflunisal or naproxen), or an opioid analgesic (such as morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, oxymorphone, or buprenorphine).

Until recently, there was evidence of three major classes of opioid receptors in the central nervous system (CNS), with each class having subtype receptors. These receptor classes are known as μ, δ and κ. As opiates have a high affinity to these receptors while not being endogenous to the body, research followed in order to identify and isolate the endogenous ligands to these receptors. These ligands were identified as endorphins, enkephalins, and dynorphins, respectively. Additional experimentation has led to the identification of the opioid receptor-like (ORL-1) receptor, which has a high degree of homology to the known opioid receptor classes. This more recently discovered receptor was classified as an opioid receptor based only on structural grounds, as the receptor did not exhibit pharmacological homology. It was initially demonstrated that non-selective ligands having a high affinity for μ, δ and κ receptors had low affinity for the ORL-1 receptor. This characteristic, along with the fact that an endogenous ligand had not yet been discovered, led to the ORL-1 receptor being designated as an "orphan receptor".

Kappa (κ) opioid receptor agonists have been evaluated as alternatives to existing analgesics for the treatment of pain. Centrally penetrating κ agonists produce antinociceptive effects in conventional preclinical assays of basal, inflammatory and neuropathic pain (Vanderah *et al.*, *J. Pharmacol. Exp. Ther. 310*:326-333 (2004); Negus *et al.*, *Psychopharmacology (Berl) 210*:149-159 (2010)). However, centrally penetrating κ agonists can also produce undesirable side-effects, such as sedative and psychotomimetic effects (Pande *et al.*, *Clin. Neuropharmacol. 19*:92-97 (1996); Pande *et al.*, *Clin. Neuropharmacol. 19*:451-456 (1996); and Wadenberg, *CNS Drug Rev. 9*:187-198 (2003)).

Opioid receptor agonists that do not readily cross the blood-brain barrier are peripherically restricted and distribute poorly to the central nervous system after systemic administration. Such compounds would retain an ability to produce analgesia by acting on peripheral opioid receptors, such as peripheral κ-opioid receptors, but their potency to produce centrally mediated side-effects would be reduced.

There is a need for effective analgesics that work by acting on opioid receptors. There is also a need for analgesics that work by acting on peripheral opioid receptors. There is also a need for analgesics that work by acting on central opioid receptors. There is also a need for analgesics that work by acting on κ-opioid receptors. There is also a need for analgesics that work by acting on peripheral κ-opioid receptors.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the invention provides compounds represented by Formulae **I -VII**, **IA** to **IC**, and **IIA** to **IIC**, delineated below, and pharmaceutically acceptable salts and solvates thereof, collectively referred to herein as "Compounds of the Invention" (each is individually referred to hereinafter as a "Compound of the Invention").

In another aspect, the invention provides the use of Compounds of the Invention as synthesis intermediates.

In another aspect, the invention provides the use of Compounds of the Invention as modulators of one or more opioid receptors. Specifically, the present disclosure provides the use of Compounds of the Invention as modulators of μ, δ, κ, and/or ORL-1 opioid receptors, and especially modulators of μ and/or κ opioid receptors.

Another aspect of the invention provides a method of treating or preventing a disorder responsive to the modulation of one or more opioid receptors in a patient, comprising administering to the patient an effective amount of a Compound of the Invention.

In still another aspect, the invention provides use of a Compound of the Invention as an analgesic to treat or prevent pain; or as an agent to treat or prevent withdrawal from alcohol or drug addiction; or as an agent to treat or prevent addictive disorders; or as an agent to treat a pruritic condition; or as an agent to treat or prevent constipation; or as an agent to treat or prevent diarrhea (each of pain, alcohol withdrawal, drug withdrawal, addictive disorders, pruritis, constipation, and diarrhea being a "Condition").

The invention further provides methods of treating or preventing a Condition, comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of the Invention. In certain embodiments, the Condition is pain (including acute

pain, chronic pain (which includes but is not limited to, neuropathic pain, postoperative pain, and inflammatory pain), and surgical pain). In one embodiment, the Compounds of the Invention are useful for treating or preventing chronic pain.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a therapeutically effective amount of a Compound of the Invention and one or more pharmaceutically acceptable carriers. Such compositions are useful for treating or preventing a Condition in a patient.

In another aspect, the present disclosure provides the Compounds of the Invention for use in treatment or prevention of a disorder responsive to the modulation of one or more opioid receptors. In certain embodiments, the disorder is responsive to modulation of the μ-opioid receptor or the κ-opioid receptor, or to modulation of a combination thereof.

In another aspect, the present disclosure provides a method of modulating one or more opioid receptors in a patient in need of said modulation, comprising administering to the patient an opioid receptor modulating amount of a Compound of the Invention.

In another aspect, the present disclosure provides the Compounds of the Invention for use in treatment or prevention of one or more Conditions in a patient in need of said treatment or prevention.

In still another aspect, the present disclosure provides the Compounds of the Invention for use in treatment or prevention of pain in a patient, such as acute pain, chronic pain (which includes, but is not limited to, neuropathic pain, postoperative pain, and inflammatory pain), or surgical pain.

In yet another aspect, the present disclosure provides the Compounds of the Invention for use in modulation of one or more opioid receptors in a patient.

In another aspect, the present disclosure provides use of the Compounds of the Invention in the manufacture of a medicament for treating or preventing a disorder responsive to the modulation of one or more opioid receptors.

In another aspect, the present disclosure provides use of the Compounds of the Invention in the manufacture of a medicament for modulating of one or more opioid receptors in a patient. In certain embodiments, μ- or κ-opioid receptors are modulated, or both the μ- and κ-opioid receptors are modulated.

In another aspect, the present disclosure provides the Compounds of the Invention for use as a medicament.

In another aspect, the present disclosure provides use of a Compound of the Invention in the manufacture of a medicament for treating or preventing a Condition in a patient.

In another aspect, the present disclosure provides use of a Compound of the Invention in the manufacture of a medicament for treating or preventing pain in a patient, such as acute pain, chronic pain, or surgical pain.

In another aspect, the present disclosure provides a pharmaceutical composition, comprising a Compound of the Invention for treating or preventing a disorder responsive to the modulation of one or more opioid receptors.

The invention further provides methods for preparing a pharmaceutical composition, comprising admixing a Compound of the Invention and a pharmaceutically acceptable carrier to form the pharmaceutical composition.

In another aspect, the invention provides radiolabeled Compounds of the Invention, especially ^{1}H, ^{11}C and ^{14}C radiolabeled Compounds of the Invention, and the use of such compounds as radioligands to detect binding to an opioid receptor in screening assays.

In another aspect, the invention provides a method for screening a candidate compound for the ability to bind to an opioid receptor, comprising a) introducing a fixed concentration of a radiolabeled Compound of the Invention to the receptor under conditions that permit binding of the radiolabeled compound to the receptor to form a complex; b) titrating the complex with a candidate compound; and c) determining the binding of the candidate compound to said receptor.

In a further aspect, the invention relates to a kit, comprising a sterile container containing an effective amount of a Compound of the Invention and instructions for therapeutic use.

In a further aspect, the invention provides a method of making the Compounds of the Invention.

Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

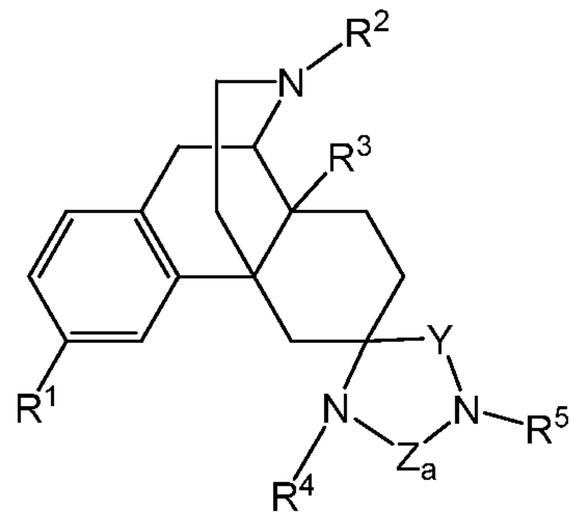
It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

DETAILED DESCRIPTION OF THE INVENTION

It has been noted that certain Compounds of the Invention are useful for modulating a pharmacodynamic response from one or more opioid receptors (μ, δ, κ, ORL-1) either centrally or peripherally, or both. The pharmacodynamic response may be attributed to the compound either stimulating (agonizing) or inhibiting (antagonizing) the one or more receptors. Certain Compounds of the Invention may antagonize one or more opioid receptors, while also agonizing one or more other receptors. Further, Compounds of the Invention having agonist activity may be either full or partial agonists.

Another aspect of the invention is based on the use of certain Compounds of the Invention as synthesis intermediates.

In one aspect, the invention provides compounds of Formula **I**:



I

or pharmaceutically acceptable salts or solvates thereof, wherein

R^1 is hydroxyl, cyano, aminocarbonyl, $-C(=NR^7)-NR^{7a}R^{7b}$, or alkoxy, wherein said alkoxy is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxyl, halo, haloalkyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, aryl, heteroaryl, heterocyclo, cycloalkyl, and cycloalkenyl;

R^2 is hydrogen or alkyl optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, aryl, and alkoxycarbonyl;

R^3 is hydrogen, hydroxyl, alkoxy, alkylamino, or dialkylamino, wherein each of said alkoxy, said alkylamino, and said dialkylamino is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxyl, halo, haloalkyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, aryl, heteroaryl, heterocyclo, cycloalkyl, and cycloalkenyl, and wherein said aryl, heteroaryl, heterocyclo, cycloalkyl, and cycloalkenyl are further optionally substituted with 1, 2, or 3 independently selected R^6 groups;

R^4 and R^5 are, each independently, hydrogen or alkyl, wherein said alkyl is optionally substituted with 1 or 2 substituents each independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo; wherein each of said cycloalkyl and said heterocyclo are optionally substituted with 1, 2, or 3 independently selected R^6 groups;

each R^6 is independently selected from the group consisting of hydroxyl, halo, alkyl, haloalkyl, cyano, nitro, amino, alkylamino, dialkylamino, carboxy, alkoxy, carboxamido, and alkoxycarbonyl;

R^7 is H, hydroxyl, alkoxy, or alkyl;

R^{7a} and R^{7b} are, each independently, hydrogen or alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo;

Y is C=O or CH_2;

Z_a is C=O or CHR^8;

wherein R^8 is hydrogen, $(C_{1\text{-}6})$alkyl, or phenyl optionally substituted with 1, 2, or 3 independently selected R^6 groups,

provided that

i) when R^1 is hydroxyl, cyano, aminocarbonyl, or methoxy, and R^3 is hydroxyl,

then R^4 and R^5 are the same; and

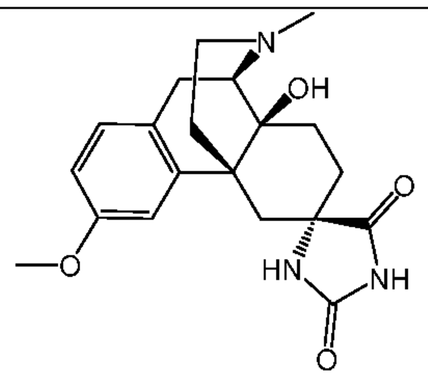
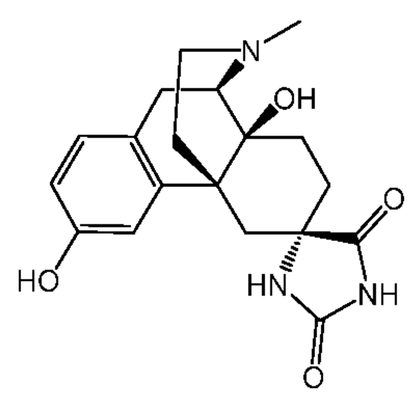
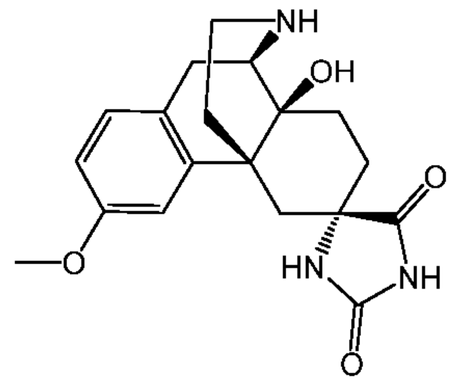
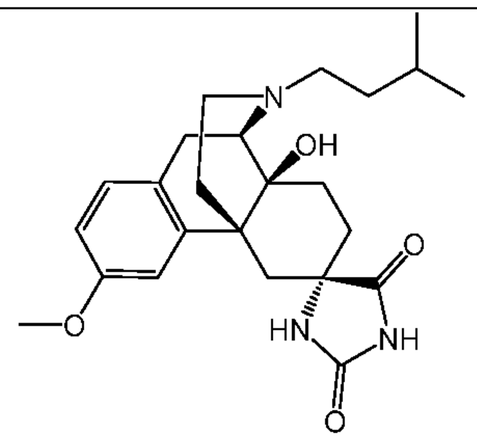
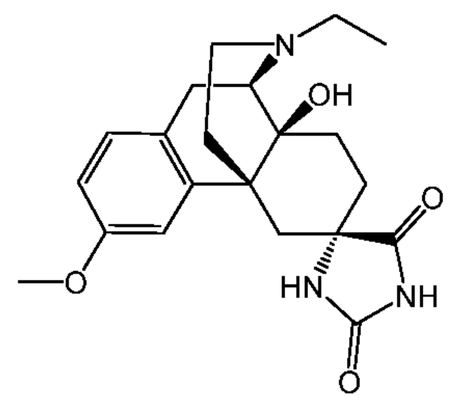
ii) when R^2 is alkyl substituted by an aryl group,

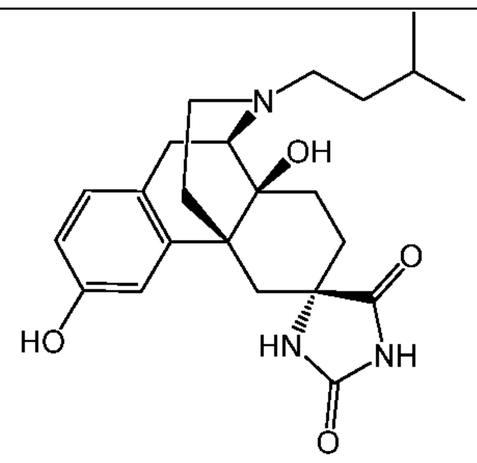
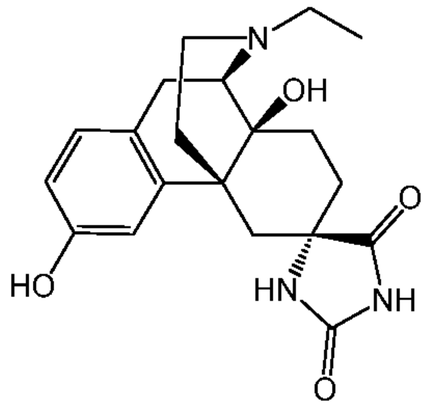
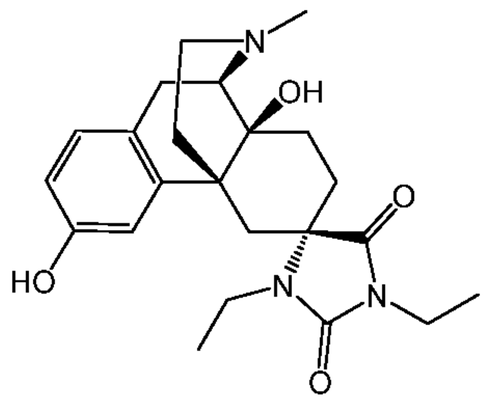
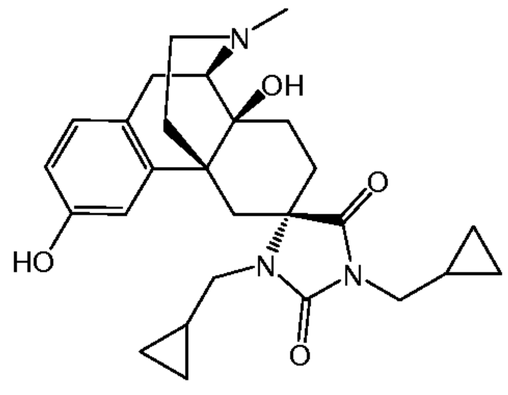
then at least one of R^4 and R^5 is optionally-substituted alkyl;

further provided that

said compound is NOT a compound selected from those provided in TABLE 1 as follows:

TABLE 1

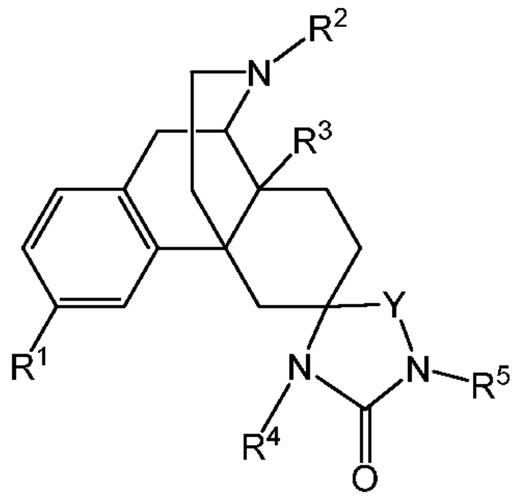
Cpd #	Structure	Chemical name
E-1		(4S,4b'R,8a'S,9'R)-8a'-hydroxy-3'-methoxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenan-threne]-2,5-dione
E-2		(4S,4b'R,8a'S,9'R)-3',8a'-dihydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione
E-3		(4S,4b'R,8a'S,9'R)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
E-4		(4S,4b'R,8a'S,9'R)-8a'-hydroxy-11'-isopentyl-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione
E-5		(4S,4b'R,8a'S,9'R)-11'-ethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione

E-6		(4S,4b'R,8a'S,9'R)-3',8a'-dihydroxy-11'-isopentyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
E-7		(4S,4b'R,8a'S,9'R)-11'-ethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
E-8		(4S,4b'R,8a'S,9'R)-1,3-diethyl-3',8a'-dihydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione
E-9		(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-3',8a'-dihydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione

In certain embodiments, Compounds of the Invention do not include any one of the compounds disclosed in the PCT Patent Publication No. WO2014/091297A1 (International Patent Application No. PCT/IB2013/002783). In one embodiment, the Compounds of the Invention do not include any compound of Compound Nos. **1-71** and **73** of WO2014/091297A1 (Application No. PCT/IB2013/002783), as well as those recited in the claims (e.g., claim 64) and those disclosed in Tables 1 and 3 in WO2014/091297A1.

In one embodiment, Compounds of the Invention are compounds of Formula **I** or pharmaceutically acceptable salts or solvates thereof, wherein Z_a is C=O. In another embodiment, Z_a is CH_2.

In certain embodiments, Compounds of the Invention are compounds of Formula **II**:

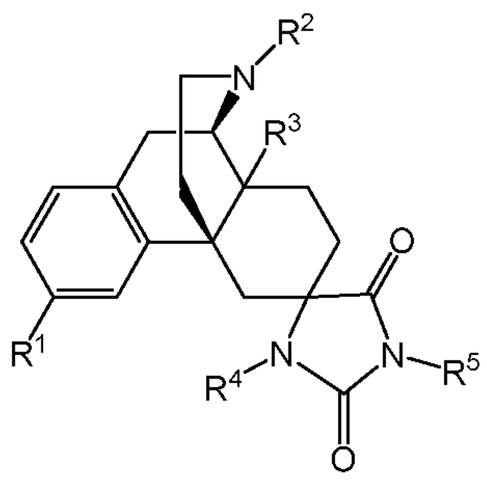


II

or pharmaceutically acceptable salts or solvates thereof, wherein R^1, R^2, R^3, R^4, R^5, and Y are defined in the way as delineated in connection with Formula **I**.

One embodiment of Formula **I** or **II** provides that Y is C=O.

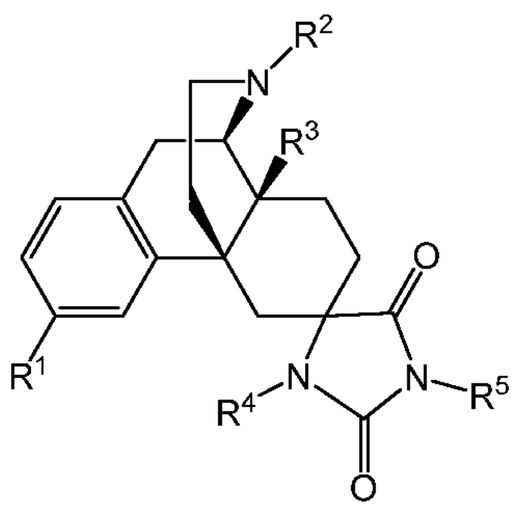
Further, the invention includes compounds of Formula **III**:



III

or pharmaceutically acceptable salts or solvates thereof, wherein R^1, R^2, R^3, R^4, and R^5 are defined in the way as above delineated.

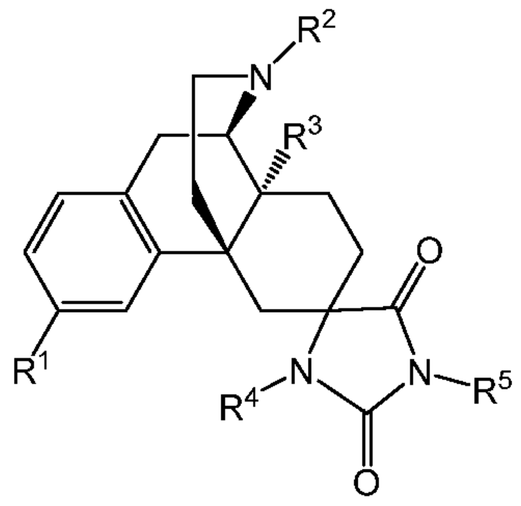
In another embodiment, Compounds of the Invention are compounds of Formula **IV**:



IV

or pharmaceutically acceptable salts or solvates thereof, wherein R^1, R^2, R^3, R^4, and R^5 are defined in the way as above delineated.

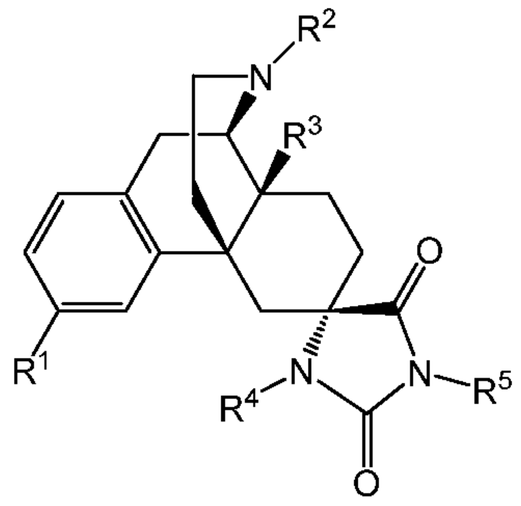
Another embodiment of the invention provides compounds of Formula **V**:



V

or pharmaceutically acceptable salts or solvates thereof, wherein R^1, R^2, R^3, R^4, and R^5 are defined in the way as above delineated.

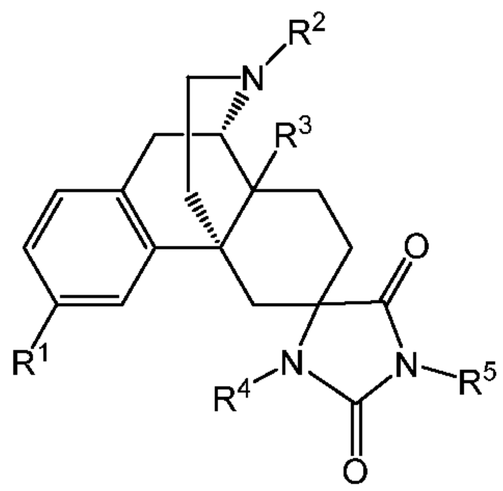
Further, a separate embodiment of the invention provides compounds of Formula **VI**:



VI

or pharmaceutically acceptable salts or solvates thereof, wherein R^1, R^2, R^3, R^4, and R^5 are defined in the way as above delineated.

A further embodiment of the invention provides compounds of Formula **VII**:



VII

or pharmaceutically acceptable salts or solvates thereof, wherein R^1, R^2, R^3, R^4, and R^5 are defined in the way as above delineated.

One embodiment in accordance with any one of Formulae **I** to **VII** provides that R^2 is hydrogen. In another embodiment in accordance with any one of Formulae **I** to **VII**, R^2 is optionally-substituted (C_{1-6})alkyl, such as (C_{1-6})alkyl optionally substituted by hydroxyl, amino, alkylamino, dialkylamino, alkoxy, aryl, or alkoxycarbonyl. In one embodiment, R^2 is unsubstituted (C_{1-6})alkyl. In another embodiment, R^2 is (C_{1-6})alkyl substituted by amino,

alkylamino, dialkylamino, or aryl (e.g., phenyl). One embodiment provides that R^2 is (C_{1-3})alkyl substituted by phenyl or di((C_{1-3})alkyl)amino.

In a separate embodiment, the invention provides compounds of any one of Formulae **I** to **VII** or pharmaceutically acceptable salts or solvates thereof, wherein R^3 is hydrogen. Another embodiment provides that R^3 is hydroxyl.

Certain embodiments of the invention provide compounds of any one of Formulae **I** to **VII** or pharmaceutically acceptable salts or solvates thereof, wherein R^4 and R^5 are, each independently, hydrogen or (C_{1-6})alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo. For example, in certain instances, one of R^4 and R^5 is hydrogen, the other is hydrogen or optionally-substituted (C_{1-6})alkyl. One embodiment provides that one of R^4 and R^5 is hydrogen, the other is (C_{1-6})alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, amino, ((C_{1-6})alkyl)amino, di((C_{1-6})alkyl)amino, carboxy, (C_{1-6})alkoxy, ((C_{1-6})alkoxy)carbonyl, carboxamido, (C_{3-8})cycloalkyl, and 5- to 6-membered heterocyclo.

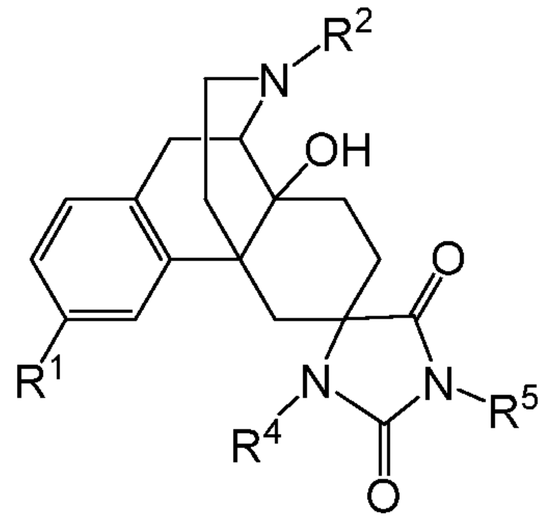
In one embodiment, Compounds of the Invention are compounds of any one of Formulae **I** to **VII** or pharmaceutically acceptable salts or solvates thereof, wherein R^4 and R^5, each independently, are optionally-substituted (C_{1-6})alkyl. One embodiment provides that R^4 and R^5, each independently, are (C_{1-6})alkyl optionally substituted by (C_{3-8})cycloalkyl or 5- to 6-membered heterocyclo. One example provides that R^4 and R^5, each independently, are (C_{1-3})alkyl substituted by (C_{3-6})cycloalkyl, such as, cyclopropylmethyl and cyclopropylethyl. In another embodiment, R^4 and R^5, each independently, are unsubstituted (C_{1-6})alkyl (e.g., methyl, and ethyl).

Compounds of the Invention include compounds in accordance with any one of Formulae **I** to **VII** or pharmaceutically acceptable salts or solvates thereof, wherein R^4 and R^5 are either same or different. In one embodiment, R^4 and R^5 are the same. In another embodiment, R^4 and R^5 are different moieties.

Certain embodiments of the invention provide compounds of any one of Formulae **I** to **VII** or pharmaceutically acceptable salts or solvates thereof, wherein R^1 is hydroxyl. In another embodiment, R^1 is optionally-substituted (C_{1-6})alkoxy, that is, substituted or unsubstituted (C_{1-6})alkoxy (e.g., methoxy). A further embodiment provides that R^1 is cyano. In another embodiment, R^1 is aminocarbonyl (e.g., $-C(O)NH_2$). A separate embodiment provides that R^1 is $-C(=NR^7)-NR^{7a}R^{7b}$. In one instance, R^7 is hydroxyl. Under certain

circumstances, R^{7a} and R^{7b}, independently, are hydrogen or unsubstituted (C_{1-3})alkyl. One embodiment provides that R^1 is $-C(=NR^7)-NR^{7a}R^{7b}$, wherein R^{7a} and R^{7b} are both hydrogen.

In another embodiment, the invention provides a compound of Formula **IA**, or a pharmaceutically acceptable salt or solvate thereof:



IA,

Wherein

R^1 is hydroxyl, cyano, aminocarbonyl, $-C(=NR^7)-NR^{7a}R^{7b}$, or alkoxy;

R^2 is hydrogen or alkyl optionally substituted with dialkylamino or aryl;

R^4 and R^5 are the same, which are hydrogen or alkyl optionally substituted with cycloalkyl;

R^7 is H, hydroxyl, or alkoxy; and

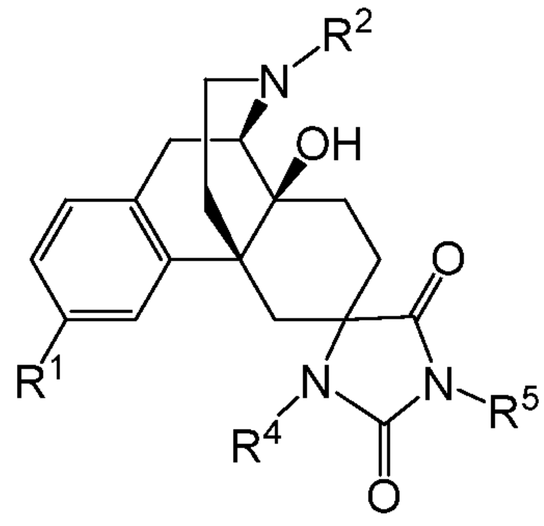
R^{7a} and R^{7b} are, each independently, hydrogen or alkyl;

Provided that

1) when R^2 is alkyl substituted with aryl, then R^4 and R^5 are alkyl optionally substituted with cycloalkyl; and

2) when R^2 is alkyl, then R^1 is cyano, aminocarbonyl, or $-C(=NR^7)-NR^{7a}R^{7b}$.

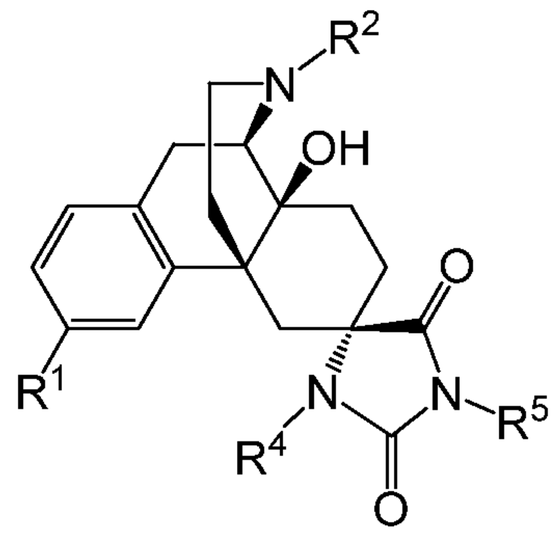
Another embodiment of the invention provides a compound of Formula **IB**, or a pharmaceutically acceptable salt or solvate thereof:



IB

Wherein R^1, R^2, R^4, and R^5 are as defined above in Formula **IA**.

In another embodiment, the invention provides a compound of Formula **IC**, or a pharmaceutically acceptable salt or solvate thereof:



IC

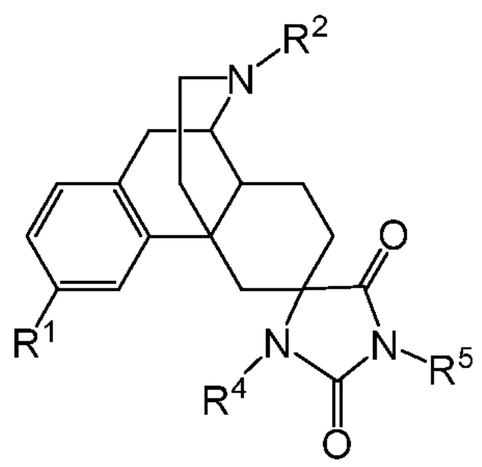
Wherein R^1, R^2, R^4, and R^5 are as defined above in Formula **IA**.

One embodiment in accordance with any one of Formulae **IA** to **IC**, or pharmaceutically acceptable salts or solvates thereof, provides that R^2 is (C_{1-6})alkyl substituted by di(C_{1-3})alkylamino (i.e., -N((C_{1-3})alkyl)$_2$). In certain embodiments, R^1 is hydroxyl or (C_{1-6})alkoxy. One example provides that R^1 is hydroxyl. Another example provides that R^1 is (C_{1-3})alkoxy (e.g., methoxy).

Another embodiment in accordance with any one of Formulae **IA** to **IC**, or pharmaceutically acceptable salts or solvates thereof, provides that R^2 is (C_{1-6})alkyl substituted by aryl (such as, phenyl). In one embodiment, R^1 is hydroxyl or (C_{1-6})alkoxy. One example provides that R^1 is hydroxyl.

A further embodiment in accordance with any one of Formulae **IA** to **IC**, or pharmaceutically acceptable salts or solvates thereof, provides that R^2 is (C_{1-6})alkyl. In certain embodiments, R^1 is cyano, aminocarbonyl (-C(O)NH_2), or -C(=N-OH)-NH_2.

Still further, the invention provides a compound of Formula **IIA**, or a pharmaceutically acceptable salt or solvate thereof:



IIA

Wherein

R^1 is hydroxyl, cyano, aminocarbonyl, -C(=NR^7)-N$R^{7a}R^{7b}$, or alkoxy;

R^2 is hydrogen or alkyl optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, aryl, and alkoxycarbonyl;

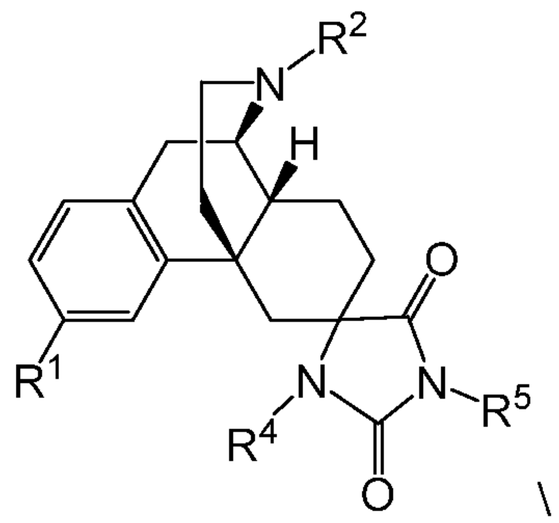
R^4 and R^5 are, each independently, hydrogen or alkyl, wherein said alkyl is optionally substituted with 1 or 2 substituents each independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo; wherein each of said cycloalkyl and said heterocyclo are optionally substituted with 1, 2, or 3 independently selected R^6 groups;

each R^6 is independently selected from the group consisting of hydroxyl, halo, alkyl, haloalkyl, cyano, nitro, amino, alkylamino, dialkylamino, carboxy, alkoxy, carboxamido, and alkoxycarbonyl;

R^7 is H, hydroxyl, alkoxy, alkyl, or cyano; and

R^{7a} and R^{7b} are, each independently, hydrogen or alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo.

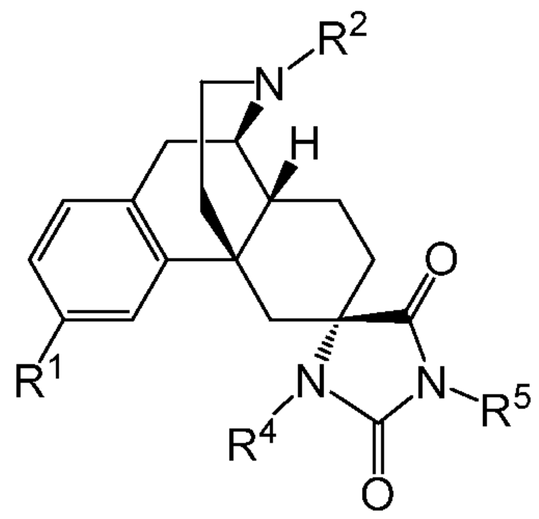
In another embodiment, the invention provides a compound of Formula **IIB**, or a pharmaceutically acceptable salt or solvate thereof:



IIB

Wherein R^1, R^2, R^4, and R^5 are as defined above in Formula **IIA**.

In still another embodiment, the invention provides a compound of Formula **IIC**, or a pharmaceutically acceptable salt or solvate thereof:



IIC

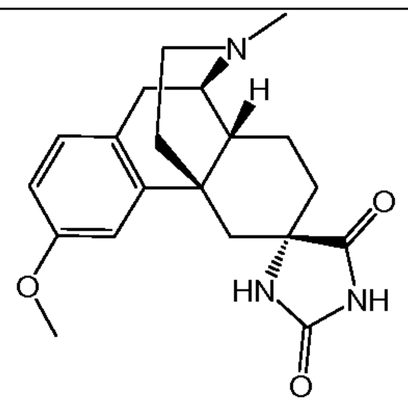
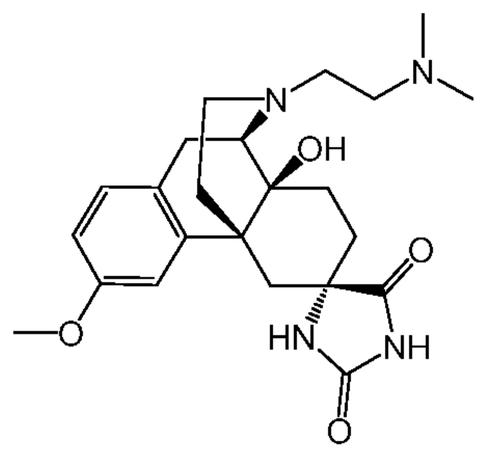
Wherein R^1, R^2, R^4, and R^5 are as defined above in Formula **IIA**.

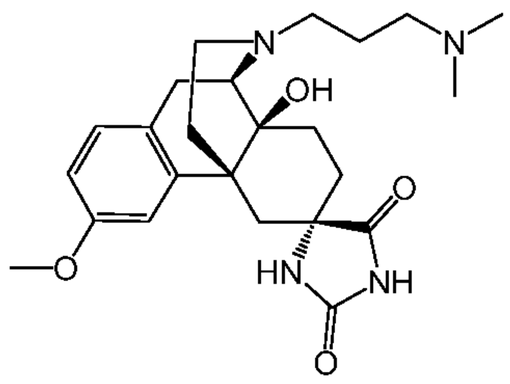
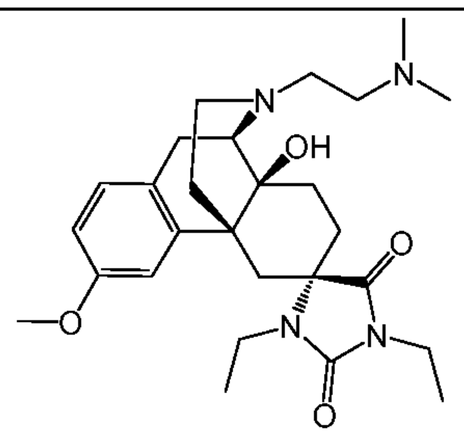
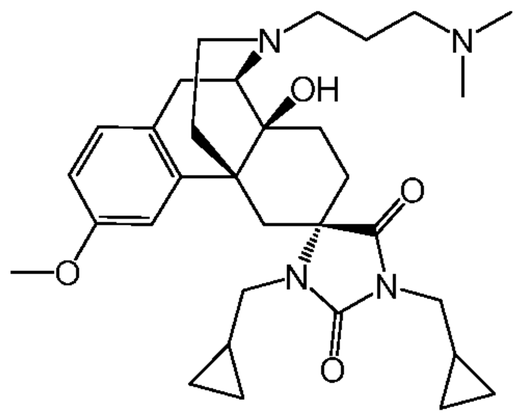
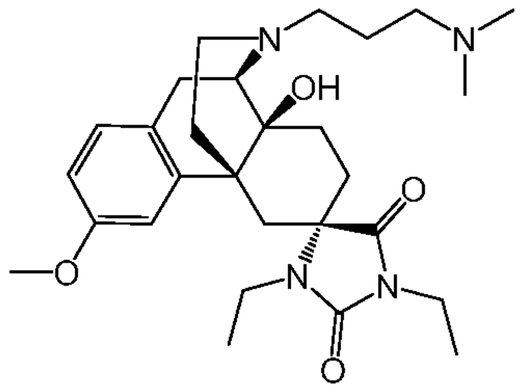
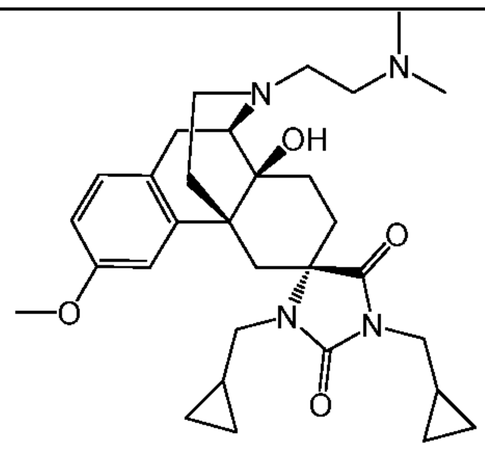
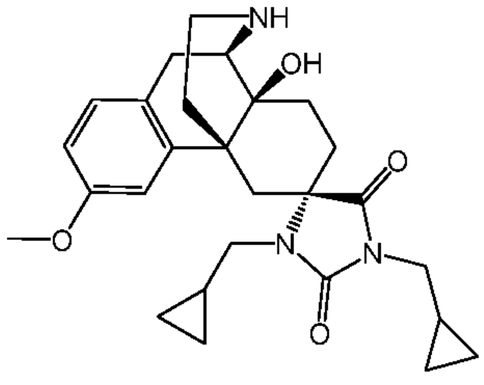
One embodiment in accordance with any one of Formulae **IIA** to **IIC**, or pharmaceutically acceptable salts or solvates thereof, provides that R^2 is (C_{1-6})alkyl. In certain embodiments, R^1 is hydroxyl or (C_{1-6})alkoxy. One example provides that R^1 is hydroxyl. Another example provides that R^1 is (C_{1-3})alkoxy (e.g., methoxy).

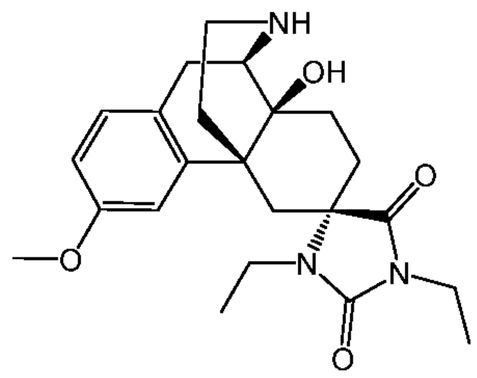
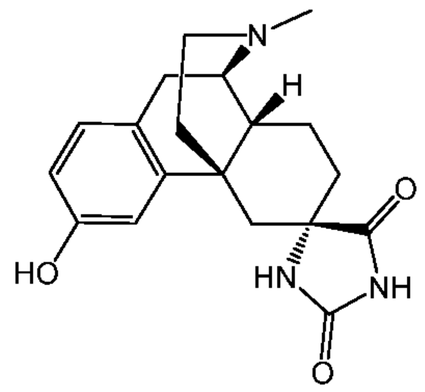
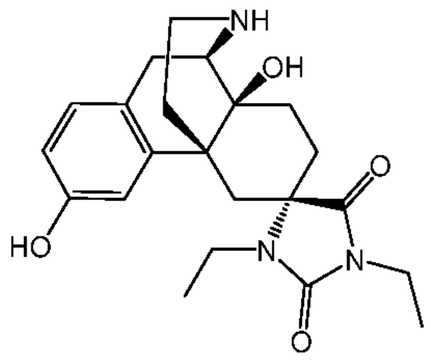
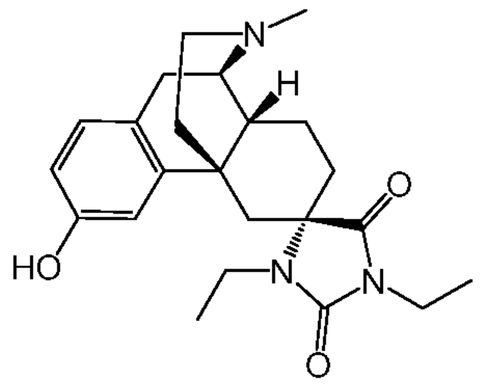
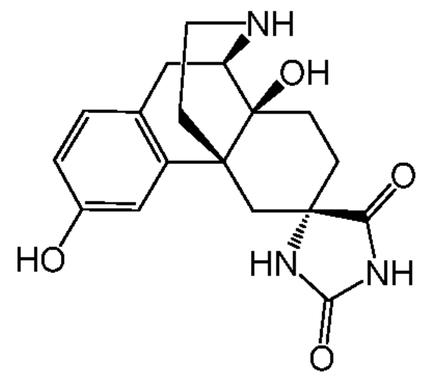
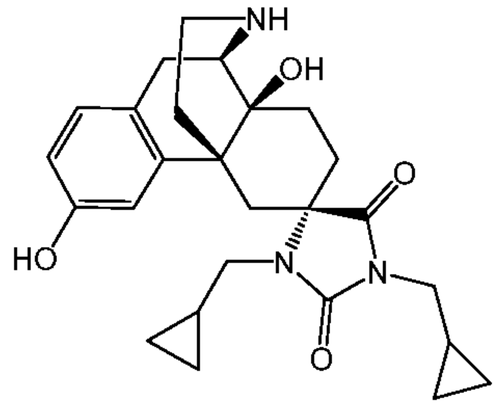
In a separate embodiment in accordance with any one of Formulae **IIA** to **IIC**, or pharmaceutically acceptable salts or solvates thereof, R^4 and R^5, each independently, are hydrogen or (C_{1-6})alkyl. One example provides that both of R^4 and R^5 are hydrogen. Another example provides that R^4 and R^5 are (C_{1-6})alkyl, which can be either the same or different.

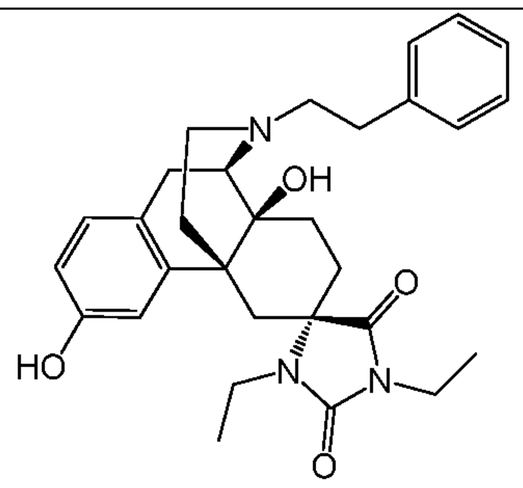
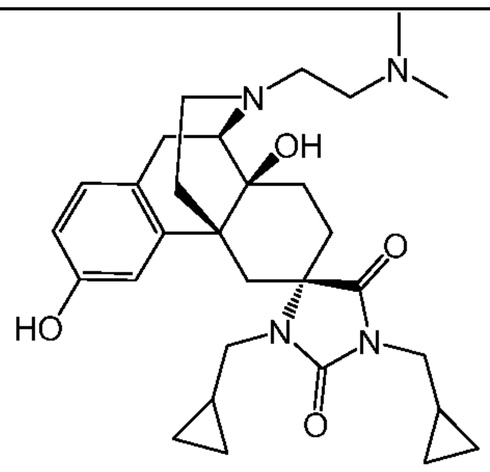
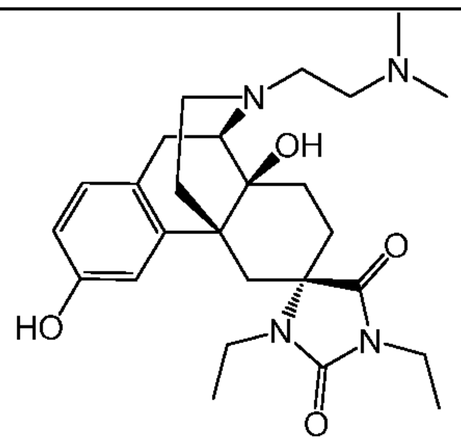
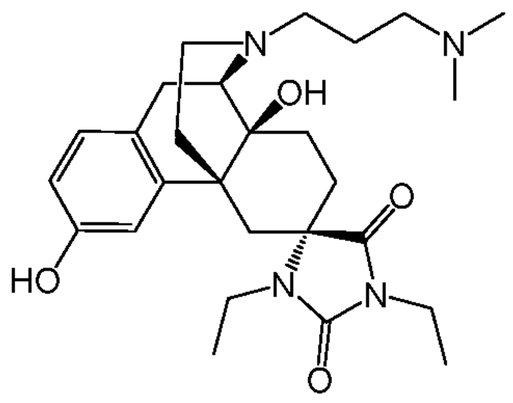
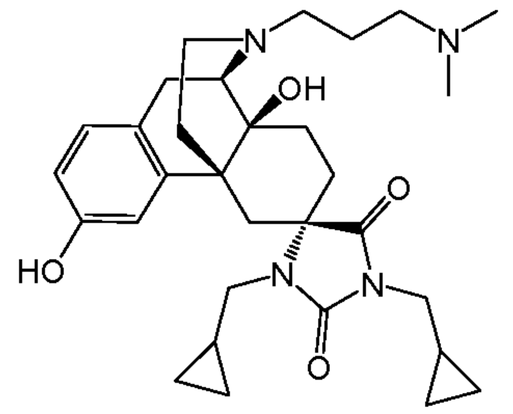
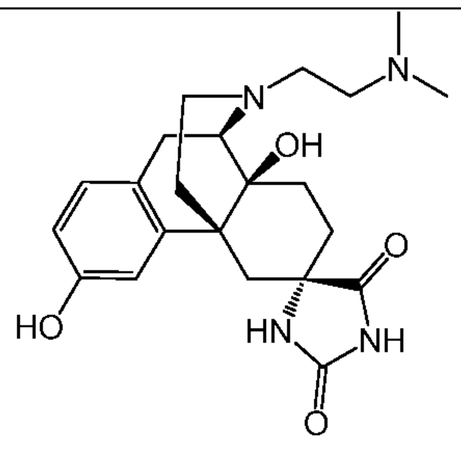
In certain embodiments, Compounds of the Invention include the compounds of TABLE 2 and the pharmaceutically acceptable salts and solvates thereof.

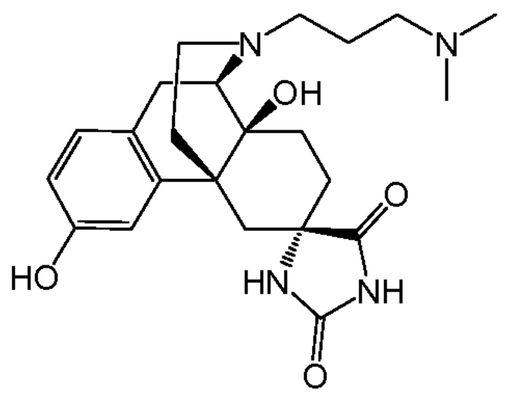
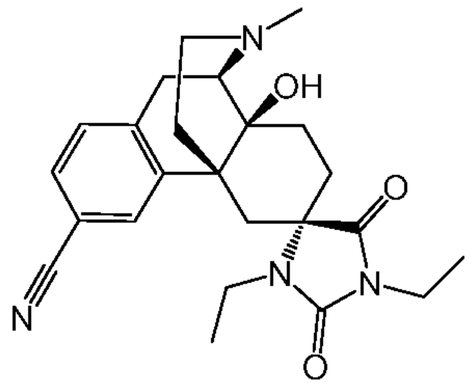
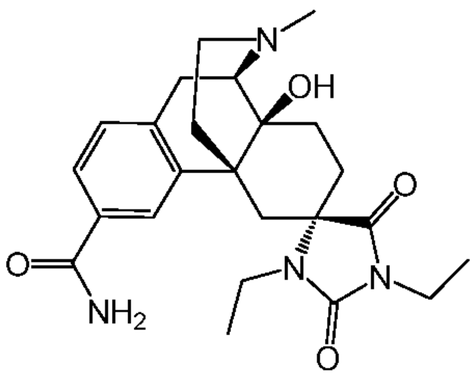
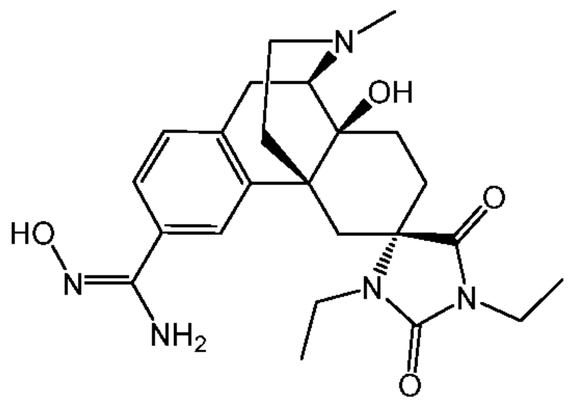
TABLE 2

Cpd #	Structure	Chemical name
2		(4S,4b'S,8a'R,9'R)-3'-methoxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione
3		(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione

4		(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
8		(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
13		(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(3-(dimethylamino)propyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione
14		(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
15		(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(2-(dimethylamino)ethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione
17		(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione

18		(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
19		(4S,4b'S,8a'R,9'R)-3'-hydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione
20		(4S,4b'R,8a'S,9'R)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
21		(4S,4b'S,8a'R,9'R)-1,3-diethyl-3'-hydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
22		(4S,4b'R,8a'S,9'R)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione
23		(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione

24		(4S,4b'R,8a'S,9'R)-1,3-diethyl-3',8a'-dihydroxy-11'-phenethyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
25		(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(2-(dimethylamino)ethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione
26		(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
27		(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
28		(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(3-(dimethylamino)propyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione
29		(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione

30		(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione
32		(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-3'-carbonitrile
33		(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-3'-carboxamide
34		(4S,4b'R,8a'S,9'R,E)-1,3-diethyl-N',8a'-dihydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-3'-carboximidamide

In yet another aspect, the invention further includes the compounds in accordance with any one of Formulae **I** to **VII**, **IA** to **IC**, and **IIA** to **IIC**, and pharmaceutically acceptable salts and solvates thereof, wherein R^1 is a protected hydroxyl group (i.e., R^1 is a –O-PG, wherein PG stands for a suitable hydroxyl protecting group that is well known in the fields of organic/medicinal chemistry). Suitable hydroxyl protecting groups as PG are well known and include, for example, any suitable hydroxyl protecting group disclosed in Wuts, P. G. M. & Greene, T. W., *Greene's Protective Groups in Organic Synthesis*, 4rd Ed., pp. 16-430 (J. Wiley & Sons, 2007), herein incorporated by reference in its entirety. The term "hydroxyl protecting group" as used herein refers to a group that blocks (i.e., protects) the hydroxyl functionality while reactions are carried out on other functional groups or parts of the molecule. Those skilled in the art will be familiar with the selection, attachment, and cleavage of protecting groups and will appreciate that many different protective groups are

known in the art, the suitability of one protective group or another being dependent on the particular synthetic scheme planned. Suitable hydroxyl protecting groups are generally able to be selectively introduced and removed using mild reaction conditions that do not interfere with other portions of the subject compounds. These protecting groups can be introduced or removed at a convenient stage using methods known in the art. The chemical properties of such groups, methods for their introduction and removal are known in the art and can be found, for example, in Greene, T.W. and Wuts, P.G.M., above. Additional hydroxyl protecting groups can be found, for example, in U.S. Patent No. 5,952,495, U.S. Patent Appl. Pub. No. 2008/0312411, WO 2006/035195, and WO 98/02033, which are herein incorporated in their entireties. Suitable hydroxyl protecting groups include the methoxymethyl, tetrahydropyranyl, tert-butyl, allyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, acetyl, pivaloyl, benzoyl, benzyl (Bn), and p-methoxybenzyl group.

It will be apparent to a person of ordinary skill in the art in view of this disclosure that certain groups included in the definitions of –O-PG overlap with the other definitions for R^1, such as methoxy, tert-butoxy, etc., and, thus, certain Compounds of the Invention having R^1 groups that include groups acting as hydroxyl protecting groups can be pharmaceutically active as described herein.

In one embodiment, the hydroxyl protecting group PG is selected from the group consisting of alkyl, arylalkyl, heterocyclo, (heterocyclo)alkyl, acyl, silyl, and carbonate, any of which are optionally substituted.

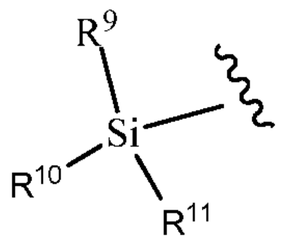
In another embodiment, the hydroxyl protecting group PG is an alkyl group, typically an optionally substituted C_{1-6} alkyl group, and suitably unsubstituted methyl or tert-butyl.

In another embodiment, the hydroxyl protecting group PG is an arylalkyl group. Suitable arylalkyl groups include, for example, an unsubstituted benzyl group, substituted benzyl groups, such as p-methoxybenzyl, and naphthylmethyl.

In another embodiment, the hydroxyl protecting group PG is a heterocyclo group, such as unsubstituted tetrahydropyranyl or optionally substituted tetrahydropyranyl.

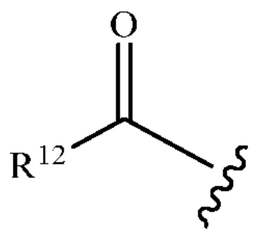
In another embodiment, the hydroxyl protecting group PG is a (heterocyclo)alkyl group. Suitable (heterocyclo)alkyl groups include, for example, 4-morpholinyl(C_{1-4})alkyl groups, such as, 2-(4-morpholinyl)ethyl.

In another embodiment, the hydroxyl protecting group PG is a silyl group. The term "silyl" as employed herein refers to the group having the following structure:



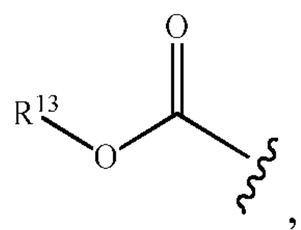
, wherein R^9, R^{10}, and R^{11} are each independently selected from the group consisting of alkyl, cycloalkyl, aryl, (cycloalkyl)alkyl, or arylalkyl, any of which is optionally substituted. In one embodiment, the silyl group is trimethyl silyl, tert-butyldimethyl silyl, tert-butyldiphenyl silyl, or tri-isopropyl silyl.

In another embodiment, the hydroxyl protecting group PG is an acyl group. The term "acyl" as employed herein refers to the following structure:



, wherein R^{12} is alkyl, cycloalkyl, aryl, (cycloalkyl)alkyl, or arylalkyl, any of which is optionally substituted. The acyl group can be, for example, C_{1-4} alkylcarbonyl (such as, for example, acetyl), arylcarbonyl (such as, for example, benzoyl), levulinoyl, or pivaloyl. In another embodiment, the acyl group is benzoyl.

A suitable hydroxyl protecting group can also be a carbonate group. The term "carbonate" as employed herein refers to the following structure:



, wherein R^{13} is alkyl, alkenyl, cycloalkyl, aryl, (cycloalkyl)alkyl, or arylalkyl, any of which is optionally substituted. Typically, R^{13} is C_{1-10} alkyl (e.g., 2,4-dimethylpent-3-yl), C_{2-6} alkenyl (e.g., ethenyl or prop-2-enyl, i.e., allyl), C_{3-12} cycloalkyl (e.g., adamantyl), phenyl, or benzyl.

Optional substituents attached to aryl, phenyl and heteroaryl rings each take the place of a hydrogen atom that would otherwise be present in any position on the aryl, phenyl or heteroaryl rings.

Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.

Useful alkyl groups are selected from straight-chain and branched-chain C_{1-10} alkyl groups. Typical C_{1-10} alkyl groups include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl, isopropyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, *iso*-pentyl, neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl,

1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl, among others. In one embodiment, useful alkyl groups are selected from straight chain C_{1-6} alkyl groups and branched chain C_{3-6} alkyl groups. Typical C_{1-6} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, pentyl, 3-pentyl, hexyl, among others. In one embodiment, useful alkyl groups are selected from straight chain C_{2-6} alkyl groups and branched chain C_{3-6} alkyl groups. Typical C_{2-6} alkyl groups include ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, pentyl, 3-pentyl, hexyl among others. In one embodiment, useful alkyl groups are selected from straight chain C_{1-4} alkyl groups and branched chain C_{3-4} alkyl groups. Typical C_{1-4} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, and *iso*-butyl.

Useful alkenyl groups are selected from straight-chain and branched-chain C_{2-6} alkenyl groups, preferably C_{2-4} alkenyl. Typical C_{2-6} alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl. Typical C_{2-4} alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec*-butenyl.

Useful alkynyl groups are selected from straight-chain and branched-chain C_{2-6} alkynyl groups, preferably C_{2-4} alkynyl. Typical C_{2-6} alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups. Typical C_{2-4} alkynyl groups include ethynyl, propynyl, butynyl, and 2-butynyl groups.

Useful haloalkyl groups include any of the above-mentioned C_{1-10} alkyl groups, preferably any of the above-mentioned C_{1-6} alkyl groups, and preferably any of the above-mentioned C_{1-4} alkyl groups, substituted by one or more fluorine, chlorine, bromine or iodine atoms (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups).

Useful hydroxyalkyl groups include any of the above-mentioned C_{1-10} alkyl groups, preferably any of the above-mentioned C_{1-6} alkyl groups, and preferably any of the above-mentioned C_{1-4} alkyl groups, substituted by one or more hydroxyl groups, such as monohydroxyalkyl and dihydroxyalkyl groups (e.g., hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, and hydroxyhexyl groups, and especially hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 2-hydroxyprop-2-yl, 3-hydroxypropyl, 2,3-dihydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl).

Useful cycloalkyl groups are selected from saturated cyclic hydrocarbon groups containing 1, 2, or 3 rings having from 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms (*i.e.*, C_3-

C_{12} cycloalkyl) or the number of carbons designated. In one embodiment, the cycloalkyl has one or two rings. In another embodiment, the cycloalkyl is a C_3-C_8 cycloalkyl. In another embodiment, the cycloalkyl is C_{3-7} cycloalkyl. In another embodiment, the cycloalkyl is C_{3-6} cycloalkyl. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, and adamantyl.

Useful cycloalkenyl groups are selected from partially unsaturated (*i.e.*, containing one or two double bonds) cyclic hydrocarbon groups containing 1, 2, or 3 rings having from 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms (*i.e.*, C_4-C_{12} cycloalkenyl) or the number of carbons designated. In one embodiment, the cycloalkenyl has one or two rings. In another embodiment, the cycloalkenyl is a C_3-C_8 cycloalkenyl. In another embodiment, the cycloalkenyl is C_{3-7} cycloalkenyl. In another embodiment, the cycloalkenyl is C_{3-6} cycloalkenyl. In one embodiment, the cycloalkenyl group contains one double bond. Exemplary cycloalkenyl groups containing one double bond include cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, and cyclodecenyl. In another embodiment, the cycloalkenyl group contains two double bonds. Preferably, the cycloalkenyl groups containing two double bonds have from five to twelve carbon atoms (*i.e.*, C_5-C_{12} cycloalkadienyl). Exemplary cycloalkenyl groups having two double bonds include cyclopentadienyl, cyclohexadienyl, cycloheptadienyl, cyclooctadienyl, cyclononadienyl, and cyclodecadienyl.

Useful alkoxy groups include oxygen substituted by one of the C_{1-10} alkyl groups mentioned above (e.g., methoxy, ethoxy, propoxy, iso-propoxy, butoxy, tert-butoxy, iso-butoxy, sec-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy), preferably by one of the C_{1-6} alkyl groups, and more preferably by one of the C_{1-4} alkyl groups.

Useful alkenyloxy groups include oxygen substituted by one of the C_{2-6} alkenyl groups, and preferably by one of the C_{2-4} alkenyl groups, mentioned above (e.g., ethenyloxy, propenyloxy, isopropenyloxy, butenyloxy, *sec*-butenyloxy, pentenyloxy, and hexenyloxy).

Useful alkynyloxy groups include oxygen substituted by one of the C_{2-6} alkynyl groups, preferably by one of the C_{2-4} alkynyl groups, mentioned above (e.g., ethynyloxy, propynyloxy, butynyloxy, 2-butynyloxy, pentynyloxy, and hexynyloxy).

Useful alkoxyalkyl groups include any of the above-mentioned C_{1-10} alkyl groups, and preferably any of the above-mentioned C_{1-6} alkyl groups, substituted with any of the above-mentioned alkoxy groups (e.g., methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, 2-ethoxyethyl, 3-ethoxypropyl, 4-ethoxybutyl, propoxymethyl,

iso-propoxymethyl, 2-propoxyethyl, 3-propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl).

Useful haloalkoxy groups include oxygen substituted by one of the C_{1-10} haloalkyl groups, and preferably one of the C_{1-6} haloalkyl groups, mentioned above (e.g., fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy).

Useful (cycloalkyl)alkyl groups include any of the above-mentioned C_{1-10} alkyl groups, and preferably any of the above-mentioned C_{1-6} alkyl groups, substituted with any of the above-mentioned cycloalkyl groups (e.g., (cyclopropyl)methyl, 2-(cyclopropyl)ethyl, (cyclopropyl)propyl, (cyclobutyl)methyl, (cyclopentyl)methyl, and (cyclohexyl)methyl).

Useful (cycloalkenyl)alkyl groups include any of the above-mentioned C_{1-10} alkyl groups, and preferably any of the above-mentioned C_{1-6} alkyl groups, substituted with any of the above-mentioned cycloalkenyl groups (e.g., (cyclobutenyl)methyl, 2-(cyclobutenyl)ethyl, (cyclobutenyl)propyl, (cyclopentenyl)methyl, (cyclohexenyl)methyl, and (cyclopentadienyl)methyl).

Useful aryl groups are C_{6-14} aryl, especially C_{6-10} aryl. Typical C_{6-14} aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups, more preferably phenyl, naphthyl, and biphenyl groups.

Useful aryloxy groups include oxygen substituted by one of the aryl groups mentioned above (e.g., phenoxy).

Useful arylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups, and preferably any of the above-mentioned C_{1-6} alkyl groups, substituted by any of the above-mentioned aryl groups (e.g., benzyl and phenethyl).

Useful arylalkenyl groups include any of the above-mentioned C_{2-6} alkenyl groups substituted by any of the above-mentioned aryl groups (e.g., phenylethenyl).

Useful arylalkynyl groups include any of the above-mentioned C_{2-6} alkynyl groups substituted by any of the above-mentioned aryl groups (e.g., phenylethynyl).

Useful aralkyloxy or arylalkoxy groups include oxygen substituted by one of the above-mentioned arylalkyl groups (e.g., benzyloxy).

Useful (arylalkoxy)carbonyl groups include a carbonyl group sunbstituted by any of the above-mentioned arylalkoxy groups (e.g., (benzyloxy)carbonyl).

The term "heteroaryl" or "heteroaromatic" as employed herein refers to groups having 5 to 14 ring atoms, with 6, 10 or 14 π electrons shared in a cyclic array, and containing carbon atoms and 1, 2, or 3 oxygen, nitrogen or sulfur heteroatoms, or 4 nitrogen atoms. In one embodiment, the heteroaryl group is a 5- to 10-membered heteroaryl group. Examples of

heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranyl, isobenzofuranyl, benzooxazonyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. Typical heteroaryl groups include thienyl (e.g., thien-2-yl and thien-3-yl), furyl (e.g., 2-furyl and 3-furyl), pyrrolyl (e.g., pyrrol-1-yl, 1H-pyrrol-2-yl and 1H-pyrrol-3-yl), imidazolyl (e.g., imidazol-1-yl, 1H-imidazol-2-yl and 1H-imidazol-4-yl), tetrazolyl (e.g., tetrazol-1-yl and tetrazol-5-yl), pyrazolyl (e.g., 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, and 1H-pyrazol-5-yl), pyridyl (e.g., pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (e.g., pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, and pyrimidin-5-yl), thiazolyl (e.g., thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (e.g., isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (e.g., oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl) and isoxazolyl (e.g., isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl). A 5-membered heteroaryl can contain up to 4 heteroatoms. A 6-membered heteroaryl can contain up to 3 heteroatoms. Each heteroatom is independently selected from nitrogen, oxygen and sulfur.

Useful heteroarylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned heteroaryl groups (e.g., (thien-2-yl)methyl, 2-furylmethyl, (pyrrol-1-yl)methyl, and 2-(1H-pyrrol-2-yl)ethyl).

Useful heteroarylalkoxy groups include oxygen substituted by one of the above-mentioned heteroaryl groups.

Useful (heteroarylalkoxy)carbonyl groups include a carbonyl group sunbstituted by any of the above-mentioned heteroarylalkoxy groups.

The terms "heterocyclic" and "heterocyclo" are used herein to mean saturated or partially unsaturated 3-7 membered monocyclic, or 7-10 membered bicyclic ring system, which consist of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on a carbon atom or on a nitrogen atom if the resulting compound is stable. In one embodiment, the 3- to 7-membered monocyclic heterocyclic ring is either a saturated, or unsaturated non-aromatic ring. A 3-membered

heterocyclo can contain up to 1 heteroatom, a 4-membered heterocyclo can contain up to 2 heteroatoms, a 5-membered heterocyclo can contain up to 4 heteroatoms, a 6-membered heterocyclo can contain up to 4 heteroatoms, and a 7-membered heterocyclo can contain up to 5 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The 3- to 7-membered heterocyclo can be attached via a nitrogen or carbon atom. A 7- to 10-membered bicyclic heterocyclo contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The 7- to 10-membered bicyclic heterocyclo can be attached via a nitrogen or carbon atom. Examples of the heterocyclic rings include, but are not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, oxazolidinyl, 2-oxooxazolidinyl, tetrahydrothienyl, imidazolidinyl, hexahydropyrimidinyl, and benzodiazepines.

Useful (heterocyclo)alkyl groups include any of the above-mentioned C_{1-10} alkyl groups, and preferably any of the above-mentioned C_{1-6} alkyl groups, substituted by any of the above-mentioned heterocyclic groups (e.g., (pyrrolidin-2-yl)methyl, (pyrrolidin-1-yl)methyl, (piperidin-1-yl)methyl, (morpholin-4-yl)methyl, (2-oxooxazolidin-4-yl)methyl, 2-(2-oxooxazolidin-4-yl)ethyl, (2-oxo-imidazolidin-1-yl)methyl, (2-oxo-imidazolidin-1-yl)ethyl, and (2-oxo-imidazolidin-1-yl)propyl).

As used herein, the term "amino" or "amino group" refers to $–NH_2$.

Useful aminoalkyl groups include any of the above-mentioned C_{1-10} alkyl groups, and preferably any of the above-mentioned C_{1-6} cycloalkyl groups, substituted with one or more amino group.

Useful alkylamino and dialkylamino groups are $—NHR^{14}$ and $—NR^{14}R^{15}$, respectively, wherein R^{14} and R^{15} are each independently selected from a C_{1-10} alkyl group.

As used herein, the term "aminocarbonyl" refers to $-C(=O)NH_2$.

Useful alkylcarbonyl groups include a carbonyl group, i.e., -C(=O)-, substituted by any of the above-mentioned C_{1-10} alkyl groups.

Useful alkoxycarbonyl groups include a carbonyl group substituted by any of the above-mentioned alkoxy groups (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, iso-propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, iso-butoxycarbonyl, sec-butoxycarbonyl, and pentyloxycarbonyl).

Useful arylcarbonyl groups include a carbonyl group substituted by any of the above-mentioned aryl groups (e.g., benzoyl).

Useful alkylcarbonyloxy or acyloxy groups include oxygen substituted by one of the above-mentioned alkylcarbonyl groups.

Useful alkylcarbonylamino or acylamino groups include any of the above-mentioned alkylcarbonyl groups attached to an amino nitrogen, such as methylcarbonylamino.

As used herein, the term "carboxamido" refers to a radical of formula $-C(=O)NR^{16}R^{17}$, wherein R^{16} and R^{17} are each independently hydrogen, optionally substituted C_{1-10} alkyl, or optionally substituted aryl. Exemplary carboxamido groups include $-CONH_2$, $-CON(H)CH_3$, $-CON(CH_3)_2$, and -CON(H)Ph.

Useful alkylaminocarbonyl and dialkylaminocarbonyl groups are any of the above-mentioned carboxamido groups, where R^{16} is H and R^{17} is C_{1-10} alkyl or where R^{16} and R^{17} are each independently selected from a C_{1-10} alkyl group, respectively.

As used herein, the term "sulfonamido" refers to a radical of formula $-SO_2NR^{18}R^{19}$, wherein R^{18} and R^{19} are each independently hydrogen, optionally substituted C_{1-10} alkyl, or optionally substituted aryl. Exemplary sulfonamido groups include $-SO_2NH_2$, $-SO_2N(H)CH_3$, and $-SO_2N(H)Ph$.

As used herein, the term "thiol" refers to -SH.

Useful mercaptoalkyl groups include any of the above-mentioned C_{1-10} alkyl groups, and preferably any of the above-mentioned C_{1-6} alkyl groups, substituted by a –SH group.

As used herein, the term "carboxy" refers to -COOH.

Useful carboxyalkyl groups include any of the above-mentioned C_{1-10} alkyl groups, and preferably any of the above-mentioned C_{1-6} alkyl groups, substituted by -COOH.

As used herein, the terms "hydroxyl" or "hydroxy" refer to –OH.

As used herein, the term "cyano" refers to –CN.

As used herein, the term “nitro” refers to $–NO_2$.

As used herein, the term "ureido" refers to $-NH-C(=O)-NH_2$.

As used herein, the term "azido" refers to $-N_3$.

The term "ambient temperature" as used herein means the temperature of the surroundings. The ambient temperature indoors is the same as room temperature, which is from about 20 °C to about 25 °C.

The term "about," as used herein in connection with a measured quantity, refers to the normal variations in that measured quantity, as expected by the skilled artisan making the measurement and exercising a level of care commensurate with the objective of measurement and the precision of the measuring equipment. Typically, the term "about" includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

As used herein, the term "optionally substituted" refers to a group that may be unsubstituted or substituted.

Optional substituents on optionally substituted groups, when not otherwise indicated, include one or more groups, typically 1, 2, or 3 groups, independently selected from the group consisting of halo, halo(C_{1-6})alkyl, aryl, heterocycle, cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, cycloalkyl(C_{1-6})alkyl, heterocyclo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, carboxy(C_{1-6})alkyl, alkoxy(C_{1-6})alkyl, nitro, amino, ureido, cyano, alkylcarbonylamino, hydroxy, thiol, alkylcarbonyloxy, aryloxy, ar(C_{1-6})alkyloxy, carboxamido, sulfonamido, azido, C_{1-6} alkoxy, halo(C_{1-6})alkoxy, carboxy, aminocarbonyl, (=O), and mercapto(C_{1-6})alkyl groups mentioned above. Preferred optional substituents include halo, halo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, hydroxy, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, halo(C_{1-6})alkoxy, and amino.

Compounds of the Invention encompass all the salts of the disclosed compounds of Formulae **I** to **VII**, **IA** to **IC**, and **IIA** to **IIC**. The invention includes all non-toxic pharmaceutically acceptable salts thereof of the disclosed compounds. Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts and basic salts. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, phosphate, sulphate and the like; organic acid salts such as citrate, lactate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, formate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; and amino acid salts such as arginate, asparginate, glutamate and the like.

Acid addition salts can be formed by mixing a solution of the particular compound of the present invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, or the like. Basic salts can be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

The Compounds of the Invention also encompass solvates of any of the disclosed compounds of Formulae **I-VII**, **IA** to **IC**, and **IIA** to **IIC**. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound of the present invention with a solvent molecule such as, e.g. a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to compound of the present invention is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. Compounds of the Invention may be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the invention includes both solvated and unsolvated forms of compounds of any of Formulae **I-VII**, **IA** to **IC**, and **IIA** to **IIC**.

One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al.*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.*: 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a compound of any one of Formulae **I-VII**, **IA** to **IC**, and **IIA** to **IIC** in a desired solvent (organic, water, or a mixture thereof) at temperatures above about 20 °C to about 25 °C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, e.g., filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

Compounds of the Invention can be isotopically-labeled (*i.e.*, radio-labeled). Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively, and preferably ^{3}H, ^{11}C, and ^{14}C. Isotopically-labeled Compounds of the Invention can be prepared by methods known in the art in view of this disclosure. For example, tritiated Compounds of the

Invention can be prepared by introducing tritium into the particular compound by catalytic dehalogenation with tritium. This method may include reacting a suitable halogen-substituted precursor of a Compound of the Invention with tritium gas in the presence of an appropriate catalyst such as Pd/C in the presence of a base. Other suitable methods for preparing tritiated compounds can be found in Filer, *Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A)*, Chapter 6 (1987). ^{14}C-labeled compounds can be prepared by employing starting materials having a ^{14}C carbon.

Isotopically labeled Compounds of the Invention, as well as the pharmaceutically acceptable salts and solvates thereof, can be used as radioligands to test for the binding of compounds to an opioid receptor. For example, a radio-labeled Compound of the Invention can be used to characterize specific binding of a test or candidate compound to the receptor. Binding assays utilizing such radio-labeled compounds can provide an *in vitro* alternative to animal testing for the evaluation of chemical structure-activity relationships. For example, the receptor assay may be performed at a fixed concentration of a radiolabeled Compound of the Invention and at increasing concentrations of a test compound in a competition assay. In a non-limiting embodiment, the present invention provides a method for screening a candidate compound for the ability to bind to an opioid receptor, comprising a) introducing a fixed concentration of a radio-labeled Compound of the Invention to the receptor under conditions that permit binding of the radio-labeled compound to the receptor to form a complex; b) titrating the complex with a candidate compound; and c) determining the binding of the candidate compound to said receptor.

The invention is also meant to encompass prodrugs of any of the disclosed compounds. As used herein, prodrugs are considered to be compounds with moieties that can be metabolized *in vivo*. In general, such prodrugs will be functional derivatives of compounds of any of the formulae delineated herein, which will be readily convertible *in vivo*, *e.g.*, by being metabolized, into the required compound of any of the formulae. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in, for example, *Design of Prodrugs*, H. Bundgaard ed., Elsevier (1985); "Drug and Enzyme Targeting, Part A," K. Widder *et al.* eds., Vol. 112 in *Methods in Enzymology*, Academic Press (1985); Bundgaard, "Design and Application of Prodrugs," Chapter 5 (pp. 113-191) in *A Textbook of Drug Design and Development*, P. Krogsgaard-Larsen and H. Bundgaard eds., Harwood Academic Publishers (1991); Bundgaard *et al.*, *Adv. Drug Delivery Revs. 8*:1-38 (1992); Bundgaard *et al.*, *J. Pharmaceut. Sci. 77*:285 (1988); and Kakeya *et al.*, *Chem. Pharm. Bull. 32*:692 (1984).

Examples of prodrugs and their use are well known in the art (*e.g.,* Berge *et al.* (1997) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19). Non-limiting examples of prodrugs include esters or amides of the Compounds of the Invention having carboxy, hydroxy or amino groups as a substituent, and these can be prepared by reacting such parent compounds with anhydrides such as succinic anhydride.

Further, some of the compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms, such as epimers. The invention is meant to encompass the uses of all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers may be separated according to methods known to those of ordinary skill in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The term "epimer" refers to diastereomers that have opposite configuration at only one of two or more tetrahedral streogenic centres present in the respective molecular entities.

The term "stereogenic center" is an atom, bearing groups such that an interchanging of any two groups leads to a stereoisomer.

The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

The terms "a" and "an" refer to one or more.

The term "treating" or "treatment" refers to administering a therapy in an amount, manner, or mode effective to improve a condition, symptom, or parameter associated with a disorder or to prevent progression of a disorder, to either a statistically significant degree or to a degree detectable to one skilled in the art. An effective amount, manner, or mode can vary depending on the subject and may be tailored to the patient.

Open terms such as "include," "including," "contain," "containing" and the like mean "comprising."

As used herein, compounds that bind to receptors and mimic the regulatory effects of endogenous ligands are defined as “agonists”. Compounds that bind to receptors and are only partly effective as agonists are defined as “partial agonists”. Compounds that bind to a receptor but produce no regulatory effect, but rather block the binding of ligands to the receptor are defined as “antagonists”. (Ross and Kenakin, “Ch. 2: Pharmacodynamics: Mechanisms of Drug Action and the Relationship Between Drug Concentration and Effect”, pp. 31-32, in *Goodman & Gilman’s the Pharmacological Basis of Therapeutics,* 10th Ed. (J.G. Hardman, L.E. Limbird and A. Goodman-Gilman eds., 2001)).

In certain embodiments, the Compound of the Invention is an agonist at one or more of the μ, δ and/or κ opioid receptors. In certain non-limiting embodiments, certain Compound of the Invention produces fewer side effects and/or less severe side effects than those currently available analgesic opioid compounds when administered at doses producing equivalent levels of analgesia and/or anti-hyperalgesia. In certain embodiments, the Compound of the Invention is an agonist at ORL-1 opioid receptor.

In certain embodiments, Compounds of the Invention can be used in combination with at least one other therapeutic agent. The other therapeutic agent can be, but is not limited to, a μ-opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, a Cox-II inhibitor, an anti-emetic, a β-adrenergic blocker, an anticonvulsant, an antidepressant, a Ca^{2+}-channel blocker, an anticancer agent, or a mixture thereof.

It is believed that certain Compounds of the Invention potently bind to the μ and/or κ and/or δ and/or ORL-1 opioid receptors. Thus, certain Compounds of the Invention can be modulators at the μ and/or κ and/or δ and/or ORL-1 opioid receptors. Therefore, certain Compounds of the Invention can be used/administered to treat, ameliorate, or prevent pain.

In some embodiments, certain Compounds of the Invention are antagonists of one or more opioid receptors. In another embodiment, certain Compounds of the Invention are antagonists of the μ and/or κ opioid receptors.

In some embodiments, certain Compounds of the Invention are partial agonists of one or more opioid receptors. In another embodiment, certain Compounds of the Invention are partial agonists of the μ and/or κ opioid receptors.

In another embodiment, certain Compounds of the Invention are agonists of one or more opioid receptors. In another embodiment, certain Compounds of the Invention are agonists of the μ and/or κ opioid receptors.

In some embodiments, Compounds of the Invention have both: (i) antagonist activity at the ORL-1 receptor; and (ii) agonist activity at one or more of the μ, δ and/or κ receptors. In other embodiments, Compounds of the Invention have both: (i) antagonist activity at the ORL-1 receptor; and (ii) agonist activity at the μ receptor. In another embodiment, Compounds of the Invention have both: (i) antagonist activity at the μ receptor; and (ii) agonist activity at the κ receptor. In certain embodiments, Compounds of the Invention have: (i) antagonist activity at the ORL-1 receptor; (ii) antagonist activity at the μ receptor; and (iii) agonist activity at the κ receptor. In other embodiments, Compounds of the Invention have: (i) antagonist activity at the μ receptor; (ii) agonist activity at the κ receptor; and (iii) antagonist activity at the δ receptor.

Compounds of the Invention that are antagonists of the μ-opioid receptor or agonists of κ-opioid receptor, or both, can be used/administered to treat or ameliorate constipation. Compounds of the Invention that are agonists of μ-opioid receptor can be used/administered to treat or ameliorate diarrhea.

The Compounds of the Invention can be used to treat or prevent acute, chronic pain (which includes but is not limited to, neuropathic pain, postoperative pain, and inflammatory pain), or surgical pain. Examples of pain that can be treated or prevented using a Compound of the Invention include, but are not limited to, cancer pain, neuropathic pain, labor pain, myocardial infarction pain, pancreatic pain, colic pain, post-operative pain, headache pain, muscle pain, arthritic pain, and pain associated with a periodontal disease, including gingivitis and periodontitis.

Acute pain includes, but is not limited to, perioperative pain, postoperative pain, post-traumatic pain, acute disease related pain, and pain related to diagnostic procedures, orthopedic manipulations, and myocardial infarction. Acute pain in the perioperative setting includes pain because of pre-existing disease, the surgical procedure, e.g., associated drains, chest or nasogastric tubes, or complications, or a combination of disease-related and procedure-related sources.

Chronic pain includes, but is not limited to, inflammatory pain, postoperative pain, cancer pain, osteoarthritis pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, and other forms of neuralgia, neuropathic, and idiopathic pain syndromes.

The Compounds of the Invention can be used to treat or prevent pain associated with inflammation or with an inflammatory disease in a patient. Such pain can arise where there is an inflammation of the body tissue which can be a local inflammatory response or a systemic inflammation. For example, a Compound of the Invention can be used to treat or prevent pain associated with inflammatory diseases including, but not limited to, organ transplant rejection; reoxygenation injury resulting from organ transplantation (see Grupp *et al.*, *J. Mol, Cell Cardiol.* 31:297-303 (1999)) including, but not limited to, transplantation of the heart, lung, liver, or kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel diseases, such as ileitis, ulcerative colitis, Barrett's syndrome, and Crohn's disease; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory disease of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory disease of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer 's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabeticorum), immune-complex vasculitis, and systemic lupus erythematosus (SLE); inflammatory disease of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and artherosclerosis; as well as various other diseases

that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer.

The Compounds of the Invention can also be used to treat or prevent pain associated with inflammatory disease that can, for example, be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, *e.g.*, shock associated with pro-inflammatory cytokines. Such shock can be induced, *e.g.*, by a chemotherapeutic agent that is administered as a treatment for cancer.

Further, the Compounds of the Invention can be used to treat or prevent pain associated with nerve injury (*i.e.*, neuropathic pain). Chronic neuropathic pain is a heterogenous disease state with an unclear etiology. In chronic pain, the pain can be mediated by multiple mechanisms. This type of pain generally arises from injury to the peripheral or central nervous tissue. The syndromes include pain associated with spinal cord injury, multiple sclerosis, post-herpetic neuralgia, trigeminal neuralgia, phantom pain, causalgia, and reflex sympathetic dystrophy and lower back pain. The chronic pain is different from acute pain in that chronic neuropathic pain patients suffer the abnormal pain sensations that can be described as spontaneous pain, continuous superficial burning and/or deep aching pain. The pain can be evoked by heat-, cold-, and mechano-hyperalgesia or by heat-, cold-, or mechano-allodynia.

Chronic neuropathic pain can be caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain can also be caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiences. Stroke (spinal or brain) and spinal cord injury can also induce neuropathic pain. Cancer-related neuropathic pain results from tumor growth compression of adjacent nerves, brain, or spinal cord. In addition, cancer treatments, including chemotherapy and radiation therapy, can cause nerve injury. Neuropathic pain includes but is not limited to pain caused by nerve injury such as, for example, the pain from which diabetics suffer.

In certain embodiments, the Compounds of the Invention can be used to treat or prevent pain associated with migraine including, but not limited to, migraine without aura ("common migraine"), migraine with aura ("classic migraine"), migraine without headache, basilar migraine, familial hemiplegic migraine, migrainous infarction, and migraine with prolonged aura.

In other embodiments, the Compounds of the Invention can also be used as an agent to treat or prevent withdrawal from alcohol addiction or drug addiction; as an agent to treat or prevent addictive disorders; as an agent to treat a pruritic condition; and in treating or ameliorating constipation and diarrhea.

The invention is also directed to the use of a compound represented by any of defined Formulae **I**-**VII**, **IA** to **IC**, and **IIA** to **IIC**, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disorder responsive to the modulation of one or more opioids receptors (e.g., any of the disorders listed above) in a patient suffering from said disorder.

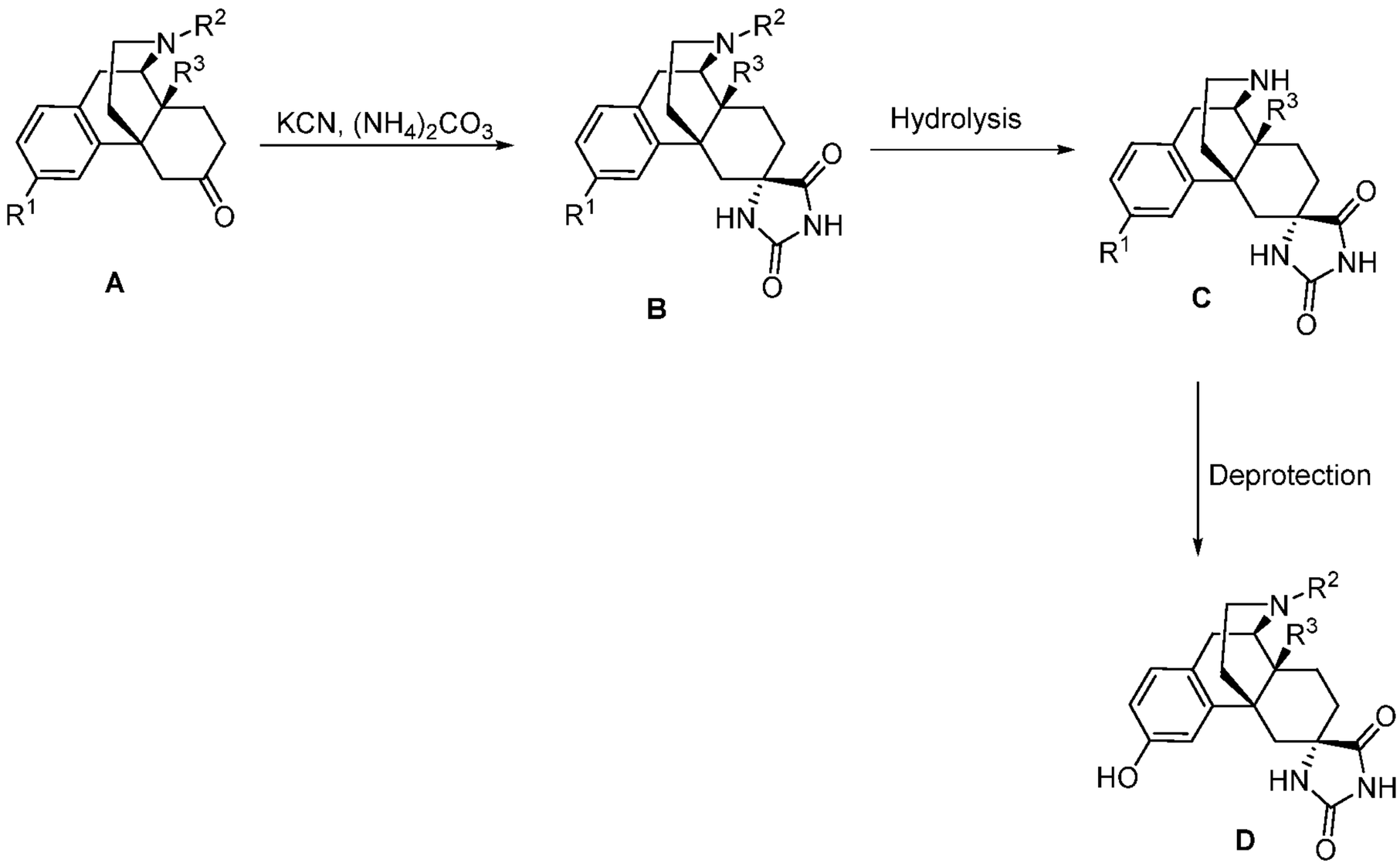
Still further, the invention provides a method of modulating, in particular activating, one or more opioid receptors in a patient in need thereof, said method comprising administering to the patient at least one compound represented by any one of Formulae **I** to **VII**, **IA** to **IC**, and **IIA** to **IIC**, provided *infra*., or a pharmaceutically acceptable salt or solvate thereof.

The invention is also directed to the use of a compound represented by any one of Formulae **I** to **VII**, **IA** to **IC**, and **IIA** to **IIC**, provided *infra*., or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament, in particular a medicament for modulating, in particular activating, one or more opioid receptors, in a patient in need thereof.

SYNTHESIS OF COMPOUNDS

The Compounds of the Invention can be prepared using methods known to those skilled in the art in view of this disclosure, or by illustrative methods shown in the schemes below. For example, the compounds of Formula **I** can be prepared using conventional organic synthesis in view of this disclosure, or by the illustrative methods shown in Schemes A-C below. Additional methods of synthesis are described and illustrated in the working examples set forth below.

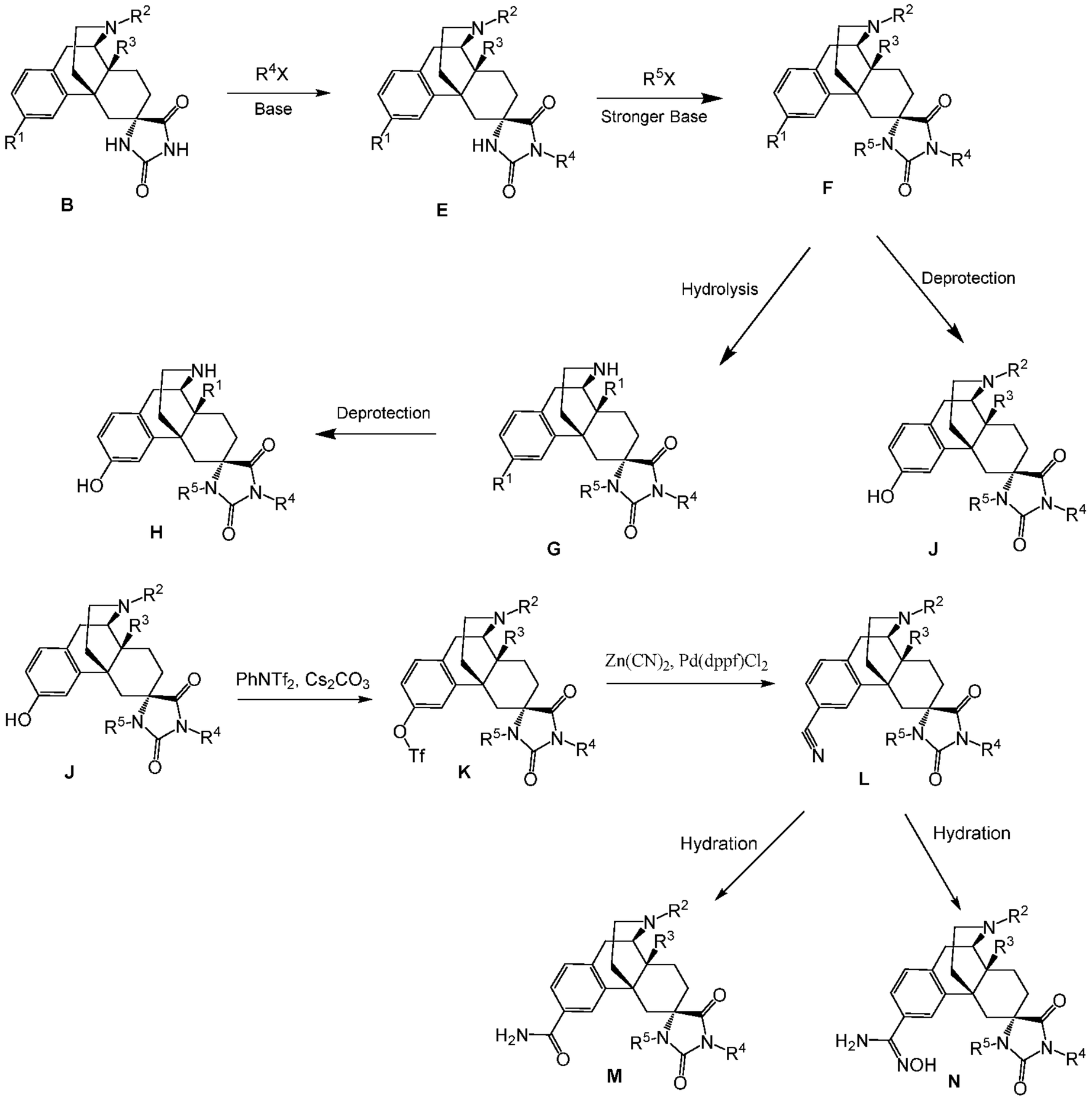
Scheme A



Compound **A** can be prepared in accordance with procedures in the literature, for example, those as described in Hupp C. D., *et al.*, *Tetrahedron Letters 51*:2359-2361 (2010) and Ida Y., *et al.*, *Bioorganic & Medical Chemistry 20*:949-961 (2012). Compound **A** is then treated with potassium cyanide, in the presence of ammonium carbonate, in a suitable solvent mixture, such as 1:1 EtOH/water, to give Compound **B**. In certain embodiments R^2 can be an amine protecting group which can be cleaved from Compound **B** using known literature methods (e.g. Greene, T.W. "Protective Groups in Organic Synthesis", J. Wiley & Sons, NY, 1981) to give Compound **C**.

In certain embodiments when R^1 is –O-PG, wherein PG is a suitable hydroxyl protecting group (such as methyl), the hydroxyl protecting group can be cleaved to yield Compound **D** by treating Compound **C** with a suitable reagent (such as boron tribromide (BBr_3)), in a suitable solvent (such as DCM) (e.g. Greene, T.W. "Protective Groups in Organic Synthesis", J. Wiley & Sons, NY, 1981).

Scheme B



Compound **B** is reacted with a suitable alkylating reagent (such as, cyclopropylmethyl bromide) in the presence of a suitable base (such as, potassium carbonate) in a suitable solvent, such as DMF, to give Compound **E**. Compound **E** is then reacted with a suitable alkylating reagent (such as, cyclopropylmethyl bromide) in the presence of a suitable stronger base (such as, sodium hydride) in a suitable solvent (such as, DMF) to give Compound **F**.

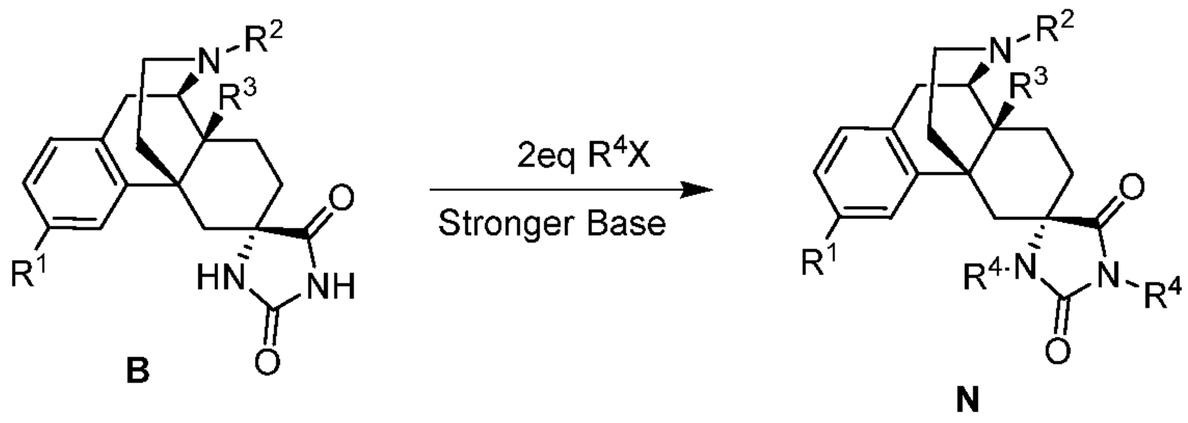
In certain embodiments, R^2 (in Compound **F**) is an amine protecting group which can be removed using known literature methods to give Compound **G**. In one embodiment when R^1 is –O-PG, wherein PG is a suitable hydroxyl protecting group (such as methyl), PG can be

cleaved to provide Compound **H** or Compound **J** by known methods including those described above in Scheme A.

Compound **J** is then reacted with a suitable triflating reagent (such as, aniline bis-triflamide) in the presence of a suitable base (such as, cesium carbonate) in a suitable solvent (such as, THF) to give Compound **K**. Thereafter, Compound **K** is reacted with zinc cyanide, in the presence of zinc powder and a suitable catalyst (such as, $Pd(dppf)Cl_2$) to give Compound **L**.

Compound **L** can be subsequently hydrated to Compound **M** when treated with a suitable catalyst (such as, hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethyl-phosphnito-kP]platinum (II)) in a suitable solvent mixture (such as, 1:1 EtOH/water), for example, in the way as described in Jiang X., *et al.*, *J. Org. Chem.*, 69:2327 (2004). Compound **L** can also be hydrated to Compound **N** by treatment with hydroxylamine in water in a suitable solvent (such as, EtOH).

Scheme C



Compound **B** is reacted with 2 eq. of a suitable alkylating reagent (such as, cyclopropylmethyl bromide) in the presence of a suitable stronger base (such as, sodium hydride) in a suitable solvent (such as, DMF) to give Compound **N**.

IN VITRO ASSAY PROTOCOLS

μ-Opioid Receptor Binding Assay Procedures: Radioligand dose-displacement binding assays for μ-opioid receptors used 0.3 nM [^{3}H]-diprenorphine (Perkin Elmer, Shelton, CT), with 5 mg membrane protein/well in a final volume of 500 μl binding buffer (10 mM $MgCl_2$, 1 mM EDTA, 5% DMSO, 50 mM HEPES, pH 7.4). Reactions were carried out in the absence or presence of increasing concentrations of unlabeled naloxone. All reactions were conducted in 96-deep well polypropylene plates for 2 hours at room temperature. Binding reactions were terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Perkin Elmer, Shelton, CT), presoaked in 0.5% polyethylenimine using a

96-well tissue harvester (Perkin Elmer, Shelton, CT) followed by performing three filtration washes with 500 µl of ice-cold binding buffer. Filter plates were subsequently dried at 50 °C for 2-3 hours. BetaScint scintillation cocktail (Perkin Elmer, Shelton, CT) was added (50 µl/well), and plates were counted using a Packard Top-Count for 1 min/well. The data were analyzed using the one-site competition curve fitting functions in GraphPad PRISM™ v. 3.0 or higher (San Diego, Calif.), or an in-house function for one-site competition curve-fitting.

µ-Opioid Receptor Binding Data: Generally, the lower the K_i value, the more effective Compounds of the Invention will be at treating or preventing pain or another Condition. In certain embodiments, the Compounds of the Invention exhibit a K_i (nM) of about 10,000 or less for binding to µ-opioid receptors. In other embodiments, the Compounds of the Invention exhibit a K_i (nM) of about 1000 or less for binding to µ-opioid receptors. In one embodiment, the Compounds of the Invention exhibit a K_i (nM) of about 300 or less for binding to µ-opioid receptors. In another embodiment, the Compounds of the Invention exhibit a K_i (nM) of about 100 or less for binding to µ-opioid receptors. In another embodiment, the Compounds of the Invention exhibit a K_i (nM) of about 10 or less for binding to µ-opioid receptors. In still another embodiment, the Compounds of the Invention exhibit a K_i (nM) of about 1 or less for binding to µ-opioid receptors. In still another embodiment, Compounds of the Invention exhibit a K_i (nM) of about 0.1 or less for binding to µ-opioid receptors.

µ-Opioid Receptor Functional Assay Procedures: [^{35}S]GTPγS functional assays were conducted using freshly thawed µ-receptor membranes (Perkin Elmer, Shelton, CT). Assay reactions were prepared by sequentially adding the following reagents to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice (final concentrations indicated): membrane protein (0.026 mg/mL), saponin (10 mg/mL), GDP (3 mM) and [^{35}S]GTPγS (0.20 nM; Perkin Elmer, Shelton, CT). The prepared membrane solution (190 µl/well) was transferred to 96-shallow well polypropylene plates containing 10 µl of 20x concentrated stock solutions of the agonist [D-Ala^2, N-methyl-Phe^4 Gly-ol^5]-enkephalin (DAMGO) prepared in dimethyl sulfoxide (DMSO). Plates were incubated for 30 min at about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Perkin Elmer, Shelton, CT) using a 96-well tissue harvester (Perkin Elmer, Shelton, CT) followed by three filtration washes with 200 µl of ice-cold wash buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. BetaScint scintillation cocktail (Perkin Elmer, Shelton, CT) was added (50 µl/well) and plates were counted using a Packard Top-Count for 1 min/well. Data were

analyzed using the sigmoidal dose-response curve fitting functions in GraphPad PRISM v. 3.0, or an in-house function for non-linear, sigmoidal dose-response curve-fitting.

μ-Opioid Receptor Functional Data: μ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a μ-opioid receptor. Typically, Compounds of the Invention exhibit a μ GTP EC_{50} (nM) of about 5000 or less. In certain embodiments, the Compounds of the Invention exhibit a μ GTP EC_{50} (nM) of about 2000 or less; or about 1000 or less; or about 100 or less; or about 10 or less; or about 1 or less; or about 0.1 or less.

μ GTP E_{max} (%) is the maximal effect elicited by a compound relative to the effect elicited by DAMGO, a standard μ agonist. Generally, the μ GTP E_{max} (%) value measures the efficacy of a compound to treat or prevent pain or other Conditions. Typically, Compounds of the Invention exhibit a μ GTP E_{max} (%) of greater than about 10%; or greater than about 20%. In certain embodiments, Compounds of the Invention exhibit a μ GTP Emax (%) of greater than about 50%; or greater than about 65%; or greater than about 75%; or greater than about 85%; or greater than about 100%.

κ-Opioid Receptor Binding Assay Procedures: Membranes from recombinant HEK-293 cells expressing the human kappa opioid receptor (κ) (cloned in house) were prepared by lysing cells in ice cold hypotonic buffer (2.5 mM $MgCl_2$, 50 mM HEPES, pH 7.4) (10 mL/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes were collected by centrifugation at 30,000 x g for 15 min at 4°C and pellets were resuspended in hypotonic buffer to a final concentration of 1-3 mg/mL. Protein concentrations were determined using the BioRad protein assay reagent with bovine serum albumen as standard. Aliquots of κ receptor membranes were stored at –80 °C.

Radioligand dose displacement assays used 0.4 nM [^{3}H]-U69,593 (GE Healthcare, Piscataway, NJ; 40 Ci/mmole) with 15 μg membrane protein (recombinant κ opioid receptor expressed in HEK 293 cells; in-house prep) in a final volume of 200 μl binding buffer (5% DMSO, 50 mM Trizma base, pH 7.4). Non-specific binding was determined in the presence of 10 μM unlabeled naloxone or U69,593. All reactions were performed in 96-well polypropylene plates for 1 hour at a temperature of about 25°C. Binding reactions were terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Perkin Elmer, Shelton, CT) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Perkin Elmer, Shelton, CT) followed by five filtration washes with 200 μl ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty

μl/well scintillation cocktail (Perkin Elmer, Shelton, CT) was added and plates were counted in a Packard Top-Count for 1 min/well.

κ-Opioid Receptor Binding Data: In certain embodiments, Compounds of the Invention exhibit a K_i (nM) for κ receptors of about 10,000 or more (which, for purposes of this invention, is interpreted as having no binding to the κ receptors). Certain Compounds of the Invention exhibit a K_i (nM) of about 20,000 or less for κ receptors. In certain embodiments, Compounds of the Invention exhibit a K_i (nM) of about 10,000 or less; or about 5000 or less; or about 1000 or less; or about 500 or less; or about 450 or less; or about 350 or less; or about 200 or less; or about 100 or less; or about 50 or less; or about 10 or less; or about 1 or less; or about 0.1 or less for κ receptors.

κ-Opioid Receptor Functional Assay Procedures: Functional [^{35}S]GTPγS binding assays were conducted as follows. κ opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.026 μg/μl κ membrane protein (in-house), 10 μg/mL saponin, 3 μM GDP and 0.20 nM [^{35}S]GTPγS to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 μl/well) was transferred to 96-shallow well polypropylene plates containing 10 μl of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30 min at a temperature of about 25°C with shaking. Reactions were terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Perkin Elmer, Shelton, CT) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200 μl ice-cold binding buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 2-3 hours. Fifty μl/well scintillation cocktail (Perkin Elmer, Shelton, CT) was added and plates were counted in a Packard Top-Count for 1 min/well.

κ-Opioid Receptor Functional Data: κ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a κ receptor. Certain Compounds of the Invention exhibit a κ GTP EC_{50} (nM) of about 20,000 or less to stimulate κ opioid receptor function. In certain embodiments, Compounds of the Invention exhibit a κ GTP EC_{50} (nM) of about 10,000 or less; or about 5000 or less; or about 2000 or less; or about 1500 or less; or about 1000 or less; or about 600 or less; or about 100 or less; or about 50 or less; or about 25 or less; or about 10 or less; or about 1 or less; or about 0.1 or less.

κ GTP E_{max} (%) is the maximal effect elicited by a compound relative to the effect elicited by U69,593. Certain Compounds of the Invention exhibit a κ GTP E_{max} (%) of greater than about 1%; or greater than about 5%; or greater than about10%; or greater than about 20%. In certain embodiments, the Compounds of the Invention exhibit a κ GTP E_{max}

(%) of greater than about 50%; or greater than about 75%; or greater than about 90%; or greater than about 100%.

δ-Opioid Receptor Binding Assay Procedures: δ-Opioid Receptor Binding Assay Procedures were conducted as follows. Radioligand dose-displacement assays used 0.3 nM [^{3}H]-Naltrindole (Perkin Elmer, Shelton, CT; 33.0 Ci/mmole) with 5 µg membrane protein (Perkin Elmer, Shelton, CT) in a final volume of 500 µl binding buffer (5 mM $MgCl_2$, 5% DMSO, 50 mM Trizma base, pH 7.4). Non-specific binding was determined in the presence of 25 µM unlabeled naloxone. All reactions were performed in 96-deep well polypropylene plates for 1 hour at a temperature of about 25°C. Binding reactions were terminated by rapid filtration onto 96-well Unifilter GF/C filter plates (Perkin Elmer, Shelton, CT) presoaked in 0.5% polyethylenimine (Sigma). Harvesting was performed using a 96-well tissue harvester (Perkin Elmer, Shelton, CT) followed by five filtration washes with 500 µl ice-cold binding buffer. Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty µl/well scintillation cocktail (Perkin Elmer, Shelton, CT) was added and plates were counted in a Packard Top-Count for 1 min/well.

δ-Opioid Receptor Binding Data: In certain embodiments, Compounds of the Invention exhibit a K_i (nM) for δ receptors of about 10,000 or more (which, for the purposes of this invention, is interpreted as having no binding to the δ receptors). Certain Compounds of the Invention exhibit a K_i (nM) of about 20,000 or less for δ receptors. In one embodiment, the Compounds of the Invention exhibit a Ki (nM) of about 10,000 or less; or of about 9000 or less for δ receptors. In another embodiment, Compounds of the Invention exhibit a K_i (nM) of about 7500 or less; or of about 6500 or less; or of about 5000 or less; or of about 3000 or less; or of about 2500 or less for δ receptors. In another embodiment, the Compounds of the Invention exhibit a K_i (nM) of about 1000 or less; or of about 500 or less; or of about 350 or less; or of about 250 or less; or of about 100 or less; or of about 10 or less for δ receptors.

δ-Opioid Receptor Functional Assay Procedures: Functional [^{35}S]GTPγS binding assays were conducted as follows. δ opioid receptor membrane solution was prepared by sequentially adding final concentrations of 0.026 µg/µl δ membrane protein (Perkin Elmer, Shelton, CT), 10 µg/mL saponin, 3 µM GDP and 0.20 nM [^{35}S]GTPγS to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 µl/well) was transferred to 96-shallow well polypropylene plates containing 10 µl of 20x concentrated stock solutions of agonist prepared in DMSO. Plates were incubated for 30 min at a temperature of about 25°C with shaking. Reactions were terminated by rapid

filtration onto 96-well Unifilter GF/B filter plates (Perkin Elmer, Shelton, CT) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200 µl ice-cold binding buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates were subsequently dried at 50°C for 1-2 hours. Fifty µl/well scintillation cocktail (Perkin Elmer, Shelton, CT) was added and plates were counted in a Packard Top-count for 1 min/well.

δ-Opioid Receptor Functional Data: δ GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at a δ receptor. Certain Compounds of the Invention exhibit a δ GTP EC_{50} (nM) of about 20,000 or less; or about 10,000 or less. In certain embodiments, Compounds of the Invention exhibit a δ GTP EC_{50} (nM) of about 3500 or less; or of about 1000 or less; or of about 500 or less; or of about 100 or less; or of about 90 or less; or of about 50 or less; or of about 25 or less; or of about 10 or less.

δ GTP E_{max} (%) is the maximal effect elicited by a compound relative to the effect elicited by met-enkephalin. Certain Compounds of the Invention exhibit a δ GTP E_{max} (%) of greater than about 1%; or of greater than about 5%; or of greater than about 10%. In one embodiment, Compounds of the Invention exhibit a δ GTP E_{max} (%) of greater than about 30%. In another embodiment, Compounds of the Invention exhibit a δ GTP E_{max} (%) of greater than about 50%; or of greater than about 75%; or of greater than about 90%. In another embodiment, Compounds of the Invention exhibit a δ GTP E_{max} (%) of greater than about 100%.

ORL-1 Receptor Binding Assay Procedure: Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like receptor (ORL-1) (Perkin Elmer, Shelton, CT) can be prepared by lysing cells in ice-cold hypotonic buffer (2.5 mM $MgCl_2$, 50 mM HEPES, pH 7.4) (10 ml/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes are collected by centrifugation at 30,000 x g for 15 min at 4°C and pellets resuspended in hypotonic buffer to a final concentration of 1-3 mg/ml. Protein concentrations are determined using the BioRad protein assay reagent with bovine serum albumen as standard. Aliquots of the ORL-1 receptor membranes are stored at -80°C.

Radioligand binding assays (screening and dose-displacement) use 0.1 nM [^{3}H]-nociceptin (Perkin Elmer, Shelton, CT; 87.7 Ci/mmole) with 12 µg membrane protein in a final volume of 500 µl binding buffer (10 mM $MgCl_2$, 1 mM EDTA, 5% DMSO, 50 mM HEPES, pH 7.4). Non-specific binding is determined in the presence of 10 nM unlabeled nociceptin (American Peptide Company). All reactions are performed in 96-deep well polypropylene plates for 1 h at room temperature. Binding reactions are terminated by rapid

filtration onto 96-well Unifilter GF/C filter plates (Perkin Elmer, Shelton, CT) presoaked in 0.5% polyethylenimine (Sigma). Harvesting is performed using a 96-well tissue harvester (Perkin Elmer, Shelton, CT) followed by three filtration washes with 500 µl ice-cold binding buffer. Filter plates are subsequently dried at 50°C for 2-3 hours. Fifty µl/well scintillation cocktail (Perkin Elmer, Shelton, CT) is added and plates are counted in a Packard Top-Count for 1 min/well. The data from screening and dose-displacement experiments are analyzed using Microsoft Excel and the curve fitting functions in GraphPad PRISM™, v. 3.0 or higher, respectively, or an in-house function for one-site competition curve-fitting.

ORL-1 Receptor Binding Data: Certain Compounds of the Invention can have a K_i (nM) of about 5000 or less. In one embodiment, certain Compounds of the Invention can have a K_i (nM) of about 1000 or less. In one embodiment, certain Compounds of the Invention can have a K_i (nM) of about 500 or less. In other embodiments, the Compounds of the Invention can have a K_i (nM) of about 300 or less; or of about 100 or less; or of about 50 or less; or of about 20 or less. In yet other embodiments, the Compounds of the Invention can have a K_i (nM) of about 10 or less; or of about 1 or less; or of about 0.1 or less.

ORL-1 Receptor Functional Assay Procedure: Membranes from recombinant HEK-293 cells expressing the human opioid receptor-like (ORL-1) (Perkin Elmer, Shelton, CT) can be prepared by lysing cells in ice-cold hypotonic buffer (2.5 mM Mg Cl_2, 50 mM HEPES, pH 7.4) (10 ml/10 cm dish) followed by homogenization with a tissue grinder/Teflon pestle. Membranes are collected by centrifugation at 30,000 x g for 15 min at 4°C, and pellets resuspended in hypotonic buffer to a final concentration of 1-3 mg/ml. Protein concentrations are determined using the BioRad protein assay reagent with bovine serum albumen as standard. Aliquots of the ORL-1 receptor membranes are stored at -80°C.

Functional [^{35}S]GTPγS binding assays are conducted as follows. ORL-1 membrane solution is prepared by sequentially adding final concentrations of 0.026 µg/µl ORL-1 membrane protein, 10 µg/ml saponin, 3 µM GDP and 0.20 nM [^{35}S]GTPγS to binding buffer (100 mM NaCl, 10 mM $MgCl_2$, 20 mM HEPES, pH 7.4) on ice. The prepared membrane solution (190 µl/well) is transferred to 96-shallow well polypropylene plates containing 10 µl of 20x concentrated stock solutions of agonist/nociceptin prepared in DMSO. Plates are incubated for 30 min at room temperature with shaking. Reactions are terminated by rapid filtration onto 96-well Unifilter GF/B filter plates (Perkin Elmer, Shelton, CT) using a 96-well tissue harvester (Packard) and followed by three filtration washes with 200 µl ice-cold binding buffer (10 mM NaH_2PO_4, 10 mM Na_2HPO_4, pH 7.4). Filter plates are subsequently dried at 50°C for 2-3 hours. Fifty µl/well scintillation cocktail (Perkin Elmer, Shelton, CT) is

added and plates are counted in a Packard Top-Count for 1 min/well. Data are analyzed using the sigmoidal dose-response curve fitting functions in GraphPad PRISM v. 3.0 or higher, or an in-house function for non-linear, sigmoidal dose-response curve-fitting.

ORL-1 Receptor Functional Data: ORL-1 GTP EC_{50} is the concentration of a compound providing 50% of the maximal response for the compound at an ORL-1 receptor. In certain embodiments, the Compounds of the Invention that have a high binding affinity (i.e. low K_i value) can have an ORL-1 GTP EC_{50} (nM) of greater than about 10,000 (i.e. will not stimulate at therapeutic concentrations) In certain embodiments Compounds of the Invention can have an ORL-1 GTP EC_{50} (nM) of about 20,000 or less. In one embodiment, the Compounds of the Invention can have an ORL-1 GTP EC_{50} (nM) of about 10,000 or less; or of about 5000 or less; or of about 1000 or less. In still other embodiments, the Compounds of the Invention can have an ORL-1 GTP EC_{50} (nM) of about 100 or less; or of about 10 or less; or of about 1 or less; or of about 0.1 or less.

ORL-1 GTP E_{max} % is the maximal effect elicited by a compound relative to the effect elicited by nociceptin, a standard ORL-1 agonist. In certain embodiments, Compounds of the Invention can have an ORL-1 GTP E_{max} of less than 10% (which, for the purposes of this invention, is interpreted as having antagonist activity at ORL-1 receptors). Certain Compounds of the Invention can have an ORL-1 GTP E_{max} (%) of greater than 1%; or of greater than 5%; or of greater than 10%. In other embodiments, Compounds of the Invention can have an ORL-1 GTP E_{max} of greater than 20%; or of greater than 50%; or of greater than 75%; or of greater than 88%; or of greater than 100%.

IN VIVO ASSAYS FOR PAIN

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a Compound of the Invention when food is removed for about 16 hours before dosing. A control group acts as a comparison to rats treated with a Compound of the Invention. The control group is administered the carrier for the Compound of the Invention. The volume of carrier administered to the control group is the same as the volume of carrier and Compound of the Invention administered to the test group.

Acute Pain: To assess the actions of a Compound of the Invention for the treatment or prevention of acute pain, the rat tail flick can be used. Rats are gently restrained by hand and the tail exposed to a focused beam of radiant heat at a point 5 cm from the tip using a tail

flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 20 seconds are removed from the tail flick unit and assigned a withdrawal latency of 20 seconds. Tail flick latencies are measured immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Compound of the Invention. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 20 seconds, is calculated as follows:

$$\% \text{ MPE} = \frac{[\text{ (post administration latency) - (pre-administration latency) }]}{(20 \text{ s - pre-administration latency})} \text{ x } 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther. 72*:74-79 (1941).

To assess the actions of a Compound of the Invention for the treatment or prevention of acute pain, the rat hot plate test can also be used. Rats are tested using a hot plate apparatus consisting of a clear plexiglass cylinder with a heated metal floor maintained at a temperature of 48-52 °C (Model 7280, commercially available from Ugo Basile of Italy). A rat is placed into the cylinder on the hot plate apparatus for a maximum duration of 30 s, or until it exhibits a nocifensive behavior (behavioral endpoint), at which time it is removed from the hot plate, and the response latency recorded. Hot plate latencies are measured immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Compound of the Invention. The nocifensive behavioral endpoint is defined as any of the following: 1) paw withdrawal, either as a sustained lift or with shaking or licking; 2) alternating foot lifting; 3) excape or attempted escape from the testing device; or 4) vocalization. Data are expressed as response latency(s) and the percentage of the maximal possible effect is calculated as described above for the tail flick test. The hot plate test is described in G. Woolfe and A.D. MacDonald, *J. Pharmacol. Exp. Ther. 80*:300-307 (1944).

Inflammatory Pain: To assess the actions of a Compound of the Invention for the treatment or prevention of inflammatory pain, the Freund's complete adjuvant ("FCA") model of inflammatory pain can be used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of Capsaicin-sensitive Neurones in Hyperalgesia and Enhanced Opioid Antinociception in Inflammation," *Naunyn-Schmiedeberg's Archives of*

Pharmacol. 342:666-670 (1990)). The left hind paw of each animal is administered a 50 μL intraplantar injection of 50% FCA. Prior to injection of FCA (baseline) and 24 hour post injection, the animal is assessed for response to noxious mechanical stimuli by determining the PWT, as described below. Rats are then administered a single injection of 1, 3, or 10 mg/kg of either a Compound of the Invention; 30mg/kg of a control drug selected from Celebrex, indomethacin or naproxen; or carrier. Responses to noxious mechanical stimuli are determined 1, 3, 5 and 24 hours post administration. Percentage reversal of hyperalgesia for each animal is defined as:

$$\% \text{ Reversal} = \frac{[\text{(post administration PWT)} - \text{(pre-administration PWT)}]}{[\text{(baseline PWT)} - \text{(pre-administration PWT)}]} \times 100$$

Neuropathic Pain: To assess the actions of a Compound of the Invention for the treatment or prevention of neuropathic pain, either the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, "A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury," *Pain 43*:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve exposed at high thigh level through a small incision and is carefully cleared of surrounding connective tissues at a site near the trocanther just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal $^1/_3$ to ½ of the nerve thickness is held within the ligature. The wound is closed with a single muscle suture (4-0 nylon (Vicryl)) and vetbond tissue glue. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animal is assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after drug administration. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ Reversal} = \frac{[\text{(post administration PWT)} - \text{(pre-administration PWT)}]}{[\text{(baseline PWT)} - \text{(pre-administration PWT)}]} \times 100$$

In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anaesthesia, a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L_4 - S_2 levels. The L_6 transverse process is carefully removed with a pair of small rongeurs to identify visually the L_4 - L_6 spinal nerves. The left L_5 (or L_5 and L_6) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a subcutaneous (*s.c.*) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being administered a Compound of the Invention. The animal can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain 50(3)*:355-363 (1992).

Response to Mechanical Stimuli as an Assessment of Mechanical Hyperalgesia: The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacol. Biochem. and Behavior 31*:451-455 (1988). The rat is gently restrained, its hindpaw is placed on a small round platform, and punctate pressure is applied to the dorsal surface of the hindpaw in a graded manner. The maximum weight that is applied to the hind paw is set at

250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point and either only the affected (ipsilateral; same side as the injury) rear paw is tested, or both the ipsilateral and contralateral (non-injured; opposite to the injury) rear paw are tested.

Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia: The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies to a noxious thermal stimulus applied to the plantar surface of the hindpaw are determined using a plantar test apparatus (commercially available from Ugo Basile of Italy) following the technique described by K. Hargreaves *et al.*, "A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," *Pain 32(1)*:77-88 (1988). The maximum exposure time is set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source is taken as the end point. Three latencies are determined at each time point and averaged. Either only the affected (ipsilateral) paw is tested, or both the ipsilateral and contralateral (non-injured) paw are tested.

Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear, plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at least 15 minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the affected (ipsilateral) foot of each rat. The series of von Frey monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

Assessment of Respiratory Depression: To assess respiratory depression, rats can be prepared by implanting a femoral artery cannula via which blood samples are taken. Blood samples are taken prior to drug administration, then 1, 3, 5 and 24 hours post-treatment. Blood samples are processed using an arterial blood gas analyzer (*e.g.*, IDEXX VetStat with Respiratory/Blood Gas test cartridges). Comparable devices are a standard tool for blood gas analysis (*e.g.*, D. Torbati *et al.*, *Intensive Care Med. (26)*: 585-591 (2000).

Assessment of Gastric Motility: Animals are treated with vehicle, reference compound or test article by oral gavage at a volume of 10 mL/kg. At one hour post-dose, all animals are treated with charcoal meal solution (5% non-activated charcoal powder in a solution of 1 % carboxymethylcellulose in water) at a volume of 10 mL/kg. At two hours post-dose (one hour post-charcoal), animals are sacrificed by carbon dioxide inhalation or

isoflurane overdose and the transit of charcoal meal identified. The stomach and small intestine are removed carefully and each placed on a saline-soaked absorbent surface. The distance between the pylorus and the furthest progression of charcoal meal is measured and compared to the distance between the pylorus and the ileocecal junction. The charcoal meal transit is expressed as a percentage of small intestinal length traveled.

PHARMACEUTICAL COMPOSITIONS

Due to their activity, the Compounds of the Invention are advantageously useful in human and veterinary medicine. As described above, the Compounds of the Invention are useful for treating or preventing a Condition in a patient in need thereof. The Compounds of the Invention can be administered to any patient requiring modulation of the opioid receptors. The term "patient" as used herein refers to any animal that may experience the beneficial effects of a Compound of the Invention. Foremost such animals are mammals, *e.g.*, humans and companion animals, although the invention is not intended to be so limited.

When administered to a patient, a Compound of the Invention can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. A Compound of the Invention can be administered by any appropriate route, as determined by the medical practitioner. Methods of administration may include intradermal, intramuscular, intraperitoneal, parenteral, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, buccal, intracerebral, intravaginal, transdermal, transmucosal, rectal, by inhalation, or topical (particularly to the ears, nose, eyes, or skin). Delivery can be either local or systemic. In certain embodiments, administration will result in the release of a Compound of the Invention into the bloodstream.

Pharmaceutical compositions of the invention can take the form of solutions, suspensions, emulsions, tablets, pills, pellets, powders, multi-particulates, capsules, capsules containing liquids, capsules containing powders, capsules containing multi-particulates, lozenges, sustained-release formulations, suppositories, transdermal patches, transmucosal films, sub-lingual tablets or tabs, aerosols, sprays, or any other form suitable for use. In one embodiment, the composition is in the form of a tablet. In another embodiment, the composition is in the form of a capsule (*see, e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

Pharmaceutical compositions of the invention may comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the patient. Such a pharmaceutical excipient can be a diluent, suspending agent, solubilizer, binder, disintegrant, preservative, coloring agent, lubricant, and the like. The pharmaceutical excipient can be a liquid, such as, water or an oil including those of petroleum, animal, vegetable, or synthetic origin (such as, peanut oil, soybean oil, mineral oil, sesame oil, and the like). The pharmaceutical excipient can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipient is sterile when administered to a patient. Water is a particularly useful excipient when a Compound of the Invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The invention compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Specific examples of pharmaceutically acceptable carriers and excipients that can be used to formulate oral dosage forms are described in the *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association (1986).

In certain embodiments, the Compounds of the Invention are formulated for oral administration. A Compound of the Invention to be orally delivered can be in the form of tablets, capsules, gelcaps, caplets, lozenges, aqueous or oily solutions, suspensions, granules, powders, emulsions, syrups, or elixirs, for example. When a Compound of the Invention is incorporated into oral tablets, such tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, multiply compressed or multiply layered.

An orally administered Compound of the Invention can contain one or more additional agents such as, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, and stabilizers, to provide stable, pharmaceutically palatable dosage forms. Techniques and compositions for making solid oral dosage forms are described in *Pharmaceutical Dosage Forms: Tablets* (Lieberman, Lachman and Schwartz, eds., 2nd ed.) published by Marcel Dekker, Inc. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in

Remington's Pharmaceutical Sciences 1553-1593 (Arthur Osol, ed., 16th ed., Mack Publishing, Easton, PA 1980). Liquid oral dosage forms include aqueous and nonaqueous solutions, emulsions, suspensions, and solutions and/or suspensions reconstituted from non-effervescent granules, optionally containing one or more suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, coloring agents, flavoring agents, and the like. Techniques and compositions for making liquid oral dosage forms are described in *Pharmaceutical Dosage Forms: Disperse Systems*, (Lieberman, Rieger and Banker, eds.) published by Marcel Dekker, Inc.

When a Compound of the Invention is formulated for parenteral administration by injection (*e.g.*, continuous infusion or bolus injection), the formulation can be in the form of a suspension, solution, or emulsion in an oily or aqueous vehicle, and such formulations can further comprise pharmaceutically necessary additives such as one or more stabilizing agents, suspending agents, dispersing agents, and the like. When a Compound of the Invention is to be injected parenterally, it can be, *e.g.*, in the form of an isotonic sterile solution. A Compound of the Invention can also be in the form of a powder for reconstitution as an injectable formulation.

In certain embodiments, a Compound of the Invention is formulated into a pharmaceutical composition for intravenous administration. Typically, such compositions comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. A Compound of the Invention for intravenous administration can optionally include a local anesthetic such as benzocaine or prilocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where a Compound of the Invention is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where a Compound of the Invention is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

When a Compound of the Invention is to be administered by inhalation, it can be formulated into a dry aerosol, or an aqueous or partially aqueous solution.

In another embodiment, a Compound of the Invention can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science 249*:1527-1533 (1990); and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In certain embodiments, a Compound of the Invention is administered locally. This can be achieved, for example, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, a Compound of the Invention can be delivered in an immediate release form. In other embodiments, a Compound of the Invention can be delivered in a controlled-release system or sustained-release system. Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over the results achieved by their non-controlled or non-sustained-release counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Compound of the Invention to treat or prevent the Condition (or a symptom thereof) in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Compound of the Invention, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially immediately release an amount of a Compound of the Invention that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Compound of the Invention to maintain a level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Compound of the Invention in the body, the Compound of the Invention can be released from the dosage form at a rate that will replace the amount of Compound of the Invention being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

Controlled-release and sustained-release means for use according to the present invention may be selected from those known in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be

used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, multiparticulates, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known in the art, including those described herein, can be readily selected for use with the active ingredients of the invention in view of this disclosure. See also Goodson, "Dental Applications" (pp. 115-138) in *Medical Applications of Controlled Release, Vol. 2, Applications and Evaluation*, R.S. Langer and D.L. Wise eds., CRC Press (1984). Other controlled- or sustained-release systems that are discussed in the review by Langer, *Science 249*:1527-1533 (1990) can be selected for use according to the present invention. In one embodiment, a pump can be used (Langer, *Science 249*:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng. 14*:201 (1987); Buchwald *et al.*, *Surgery 88*:507 (1980); and Saudek *et al.*, *N. Engl. J. Med. 321*:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem. 23*:61 (1983); Levy *et al.*, *Science 228*:190 (1985); During *et al.*, *Ann. Neurol. 25*:351 (1989); and Howard *et al.*, *J. Neurosurg. 71*:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of a Compound of the Invention, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

When in tablet or pill form, a pharmaceutical composition of the invention can be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

Pharmaceutical compositions of the invention include single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

The amount of the Compound of the Invention that is effective for the treatment or prevention of a condition can be determined by standard clinical techniques. In addition, *in vitro* and/or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on, *e.g.*, the route of administration and the extent of the Condition to be treated, and can be decided according to the judgment of a practitioner and/or each patient's circumstances. Variations in dosing may occur depending upon typical factors such as the weight, age, gender and physical condition (*e.g.*, hepatic and renal function) of the patient being treated, the affliction to be treated, the severity of the symptoms, the frequency of the dosage interval, the presence of any deleterious side-effects, and the particular compound utilized, among other things.

Suitable effective dosage amounts can range from about 0.01mg/kg of body weight to about 3000 mg/kg of body weight of the patient per day, although they are typically from about 0.01mg/kg of body weight to about 2500 mg/kg of body weight of the patient per day or from about 0.01mg/kg of body weight to about 1000 mg/kg of body weight of the patient per day. In one embodiment, the effective dosage amount is about 100 mg/kg of body weight of the patient per day or less. In another embodiment, the effective dosage amount ranges from about 0.01mg/kg of body weight to about 100 mg/kg of body weight of the patient per day of a Compound of the Invention, in another embodiment, about 0.02 mg/kg of body weight to about 50 mg/kg of body weight of the patient per day, and in another embodiment, about 0.025 mg/kg of body weight to about 20 mg/kg of body weight of the patient per day.

Administration can be as a single dose or as a divided dose. In one embodiment, an effective dosage amount is administered about every 24 hours until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 12 hours until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 8 hours until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 6 hours until the Condition is abated. In another embodiment, an effective dosage amount is administered about every 4 hours until the Condition is abated. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one Compound of the Invention is administered, the effective dosage amounts correspond to the total amount administered.

Where a cell capable of expressing the μ-opioid receptors is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting or activating the μ-opioid receptors function in a cell can typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, or from about 10^{-12} mol/L to about 10^{-5} mol/L, or from about 10^{-12} mol/L to about 10^{-6} mol/L, or from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of the Compound of the Invention in a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention can be from about 0.01 μL to about 1 mL. In another embodiment, the volume of solution or suspension can be about 200 μL.

Where a cell capable of expressing the δ-opioid receptors is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting or activating the δ-opioid receptors function in a cell can typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, or from about 10^{-12} mol/L to about 10^{-5} mol/L, or from about 10^{-12} mol/L to about 10^{-6} mol/L, or from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of the Compound of the Invention in a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention can be from about 0.01 μL to about 1 mL. In another embodiment, the volume of solution or suspension can be about 200 μL.

Where a cell capable of expressing the κ-opioid receptors is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting or activating the κ-opioid receptors function in a cell can typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, or from about 10^{-12} mol/L to about 10^{-5} mol/L, or from about 10^{-12} mol/L to about 10^{-6} mol/L, or from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of the Compound of the Invention in a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention can be from about 0.01μL to about 1 mL. In another embodiment, the volume of solution or suspension can be about 200 μL.

Where a cell capable of expressing the ORL-1 receptor is contacted with a Compound of the Invention *in vitro*, the amount effective for inhibiting or activating the ORL-1 receptor function in a cell can typically range from about 10^{-12} mol/L to about 10^{-4} mol/L, or from about 10^{-12} mol/L to about 10^{-5} mol/L, or from about 10^{-12} mol/L to about 10^{-6} mol/L, or from about 10^{-12} mol/L to about 10^{-9} mol/L of a solution or suspension of the compound in a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension comprising the Compound of the Invention can be from about 0.01μL to about

1mL. In another embodiment, the volume of solution or suspension can be about 200 μL.

The Compounds of the Invention can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy. Certain Compounds of the Invention are expected to have an ED_{50} for treating inflammatory pain ranging from about 0.5 mg/kg to about 20 mg/kg. Certain Compounds of the Invention are expected to produce significant analgesia and/or anti-hyperalgesia at doses that do not induce respiratory depression. In contrast, oxygen tension, oxygen saturation and pH are significantly decreased, while carbon dioxide is significantly increased, in blood samples from rats given effective doses of conventional opioids, such as morphine.

According to the invention, the methods for treating or preventing a Condition in apatient in need thereof can further comprise co-administering to the patient an effective amount of a second therapeutic agent in addition to a Compound of the Invention (*i.e.*, a first therapeutic agent). An effective amount of the second therapeutic agent can be known or determinable by a medical practitioner in view of this disclosure and published clinical studies. In one embodiment of the invention, where a second therapeutic agent is administered to a patient for treatment of a Condition (*e.g.*, pain), the minimal effective amount of the Compound of the Invention (*i.e.*, the first therapeutic agent) will be less than its minimal effective amount would be in circumstances where the second therapeutic agent is not administered. In this embodiment, the Compound of the Invention and the second therapeutic agent can act either additively or synergistically to treat or prevent a Condition. Alternatively, the second therapeutic agent may be used to treat or prevent a disorder that is different from the Condition for which the first therapeutic agent is being administered, and which disorder may or may not be a Condition as defined hereinabove. In one embodiment, a Compound of the Invention is administered concurrently with a second therapeutic agent as a single composition comprising an effective amount of a Compound of the Invention and an effective amount of the second therapeutic agent. Alternatively, a composition comprising an effective amount of a Compound of the Invention and a second composition comprising an effective amount of the second therapeutic agent are concurrently administered. In another embodiment, an effective amount of a Compound of the Invention is administered prior or subsequent to administration of an effective amount of the second therapeutic agent. In this embodiment, the Compound of the Invention is administered while the second therapeutic agent exerts its therapeutic effect, or the second therapeutic agent is administered while the

Compound of the Invention exerts its therapeutic effect for treating or preventing a Condition.

The second therapeutic agent can be, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, an antimigraine agent, a Cox-IA inhibitor, a 5-lipoxygenase inhibitor, an anti-emetic, a β-adrenergic blocker, an anticonvulsant, an antidepressant, a Ca^{2+}-channel blocker, an anti-cancer agent, an agent for treating or preventing UI, an agent for treating or preventing anxiety, an agent for treating or preventing a memory disorder, an agent for treating or preventing obesity, an agent for treating or preventing constipation, an agent for treating or preventing cough, an agent for treating or preventing diarrhea, an agent for treating or preventing high blood pressure, an agent for treating or preventing epilepsy, an agent for treating or preventing anorexia/cachexia, an agent for treating or preventing drug abuse, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for treating or preventing IBS, an agent for treating or preventing addictive disorder, an agent for treating or preventing Parkinson's disease and parkinsonism, an agent for treating or preventing a stroke, an agent for treating or preventing a seizure, an agent for treating or preventing a pruritic condition, an agent for treating or preventing psychosis, an agent for treating or preventing Huntington's chorea, an agent for treating or preventing ALS, an agent for treating or preventing a cognitive disorder, an agent for treating or preventing a migraine, an agent for treating, preventing or inhibiting vomiting, an agent for treating or preventing dyskinesia, an agent for treating or preventing depression, or any mixture thereof.

A composition of the invention is prepared by a method comprising admixing a Compound of the Invention with a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods known for admixing a compound (or derivative) and a pharmaceutically acceptable carrier or excipient. In one embodiment, the Compound of the Invention is present in the composition in an effective amount.

The invention also provides a kit, comprising a sterile container containing an effective amount of a Compound of the Invention and instructions for therapeutic use.

The following examples are illustrative, but not limiting, of the compounds, compositions and methods of the invention. Suitable modifications on the preparation methods are obvious to those skilled in the art in view of this disclosure, and therefore are within the spirit and scope of the invention. Further, modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are

obvious to those skilled in the art in view of this disclosure are also within the spirit and scope of the invention.

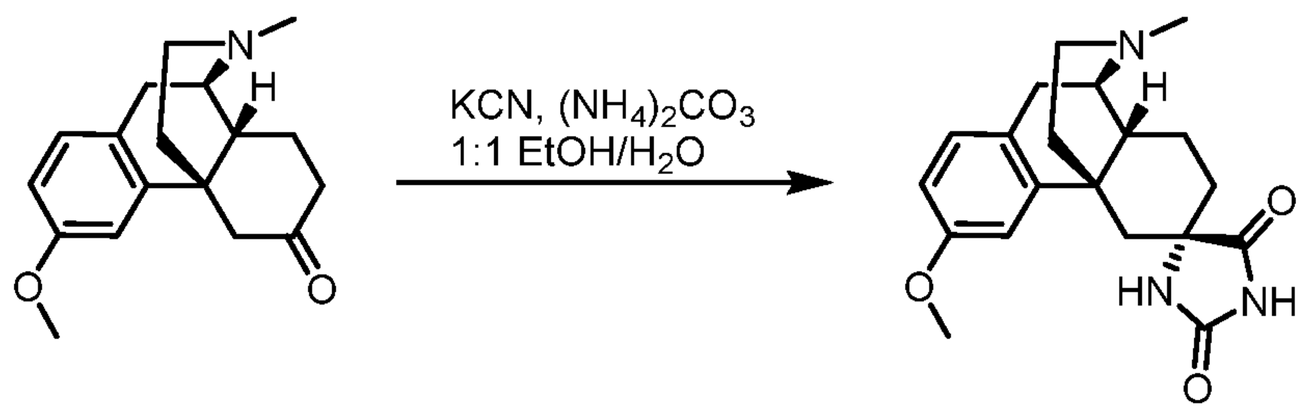
EXAMPLES

The following list provides exemplary abbreviations used in this disclosure:

CAN	acetonitrile
AcOH	acetic acid
aq.	aqueous
°C	degrees Celcius
conc.	concentrated
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Eq.	equivalent
h	hour(s)
HPLC	high pressure liquid chromatography
LAH	lithium aluminum hydride
MeOH	methanol
min	minute(s)
psi	pounds per square inch
RT	room temperature
satd.	saturated
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran.

EXAMPLE 1

(4**S**,4b'**S**,8a'R,9'R)-3'-methoxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **2**)

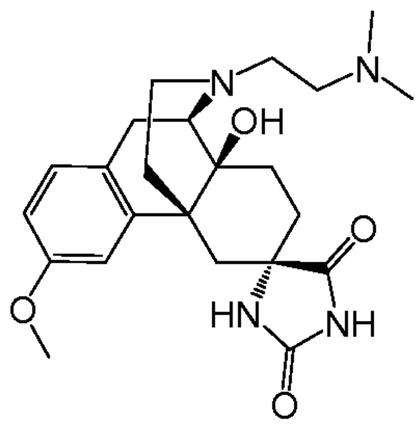


1 2

The starting material (Compound **1**) can be prepared in the way as those described in, for example, Hupp C. D., *et al.*, *Tetrahedron Letters 51*:2359-2361 (2010). To a mixture of Compound **1** (5.01 g, 17.56 mmol) in EtOH (60 mL) and water (60 mL) was added KCN (1.722 g, 26.4 mmol) and $(NH_4)_2CO_3$ (11.82 g, 123 mmol). The reaction mixture was heated at 60 °C overnight. The reaction mixture was evaporated in vacuo to remove the organics and the remainder partitioned between 100 mL DCM and 25 mL water. The layers were separated and the aqueous extracted twice more with 50 mL DCM. The combined organics were dried over MgSO4, filtered and evaporated in vacuo. The residue was purified over silica gel with 0-14% (10% NH_4OH in MeOH) in DCM. Evaporation of the proper fractions yielded Compound **2** as an off-white solid (5.62 g, yield 90%).

Compound **2**: ^1H NMR δ_H (400 MHz, DMSO-d_6): 10.66 (s, 1H), 7.02 (d, J=8.4 Hz, 1H), 6.86 (d, J=2.5 Hz, 1H), 6.72 (dd, J=8.4, 2.6 Hz, 1H), 6.57 (s, 1H), 3.69 (s, 3H), 2.91 (d, J=17.9 Hz, 1H), 2.80-2.73 (m, 1H), 2.59 (d, J=14.7 Hz, 1H), 2.54-2.46 (m, 1H, overlap with DMSO), 2.32-2.20 (m, 4H), 1.89-1.70 (m, 3H), 1.68-1.35 (m, 5H), 1.28-1.19 (m, 1H); LC/MS, *m/z* = 356.3 $[M + H]^+$ (Calc: 355.4).

In a similar manner, the following compounds were prepared:



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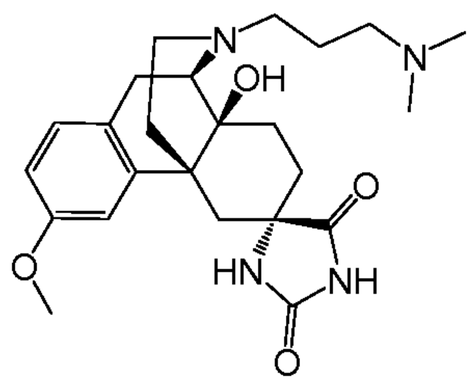

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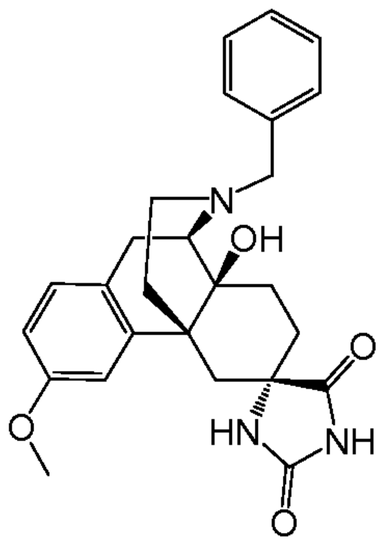

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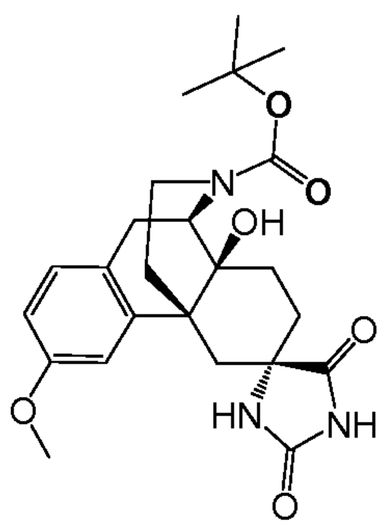

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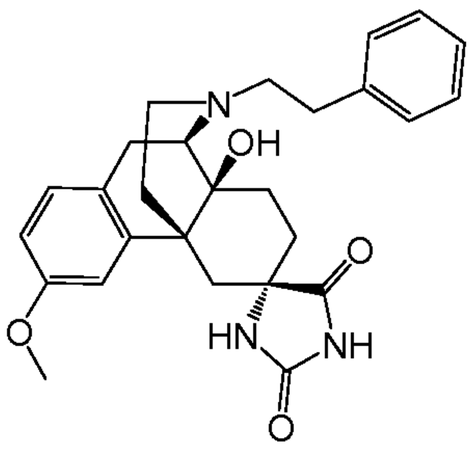


7

(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **3**): ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.06 - 1.17 (m, 1 H) 1.43 (dd, *J*=11.69, 1.90 Hz, 1 H) 1.54 (dt, *J*=13.45, 3.31 Hz, 1 H) 1.82 (td, *J*=13.89, 3.96 Hz, 1 H) 1.96 - 2.05 (m, 1 H) 2.13 (td, *J*=12.57, 4.68 Hz, 1 H) 2.31 (s, 6 H) 2.34 - 2.37 (m, 2 H) 2.41 - 2.59 (m, 4 H) 2.61 - 2.76 (m, 2 H) 2.79 (d, *J*=5.34 Hz, 1 H) 2.84 - 2.97 (m, 1 H) 3.13 (d, *J*=18.21 Hz, 1 H) 3.78 (s, 3 H) 6.80 (dd, *J*=8.45, 2.56 Hz, 1 H) 6.92 (d, *J*=2.53 Hz, 1 H) 7.09 (d, *J*=8.47 Hz, 1 H); LC/MS, *m/z* =429 $[M + H]^+$ (Calc: 428).

(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **4**): ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.26 (d, *J*=11.94 Hz, 1 H) 1.41 (d, *J*=13.75 Hz, 1 H) 1.58 - 1.65 (m, 1 H) 1.86 (td, *J*=14.11, 3.91 Hz, 1 H) 1.92 - 2.06 (m, 1H) 2.13 - 2.28 (m, 1 H) 2.31 - 2.43 (m, 4 H) 2.52 (m, 1 H) 2.84 (s, 6 H) 2.98 - 3.07 (m, 2 H) 3.11 (t, *J*=7.98 Hz, 2 H) 3.22 - 3.31 (m, 3 H) 3.51 (br. s., 1 H) 3.69 (s, 3 H) 6.81 (dd, *J*=8.50, 2.50 Hz, 1 H) 6.92 (d, *J*=2.48 Hz, 1 H) 7.09 (d, *J*=8.53 Hz, 1 H); LC/MS, *m/z* =443 $[M + H]^+$ (Calc: 442).

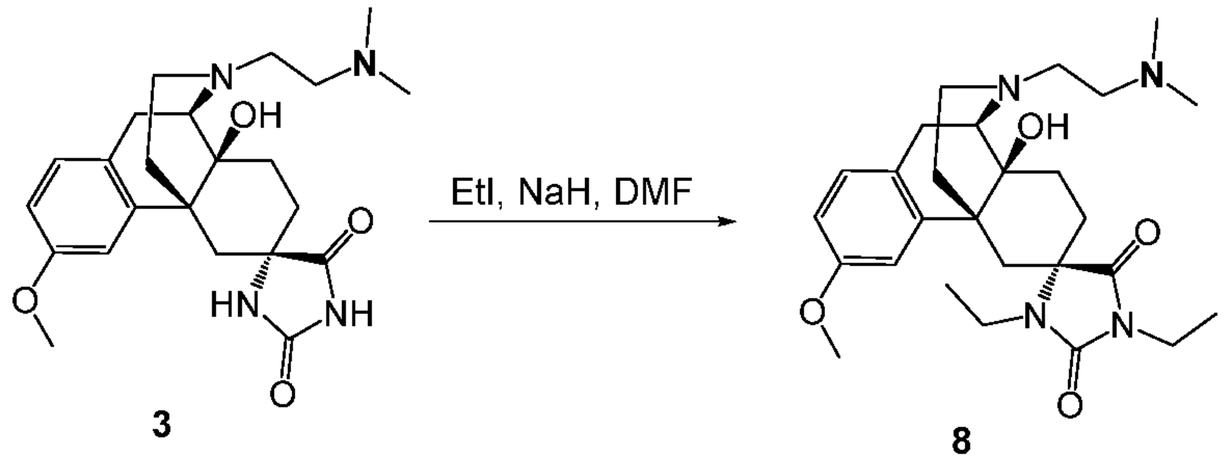
(4S,4b'R,8a'S,9'R)-11'-benzyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **5**): LC/MS, *m/z* = 448 $[M + H]^+$ (Calc: 447).

Tert-butyl (4S,4b'R,8a'S,9'R)-8a'-hydroxy-3'-methoxy-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-11'-carboxylate (Compound **6**): LC/MS, *m/z* = 480 $[M + Na]^+$ (Calc: 457).

(4S,4b'R,8a'S,9'R)-8a'-hydroxy-3'-methoxy-11'-phenethyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **7**): LC/MS, *m/z* = 462.2 $[M + H]^+$ (Calc: 461.6).

EXAMPLE 2

(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **8**)



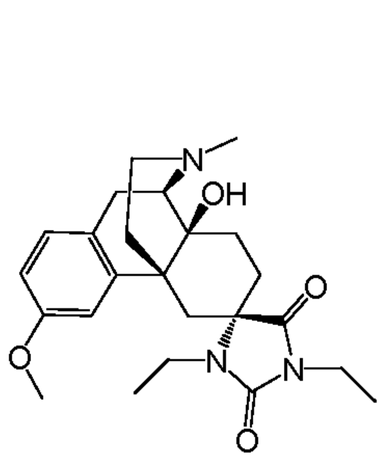
3 **8**

To a solution of Compound **3** (0.502 g, 1.41 mmol) in DMF (10 mL) was added 60% NaH (0.171 g, 4.28 mmol). After stirring for 5 minutes, the ethyl iodide (0.25 mL, 3.1 mmol) was added. After stirring overnight the reaction mixture was diluted with 200 mL water with NaCl and extracted three times with 50 mL 1:1 DCM / hexanes. The organics were dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by flash chromatography (SiO_2, 0-14% (10% NH_4OH in MeOH) in DCM) to give Compound **8** as a cream-colored solid (2.524 g, yield 74%).

Compound **8**: ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 0.77 (t, *J*=7.07 Hz, 3 H) 1.09 (t, *J*=7.18 Hz, 3 H) 1.25 (d, *J*=10.40 Hz, 1 H) 1.53 - 1.76 (m, 3 H) 1.87 (td, *J*=13.96, 4.32 Hz, 1 H) 2.20 - 2.32 (m, 3 H) 2.37 - 2.52 (m, 2 H) 2.83 (s, 6 H) 2.86 - 2.94 (m, 1 H) 2.97 - 3.10 (m, 1 H) 3.11 - 3.20 (m, 6 H) 3.38 - 3.48 (m, 3 H) 3.67 (s, 3 H) 6.77 (dd, *J*=8.47, 2.48

Hz, 1 H) 6.85 (d, *J*=2.42 Hz, 1 H) 7.09 (d, *J*=8.53 Hz, 1 H); LC/MS, *m/z* = 485 $[M + H]^+$ (Calc: 484).

In a similar manner, the following compounds were prepared:



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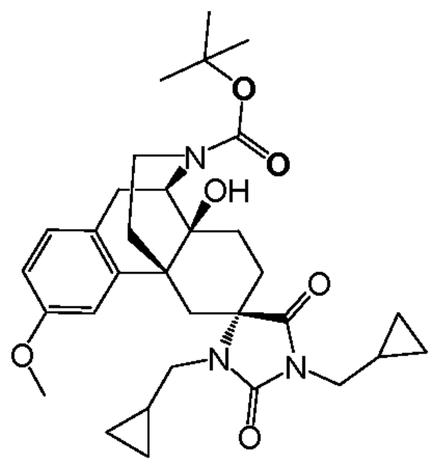

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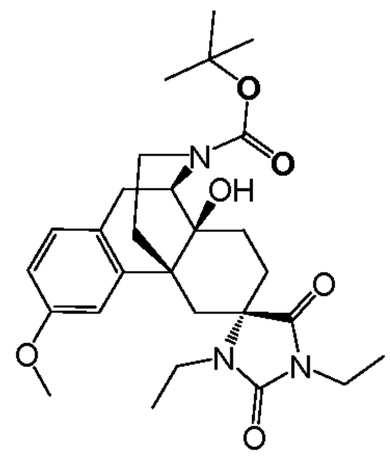

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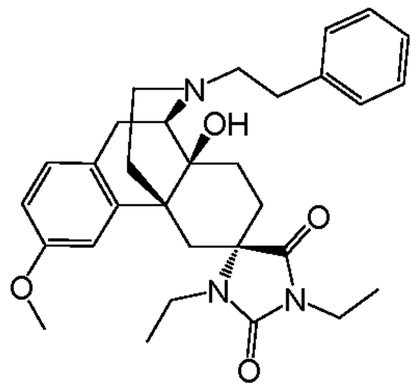

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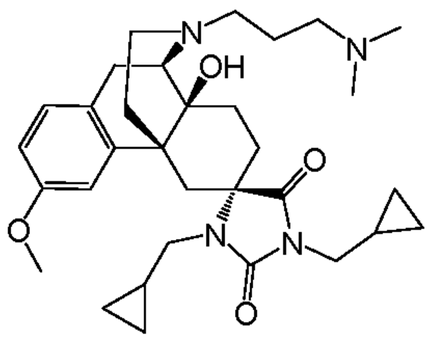
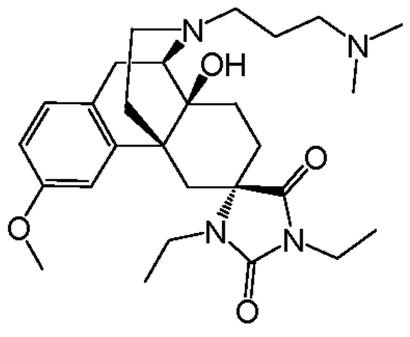
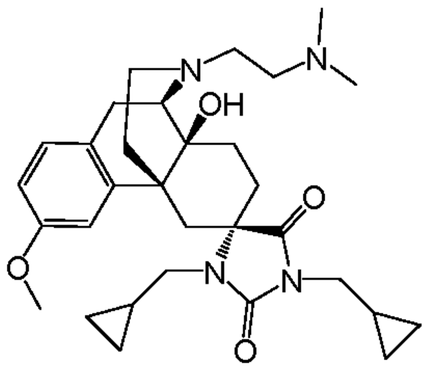


13



14



15

(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-3'-methoxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **9**): LC/MS, *m/z* = 412.3 $[M + H]^+$ (Calc: 411.5).

Tert-butyl (4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-8a'-hydroxy-3'-methoxy-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-11'-carboxylate (Compound **10**): LC/MS, *m/z* = 588 $[M + Na]^+$ (Calc: 565).

Tert-butyl (4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-3'-methoxy-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-11'-carboxylate (Compound **11**): LC/MS, *m/z* = 536 $[M + Na]^+$ (Calc: 513).

(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-3'-methoxy-11'-phenethyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **12**): LC/MS, *m/z* = 518.3 $[M + H]^+$ (Calc: 517.7).

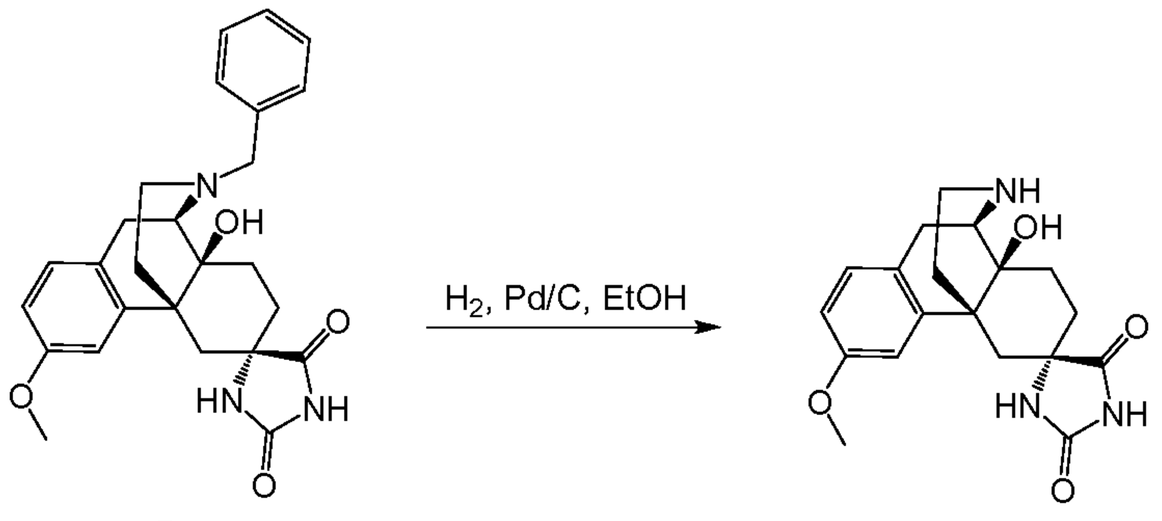
(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(3-(dimethylamino)propyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione (Compound **13**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm -0.05 - 0.04 (m, 1 H), 0.22 - 0.32 (m, 1 H), 0.41 - 0.55 (m, 4 H), 0.61 - 0.70 (m, 2 H), 0.85 - 1.00 (m, 1 H), 1.23 - 1.36 (m, 1 H), 1.60 (d, *J*=13.26 Hz, 1 H), 1.84 (dd, *J*=15.52, 6.33 Hz, 1 H), 2.00 (m, 2H), 2.11 - 2.30 (m, 2 H), 2.37 - 2.51 (m, 1 H), 2.57 - 2.80 (m, 5 H), 3.03 (dd, *J*=15.54, 7.51 Hz, 1 H), 3.09 (s, 6 H), 3.23 - 3.40 (m, 4 H), 3.48 - 3.57 (m, 5 H), 3.80 (m, 1 H) 3.91 (s, 3 H), 7.07 (dd, *J*=8.50, 2.23 Hz, 1 H), 7.12 (d, *J*=2.20 Hz, 1 H), 7.39 (d, *J*=8.53 Hz, 1 H); LC/MS, *m/z* = 541, $[M + H]^+$ (Calc: 540).

(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **14**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm 0.79 (t, *J*=7.04 Hz, 3 H), 1.09 (t, *J*=7.15 Hz, 3 H), 1.35 (d, *J*=12.93 Hz, 1 H), 1.61 (m, 1 H), 1.69 - 1.80 (m, 2 H), 1.86 - 2.04 (m, 2 H), 2.12 - 2.25 (m, 1 H), 2.33 - 2.54 (m, 5 H), 2.85 (s, 6 H), 2.87 - 2.96 (m, 1 H), 3.00 - 3.16 (m, 4 H), 3.25 - 3.39 (m, 3 H), 3.45 (q, *J*=7.13 Hz, 2 H), 3.56 (d, *J*=3.80 Hz, 1 H), 3.68 (s, 3 H), 6.83 (dd, *J*=8.47, 2.20 Hz, 1 H), 6.90 (d, *J*=2.20 Hz, 1 H), 7.14 (d, *J*=8.53 Hz, 1 H); LC/MS, *m/z* = 471, $[M + H]^+$ (Calc: 470).

(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(2-(dimethylamino)ethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione (Compound **15**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm -0.25 (m, 1 H), -0.04 (m, 1 H) 0.16 - 0.29 (m, 4 H), 0.38 - 0.47 (m, 2 H), 0.61 - 0.76 (m, 1 H), 1.00 - 1.12 (m, 1 H), 1.25 (d, *J*=9.46 Hz, 1 H), 1.55 (dd, *J*=15.54, 6.41 Hz, 1 H), 1.61 - 1.76 (m, 2 H), 1.89 (td, *J*=13.64, 4.29 Hz, 1 H), 2.17 - 2.32 (m, 3 H), 2.37 - 2.43 (m, 1 H), 2.50 (td, *J*=13.82, 4.81 Hz, 1 H), 2.75 (dd, *J*=15.60, 7.51 Hz, 2 H), 2.82 (s, 6 H), 2.92 - 3.20 (m, 6 H), 3.28 (d, *J*=7.15 Hz, 2 H), 3.34 - 3.43 (m, 1 H), 3.66 (s, 3 H), 6.77 (dd, *J*=8.47, 2.48 Hz, 1 H), 6.82 (d, *J*=2.37 Hz, 1 H), 7.09 (d, *J*=8.47 Hz, 1 H); LC/MS, *m/z* = 537, $[M + H]^+$ (Calc: 536).

EXAMPLE 3

(4S,4b'R,8a'S,9'R)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **16**)



5 16

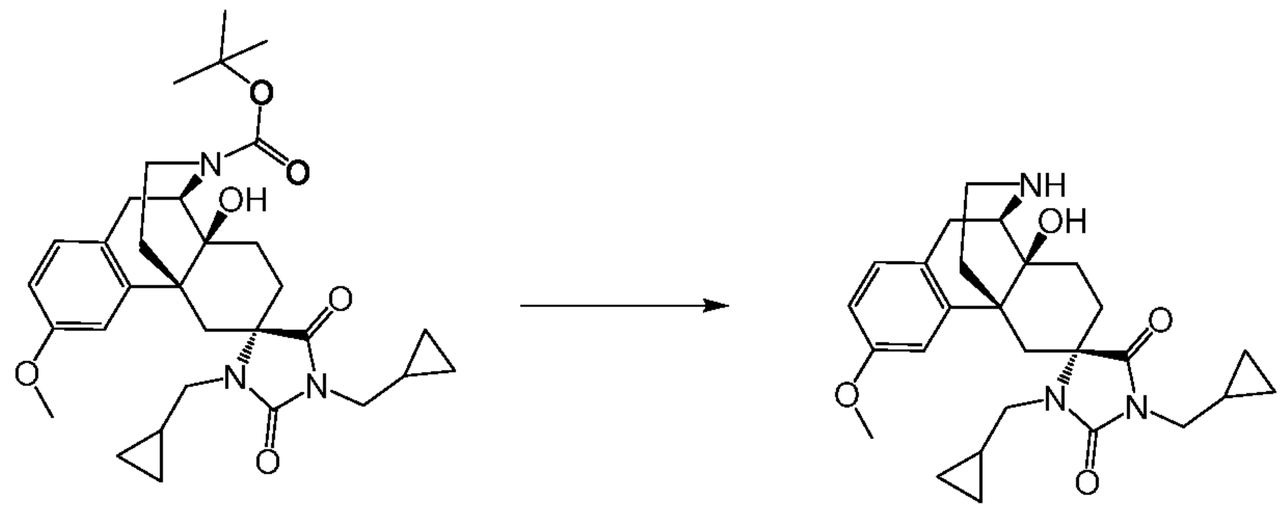
A mixture of Compound **5** (11.516 g, 25.7 mmol) in AcOH (115 mL) in a Parr hydrogenation flask with $Pd(OH)_2$ (1.140 g) was hydrogenated at 50 psi of hydrogen overnight. The reaction mixture was filtered through a pad of Celite and rinsed with MeOH. The filtrate was concentrated, treated with 10 mL conc. NH_4OH, water, MeOH and DCM and concentrated again. The residue was purified by flash chromatography (SiO_2, 0-50% (10% NH_4OH in MeOH) in DCM) followed by trituration with MeOH to give Compound **16** as a white powder (8.359 g, yield 91%).

Compound **16**: ^1H NMR δ_H (400 MHz, DMSO-d_6): 10.49 (br s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.74 (dd, J = 8.4, 2.4 Hz, 1H), 6.51 (s, 1H), 4.51 (s, 1H), 3.69 (s, 3H), 3.08 (dd, J = 17.6, 5.7 Hz, 1H), 2.82 (d, J = 17.6 Hz, 1H), 2.68 (d, J = 5.5 Hz, 1H), 2.42 (dd, J = 12.8, 4.4 Hz, 1H), 2.34-2.11 (m, 4H), 1.88 (dt, J = 12.3, 4.8 Hz, 1H), 1.73 (dt, J = 13.9, 3.7 Hz, 1H), 1.33-1.25 (m, 1H), 1.20 (d, J = 13.0 Hz, 1H), 0.79 (d, J = 11.4 Hz, 1H); LC/MS, *m/z* = 358 $[M + H]^+$ (Calc: 357).

EXAMPLE 4

(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione

(Compound **17**)



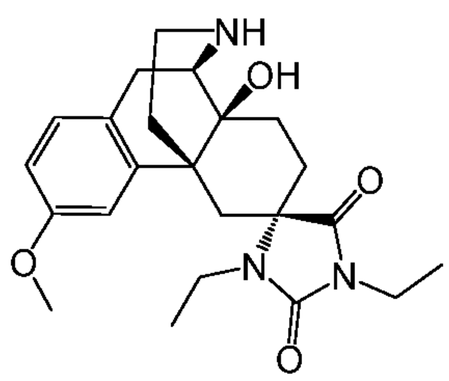
10 17

To a solution of Compound **10** (1.15 g, 2.57 mmol) in DCM (20 mL) was slowly added TFA (5 mL) at 0°C. Then the mixture was stirred at rt for 4 hrs. Cooled down to 0°C,

then neutralized to pH ~ 9 with aq. $NaHCO_3$ and diluted with DCM (50 mL) The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2, 0-20% (10% NH_4OH in MeOH) in DCM) followed by trituration with MeOH to give Compound **17** as a white powder (0.836 g, yield 91%).

Compound **17**: ^1H NMR (400 MHz, MEOH-d_4) δ ppm -0.04 - 0.04 (m, 1 H), 0.21 - 0.29 (m, 1 H), 0.42 - 0.52 (m, 4 H), 0.62 - 0.70 (m, 2 H), 0.89 - 0.99 (m, 1 H), 1.20 (dd, *J*=12.41, 2.23 Hz, 1 H), 1.25 - 1.37 (m, 1 H), 1.71 - 1.85 (m, 2 H), 1.93 (m, 1 H), 2.02 - 2.13 (m, 1 H), 2.30 - 2.40 (m, 2 H), 2.51 (td, *J*=13.20, 3.41 Hz, 1 H), 2.67 (d, *J*=14.97 Hz, 1 H), 2.73 - 2.84 (m, 2 H), 2.99 (dd, *J*=15.57, 7.43 Hz, 1 H), 3.07 (d, *J*=6.11 Hz, 1 H), 3.14 (d, *J*=18.21 Hz, 1 H), 3.47 - 3.50 (m, 2 H), 3.53 (d, *J*=6.93 Hz, 2 H), 3.90 (s, 3 H), 6.95 - 7.03 (m, 2 H), 7.30 (d, *J*=8.31 Hz, 1 H); LC/MS, *m/z* = 466 $[M + H]^+$ (Calc: 465).

In a similar manner, the following compounds were prepared:

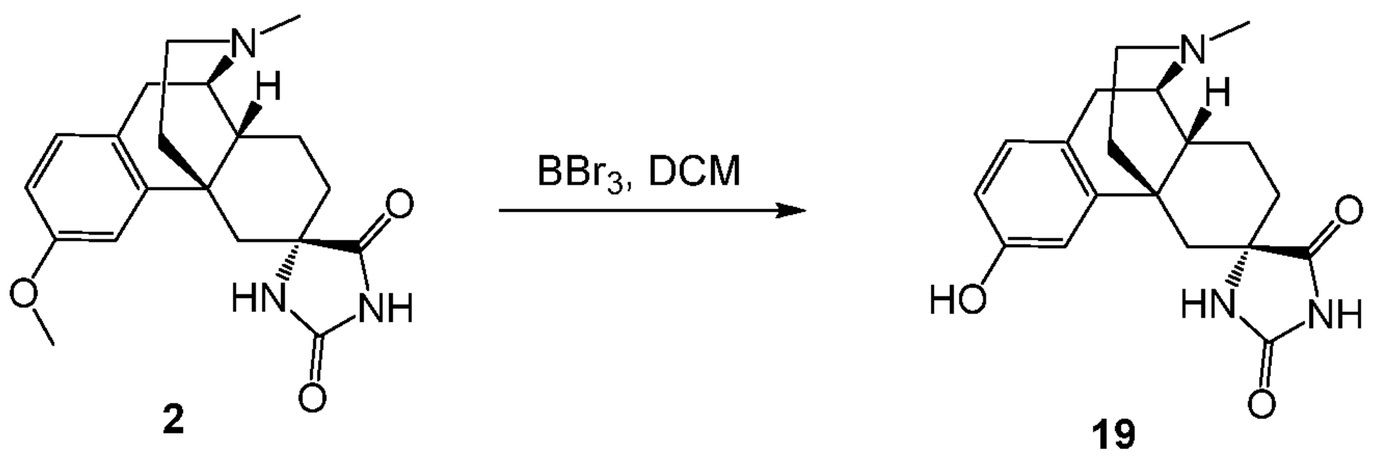


18

(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **18**): ^1H NMR (400 MHz, MEOH-d_4) δ ppm 0.86 (t, *J*=7.10 Hz, 3 H), 1.06 (dd, *J*=12.46, 2.45 Hz, 1 H), 1.20 (t, *J*=7.18 Hz, 3 H), 1.56 - 1.68 (m, 2 H), 1.78 - 1.96 (m, 2 H), 2.17 - 2.28 (m, 2 H), 2.37 (td, *J*=13.19, 3.44 Hz, 1 H), 2.52 (d, *J*=14.97 Hz, 1 H), 2.55 - 2.69 (m, 2 H), 2.90 - 3.04 (m, 3 H), 3.34 - 3.41 (m, 1 H), 3.55 (q, *J*=7.17 Hz, 2 H), 3.77 (s, 3 H), 6.83 (dd, *J*=8.42, 2.59 Hz, 1 H), 6.89 (d, *J*=2.53 Hz, 1 H), 7.15 (d, *J*=8.42 Hz, 1 H); LC/MS, *m/z* = 414, $[M + H]^+$ (Calc: 413).

EXAMPLE 5

(4S,4b'S,8a'R,9'R)-3'-hydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **19**)

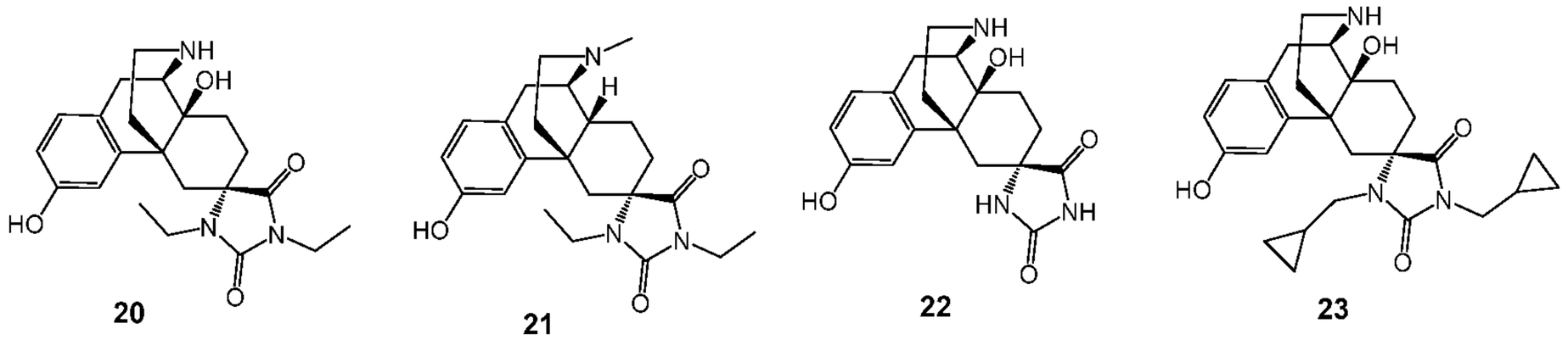


2 19

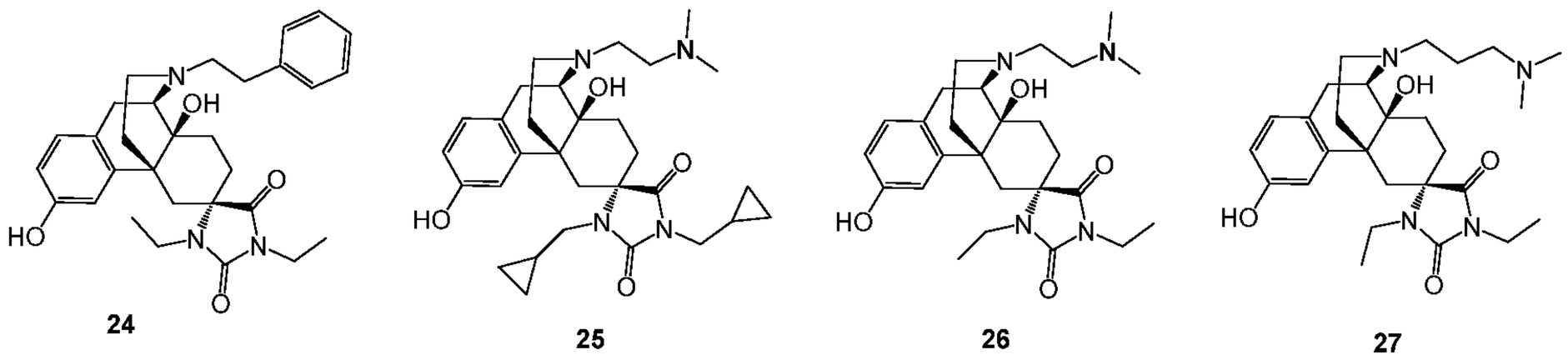
To a mixture of Compound **2** (0.507 g, 1.43 mmol) in DCM (25 mL) was added 1M BBr3 in DCM (4.3 mL, 4.3 mmol). After 3 hours an additional amount of 1M BBr3 in DCM was added (1.4 mL, 1.4 mmol). After an additional hour a third portion of 1M BBr3 in DCM was added (1.4 mL, 1.4 mmol). After an hour the reaction was quenched with 5 mL 5M concentrated NH4OH in MeOH. The mixture was evaporated in vacuo. The residue was purified over silica gel with 0-30% (10% NH_4OH in MeOH) in DCM. Evaporation of the proper fractions yielded a solid that was triturated with 6 mL acetonitrile, filtered and rinsed with 1 mL acetonitrile. The sample was dried to yield Compound **19** as a cream-colored powder (0.254 g). Yield 52%

Compound **19**: ^{1}H NMR δ_H (400 MHz, DMSO-d_6): 10.68 (br. s., 1H), 8.98 (s, 1H), 6.90 (d, J=8.2 Hz, 1H), 6.68 (d, J=2.3 Hz, 1H), 6.58-6.51 (m, 2H), 2.86 (d, J=17.8 Hz, 1H), 2.79-2.72 (m, 1H), 2.53-2.44 (m, 1H), 2.39 (d, J=14.5 Hz, 1H), 2.32-2.20 (m, 4H), 1.89-1.80 (m, 1H), 1.80-1.69 (m, 2H), 1.65 (d, J=14.4 Hz, 1H), 1.61-1.44 (m, 3H), 1.44-1.35 (m, 1H), 1.24-1.16 (m, 1H); LC/MS, *m/z* = 342.1 $[M + H]^+$ (Calc: 341.4).

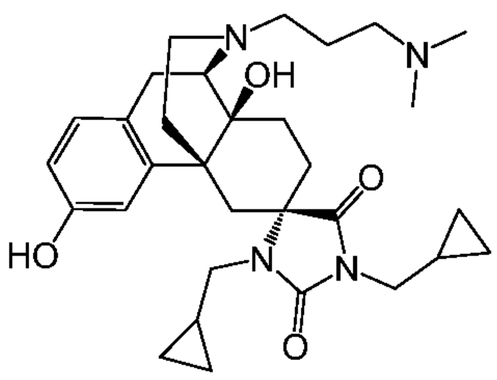
In a similar manner, the following compounds were prepared:



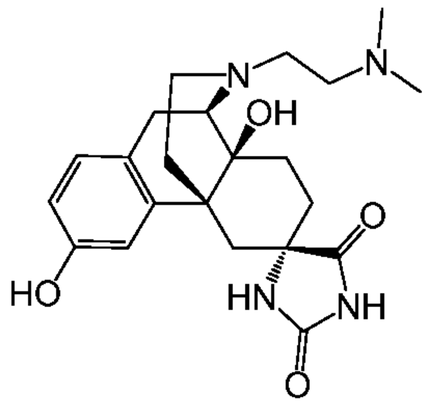
20 21 22 23



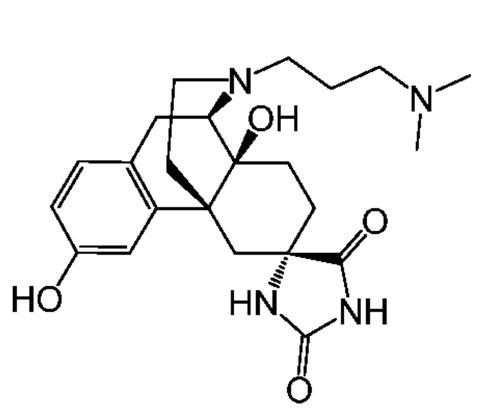
24 25 26 27



28



29



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(4S,4b'R,8a'S,9'R)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **20**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm 0.77 (t, *J*=7.07 Hz, 3 H), 0.96 (dd, *J*=12.49, 2.31 Hz, 1 H), 1.07 (t, *J*=7.18 Hz, 3 H), 1.46 -1.58 (m, 2 H), 1.76 - 1.90 (m, 2 H), 2.03 (d, *J*=15.02 Hz, 1 H), 2.13 (td, *J*=12.72, 4.81 Hz, 1 H), 2.31 (td, *J*=13.22, 3.55 Hz, 1 H), 2.38 (s, 1 H), 2.47 (td, *J*=14.28, 5.17 Hz, 1 H), 2.61 (dd, *J*=13.51, 4.04 Hz, 1 H), 2.81 - 3.00 (m, 3 H), 3.27 (d, *J*=6.55 Hz, 1 H), 3.35 - 3.51 (m, 2 H), 6.58 (dd, *J*=8.28, 2.39 Hz, 1 H), 6.65 (d, *J*=2.37 Hz, 1 H), 6.95 (d, *J*=8.31 Hz, 1 H); LC/MS, *m/z* = 400, $[M + H]^+$ (Calc: 399).

(4S,4b'S,8a'R,9'R)-1,3-diethyl-3'-hydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **21**): ^{1}H NMR δ_H (400 MHz, DMSO-d_6): 9.08 (s, 1H), 6.96 (d, J=8.3 Hz, 1H), 6.68 (d, J=2.2 Hz, 1H), 6.56 (dd, J=8.2, 2.3 Hz, 1H), 3.41 (q, J=7.1 Hz, 2H), 2.94-2.79 (m, 3H), 2.57 (dd, J=17.9, 4.7 Hz, 1H), 2.40 (d, J=14.9 Hz, 1H), 2.36-2.29 (m, 1H), 2.27 (s, 3H), 1.97-1.68 (m, 6H), 1.63-1.51 (m, 2H), 1.47-1.37 (m, 1H), 1.37-1.27 (m, 1H), 1.09 (t, J=7.1 Hz, 3H), 0.76 (t, J=7.0 Hz, 3H); LC/MS, *m/z* = 398.3 $[M + H]^+$ (Calc: 397.5).

(4S,4b'R,8a'S,9'R)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **22**): ^{1}H NMR δ_H (400 MHz, D2O with DCl): 6.94 (d, J=8.4 Hz, 1H), 6.70 (d, J=2.5 Hz, 1H), 6.62 (dd, J=8.4, 2.5 Hz, 1H), 3.44 (d, J=5.6 Hz, 1H), 3.19 (dd, J=19.3, 6.0 Hz, 1H), 2.93 (d, J=19.3 Hz, 1H), 2.85 (dd, J=13.3, 4.2 Hz, 1H), 2.46 (td, J=13.5, 4.0 Hz, 1H), 2.24 (d, J=14.7 Hz, 1H), 2.15-1.97 (m, 3H), 1.63-1.44 (m, 2H), 1.41-1.31 (m, 1H), 1.11 (dd, J=13.8, 3.0 Hz, 1H); LC/MS, *m/z* = 344.3 $[M + H]^+$ (Calc: 343.4).

(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **23**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm -0.04 - 0.03 (m, 1 H), 0.21 - 0.29 (m,

1 H), 0.42 - 0.52 (m, 4 H), 0.61 - 0.69 (m, 2 H), 0.90 - 1.00 (m, 1 H), 1.19 (dd, *J*=12.41, 2.28 Hz, 1 H), 1.25 - 1.33 (m, 1 H), 1.71 - 1.78 (m, 1 H), 1.85 - 1.96 (m, 2 H), 2.04 - 2.14 (m, 1 H), 2.26 (d, *J*=15.57 Hz, 1 H), 2.35 (td, *J*=12.65, 4.84 Hz, 1 H), 2.54 (td, *J*=13.22, 3.49 Hz, 1 H), 2.65 (d, *J*=14.91 Hz, 1 H), 2.71 - 2.86 (m, 2 H), 3.03 - 3.14 (m, 3 H), 3.48 - 3.54 (m, 3 H), 6.83 (dd, *J*=8.25, 2.42 Hz, 1 H), 6.87 (d, *J*=2.42 Hz, 1 H), 7.19 (d, *J*=8.31 Hz, 1 H); LC/MS, *m/z* = 452, $[M + H]^+$ (Calc: 451).

(4S,4b'R,8a'S,9'R)-1,3-diethyl-3',8a'-dihydroxy-11'-phenethyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **24**): ^{1}H NMR δ_H (400 MHz, DMSO-d_6): 9.13 (s, 1H), 7.33-7.26 (m, 2H), 7.26-7.16 (m, 3H), 6.97 (d, J=8.3 Hz, 1H), 6.68 (d, J=2.3 Hz, 1H), 6.58 (dd, J=8.3, 2.3 Hz, 1H), 4.21 (s, 1H), 3.40 (q, J=7.1 Hz, 2H), 3.03-2.93 (m, 1H), 2.92-2.62 (m, 7H), 2.58-2.50 (m, 1H, overlap with DMSO), 2.39 (td, J=14.1, 4.1 Hz, 1H), 2.26 (d, J=14.7 Hz, 1H), 2.05 (d, J=14.8 Hz, 1H), 1.96-1.83 (m, 2H), 1.80-1.60 (m, 2H), 1.54-1.40 (m, 2H), 1.09 (t, J=7.2 Hz, 3H), 1.05-0.96 (m, 1H), 0.75 (t, J=7.0 Hz, 3H); LC/MS, *m/z* = 504.3 $[M + H]^+$ (Calc: 503.6).

(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(2-(dimethylamino)ethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **25**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm -0.16 (m, 1 H), 0.06 - 0.16 (m, 1 H), 0.24 - 0.38 (m, 4 H), 0.47 - 0.54 (m, 2 H), 0.74 - 0.86 (m, 1 H), 1.09 - 1.20 (m, 1 H), 1.30 (m, 1 H), 1.68 - 1.85 (m, 3 H), 1.99 (m, 1 H), 2.25 (t, *J*=14.72 Hz, 3 H), 2.49 (d, *J*=14.97 Hz, 1 H), 2.59 (m, 1 H), 2.90 (s, 6 H), 2.92 (m, 1 H), 2.99 - 3.26 (m, 6 H), 3.34 - 3.51 (m, 3 H), 6.71 (dd, *J*=8.31, 2.31 Hz, 1 H), 6.76 (d, *J*=2.26 Hz, 1 H), 7.08 (d, *J*=8.31 Hz, 1 H); LC/MS, *m/z* = 458, $[M + H]^+$ (Calc: 457).

(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **26**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm 0.79 (t, *J*=7.07 Hz, 3 H), 1.08 (t, *J*=7.18 Hz, 3 H), 1.22 (m, 1 H), 1.54 - 1.68 (m, 2 H), 1.76 - 1.96 (m, 2 H), 2.11 - 2.32 (m, 3 H), 2.36 - 2.51 (m, 2 H), 2.82 (s, 6 H), 2.83 - 2.88 (m, 1 H), 2.90 - 3.20 (m, 7 H), 3.35 - 3.50 (m, 3 H), 6.62 (dd, *J*=8.31, 2.37 Hz, 1 H), 6.70 (d, *J*=2.37 Hz, 1 H), 7.00 (d, *J*=8.36 Hz, 1 H); LC/MS, *m/z* = 471, $[M + H]^+$ (Calc: 470).

(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **27**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm 0.81 (t, *J*=7.07 Hz, 3 H), 1.08 (t, *J*=7.18 Hz, 3 H), 1.30 (m, 1 H), 1.61 (m, 1 H), 1.68 - 1.78 (m, 1 H), 1.79 - 2.02 (m, 3 H), 2.12 - 2.27 (m, 2 H), 2.31 - 2.55 (m, 4 H), 2.84 (s, 6 H), 2.92 - 3.18 (m, 6 H), 3.25 (m, 2 H) 3.40 - 3.57 (m, 3 H), 6.67 (dd, *J*=8.31, 2.31 Hz, 1 H), 6.74 (d, *J*=2.31 Hz, 1 H), 7.04 (d, *J*=8.36 Hz, 1 H); LC/MS, *m/z* = 485, $[M + H]^+$ (Calc: 484).

(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(3-(dimethylamino)propyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **28**): ^{1}H NMR (400 MHz, MEOH-d_4) δ ppm -0.05 - 0.04 (m, 1 H), 0.22 - 0.33 (m, 1 H), 0.42 - 0.54 (m, 4 H), 0.61 - 0.68 (m, 2 H), 0.90 - 1.00 (m, 1 H), 1.23 - 1.34 (m, 1 H), 1.55 (m, 1 H), 1.89 - 2.02 (m, 3 H), 2.12 - 2.27 (m, 2 H), 2.34 - 2.79 (m, 7 H), 3.08 (s, 6 H), 3.10 - 3.16 (m, 1 H), 3.20 - 3.38 (m, 5 H), 3.48 - 3.58 (m, 5 H), 3.77 (m, 1 H), 6.91 (dd, *J*=8.34, 2.28 Hz, 1 H), 6.96 (d, *J*=2.26 Hz, 1 H), 7.28 (d, *J*=8.36 Hz, 1 H); LC/MS, *m/z* = 536, $[M + H]^+$ (Calc: 535).

(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **29**): ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.19 (d, *J*=10.40 Hz, 1 H) 1.46 (d, *J*=13.04 Hz, 1 H) 1.62 (d, *J*=13.42 Hz, 1 H) 1.92 (td, *J*=13.98, 3.96 Hz, 1 H) 2.15 - 2.33 (m, 3 H) 2.41 - 2.57 (m, 2 H) 2.76 (br. s., 1 H) 2.88 (s, 6 H) 2.98 - 3.21 (m, 5 H) 3.34 - 3.46 (m, 2 H) 6.72 (dd, *J*=8.34, 2.45 Hz, 1 H) 6.83 (d, *J*=2.42 Hz, 1 H) 7.06 (d, *J*=8.36 Hz, 1 H); LC/MS, *m/z* = 413 $[M + H]^+$ (Calc: 414).

(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **30**): ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 1.18 - 1.27 (m, 1 H) 1.41 (d, *J*=13.64 Hz, 1 H) 1.66 - 1.75 (m, 1 H) 1.82 - 1.93 (m, 1 H) 1.97 - 2.10 (m, 1 H) 2.19 - 2.43 (m, 5 H) 2.53 (td, *J*=12.96, 3.47 Hz, 1 H) 2.87 (s, 6 H) 3.02 - 3.11 (m, 2 H) 3.12 - 3.20 (m, 2 H) 3.25 (br. s., 2 H) 3.32 (td, *J*=12.12, 5.09 Hz, 1 H) 3.64 (br. s., 1 H) 6.67 (dd, *J*=8.34, 2.39 Hz, 1 H) 6.78 (d, *J*=2.37 Hz, 1 H) 7.04 (d, *J*=8.42 Hz, 1 H).

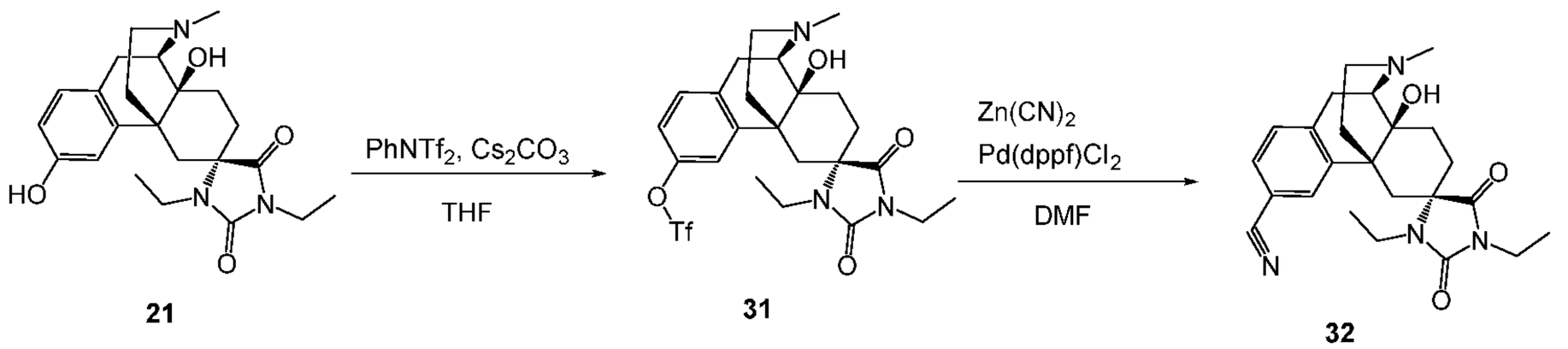
EXAMPLE 6

(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-3'-carbonitrile

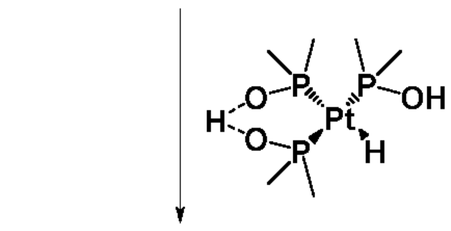
(Compound **32**)

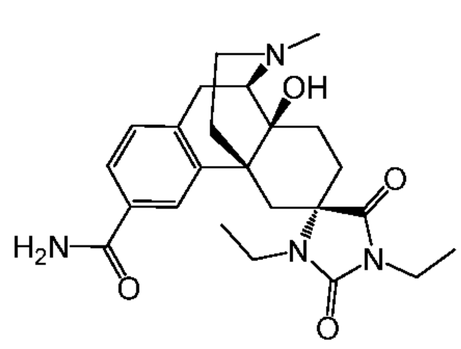
(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-3'-carboxamide

(Compound **33**)



21 **31** **32**





33

To a solution of Compound **21** (2.09 g, 5.08 mmol) in THF (50 mL) was added cesium carbonate (2.16 g, 6.63 mmol) and aniline bis-triflamide (2.02 g, 5.66 mmol) (Aldrich). The reaction was stirred at ambient temperature overnight, then an additional amount of cesium carbonate (1.10 g, 3.38 mmol) and aniline bis-triflamide (1.01 g, 2.83 mmol) were added. After 4 h, an additional amount of cesium carbonate (1.06 g, 3.26 mmol) and aniline bis-triflamide (0.97 g, 2.71 mmol) were added. After stirring at ambient temperature overnight the reaction mixture was evaporated in vacuo. The residue was partitioned between water (50 mL) and DCM (50 mL). The organic phase was cut away, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography (SiO2, 0-8% (10% NH_4OH in MeOH) in DCM) to give Compound **31** as a tan solid (2.536 g, yield 92%).

Compound **31**: LC/MS, *m/z* = 546.0 $[M + H]^+$ (Calc: 545.6).

To a solution of Compound **31** (2.54 g, 4.65 mmol) in DMF (25 mL) was added zinc cyanide (0.33 g, 2.80 mmol), zinc powder (0.08 g, 1.24 mmol) and $Pd(dppf)Cl_2$ (0.192 g, 0.235 mmol). After deoxygenating the mixture with argon, the reaction vessel was sealed and heated at 120 °C overnight. The reaction mixture was evaporated in vacuo and the residue purified by flash chromatography (SiO_2, 0-13% (10% NH_4OH in MeOH) in DCM) to give crude Compound **32**. Isolation of pure Compound **32** was accomplished by simple trituration with MeOH. Compound **32** was isolated as a tan powder (1.24 g, yield 63%).

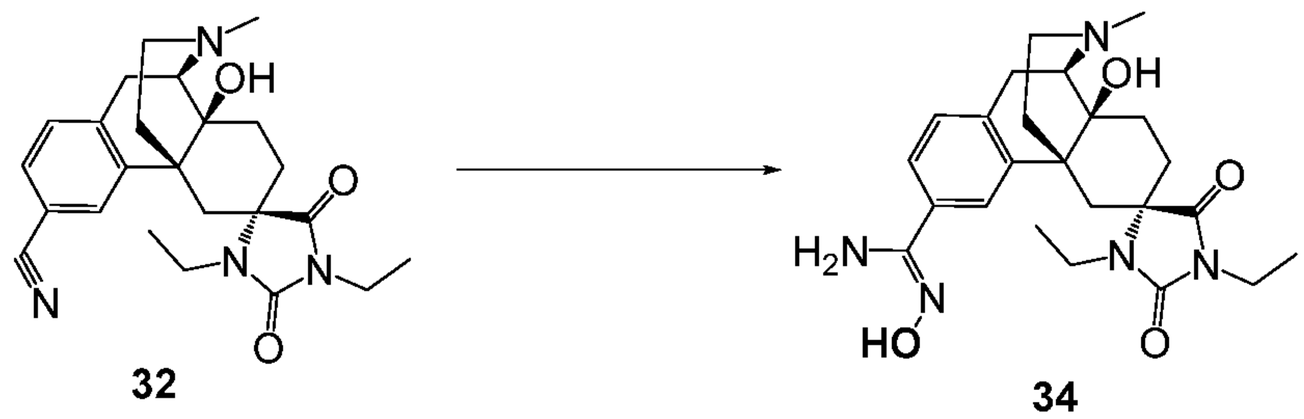
Compound **32**: ^1H NMR δ_H (400 MHz, DMSO-d_6): 7.94 (s, 1H), 7.62 (dd, J=7.9, 1.1 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H), 4.59 (s, 1H), 3.42 (q, J=7.2 Hz, 2H), 3.22 (d, J=19.6 Hz, 1H), 2.97 (dd, J=19.6, 5.4 Hz, 1H), 2.74 (sxt, J=7.2 Hz, 2H), 2.48-2.38 (m, 2H), 2.38-2.32 (m, 1H), 2.32-2.22 (m, 4H), 2.04 (td, J=12.6, 4.6 Hz, 1H), 1.78-1.66 (m, 1H), 1.65-1.42 (m, 4H), 1.11 (t, J=7.2 Hz, 3H), 1.06-0.98 (m, 1H), 0.75 (t, J=7.0 Hz, 3H); LC/MS, *m/z* = 423.3 $[M + H]^+$ (Calc: 422.5).

To a suspension of Compound **32** (0.50 g, 1.19 mmol) in 1:1 EtOH / water (20 mL) was added hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphnito-kP]platinum (II) (0.03 g, 0.061 mmol) (Strem Chemicals). The reaction was heated to reflux for 3.5 h. The reaction mixture was evaporated in vacuo and the residue purified by flash chromatography (SiO2, 0-13% (10% NH_4OH in MeOH) in DCM) to give crude Compound **33**. Isolation of pure Compound **33** was accomplished by simple trituration with MeCN. Compound **33** was isolated as a white powder (0.410 g, yield 78%).

Compound **33**: ^1H NMR δ_H (400 MHz, DMSO-d_6): 7.94-7.83 (m, 2H), 7.69 (dd, J=8.0, 1.2 Hz, 1H), 7.32-7.24 (m, 2H), 4.56 (s, 1H), 3.41 (q, J=7.1 Hz, 2H), 3.17 (d, J=19.1 Hz, 1H), 2.91 (dd, J=19.2, 5.1 Hz, 1H), 2.73 (d, J=4.8 Hz, 1H), 2.62 (dq, J=14.7, 7.1 Hz, 1H), 2.48-2.39 (m, 1H), 2.39-2.24 (m, 6H), 2.11-2.00 (m, 1H), 1.82-1.71 (m, 1H), 1.70-1.59 (m, 1H), 1.56-1.42 (m, 3H), 1.10 (t, J=7.2 Hz, 3H), 1.06-0.98 (m, 1H), 0.70 (t, J=7.0 Hz, 3H); LC/MS, *m/z* = 441.1 $[M + H]^+$ (Calc: 440.5).

EXAMPLE 7

(4S,4b'R,8a'S,9'R,E)-1,3-diethyl-N',8a'-dihydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-3'-carboximidamide (Compound **34**)



32 34

To a solution of Compound **32** (0.252 g, 0.596 mmol) in EtOH (6 mL) was added 50% hydroxylamine in water (0.15 mL, 2.45 mmol). The reaction mixture was heated in a sealed vessel at 80 °C overnight. The reaction mixture was evaporated in vacuo and the residue was purified first by flash chromatography (SiO_2, 0-20% (10% NH_4OH in MeOH) in DCM) and then by reverse-phase chromatography (C18, 0-60% 0.1% TFA in ACN/0.1% TFA in water). The product fractions were lyophilized to give the TFA salt of Compound **34** as a white powder (0.169 g, yield 50%).

(4S,4b'R,8a'S,9'R,E)-1,3-diethyl-N',8a'-dihydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-3'-carboximidamide (Compound **34**): ^1H NMR δ_H (400 MHz, CD_3OD): 7.81 (d, J=1.6 Hz, 1H), 7.65 (dd, J=8.1, 1.7 Hz, 1H), 7.57 (d, J=8.1 Hz, 1H), 3.68-3.49 (m, 5H), 3.21-3.09 (m, 1H), 2.92 (s, 3H), 2.90-2.80 (m, 1H), 2.63-2.41 (m, 5H), 1.97-1.80 (m, 2H), 1.77-1.68 (m, 1H), 1.63-1.50 (m, 1H), 1.50-1.43 (m, 1H), 1.19 (t, J=7.2 Hz, 3H), 0.86 (t, J=7.0 Hz, 3H); LC/MS, *m/z* = 456.1 $[M + H]^+$ (Calc: 455.6).

EXAMPLE 8

The following tables provide results on the efficacy of binding and activity response of exemplified Compounds of the Invention at one or more of the μ-, δ- and κ-opioid receptors.

In TABLE 3, binding affinity of certain Compounds of the Invention to the μ-, δ- and/or κ-opioid receptors was determined in the way as described above.

In TABLE 4, activity response of certain Compounds of the Invention to the μ-, δ- and/or κ-opioid receptors was determined in the way as described above for functional assays.

TABLE 3

Compound No.	Opioid Receptor K_i (nM)	
	μ	κ
21		10.5 ± 1.11

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TABLE 4

Compd No.	Opioid Receptor			
	μ		κ	
	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)
2	17968 ± 1105	75.7 ± 0.88		
3	>20uM	-0.80		
4	>20uM	-1.00 ± 0.003		
8	>20uM	1.00		
13	>20uM	1.00		
14	>20 uM	1.00		
15	>20 uM	1.00		
17	>20 uM	26.0 ± 5.51		
18	>20 uM	35.7 ± 1.20		

Compd No.	Opioid Receptor			
	μ		κ	
	EC_{50} (nM)	E_{max} (%)	EC_{50} (nM)	E_{max} (%)
19	97.0 ± 11.5	54.6 ± 3.04		
20	1884 ± 251.6	28.0 ± 1.53		
21	54.7±7.76	24.7 ± 2.46	220.7 ± 22.6	56.7 ± 3.66
22	2847 ± 216.2	71.7 ± 2.60		
23	3788 ± 287.3	15.7 ± 0.33		
24	73.0 ± 19.7	65.3 ± 4.26		
25	>20uM	1.00		
26	>20uM	0.50		
27	>20uM	1.00		
28	>20uM	1.36		
29	3915 ± 570.6	23.4 ± 1.68		
30	>20uM	1.00		
32	>20uM	16.3 ± 1.76		
33	973.9 ± 117.5	39.3 ± 1.78		
34	17200 ± 1203	29.7 ± 1.18		

The *in vitro* test results provided in Tables 3 and 4 show that representative Compounds of the Invention generally have good binding affinity for one or more opioid receptors. It is believed that these compounds activate these receptors as partial to full agonists. The Compounds of the Invention are therefore expected to be useful to treat Conditions, particularly pain, that are responsive to the activation of one or more opioid receptors.

Further, certain Compounds of the Invention exhibit a reduced propensity to blood-brain barrier penetration as measured by the Madine Darby canine kidney (MDCK) cell-line transport assay.

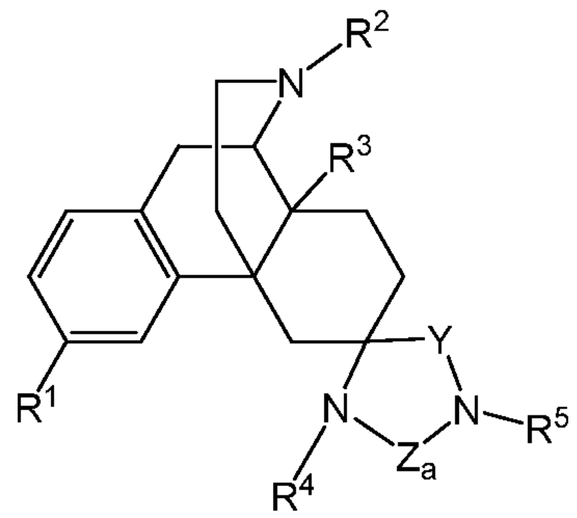
Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

All patents, patent applications, and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A compound having Formula **I**:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is hydroxyl, cyano, aminocarbonyl, $-C(=NR^7)-NR^{7a}R^{7b}$, or alkoxy, wherein said alkoxy is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxyl, halo, haloalkyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, aryl, heteroaryl, heterocyclo, cycloalkyl, and cycloalkenyl;

R^2 is hydrogen or alkyl optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, aryl, and alkoxycarbonyl;

R^3 is hydrogen, hydroxyl, alkoxy, alkylamino, or dialkylamino, wherein each of said alkoxy, said alkylamino, and said dialkylamino is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of hydroxyl, halo, haloalkyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, aryl, heteroaryl, heterocyclo, cycloalkyl, and cycloalkenyl, and wherein said aryl, heteroaryl, heterocyclo, cycloalkyl, and cycloalkenyl are further optionally substituted with 1, 2, or 3 independently selected R^6 groups;

R^4 and R^5 are, each independently, hydrogen or alkyl, wherein said alkyl is optionally substituted with 1 or 2 substituents each independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo; wherein each of said cycloalkyl and said heterocyclo are optionally substituted with 1, 2, or 3 independently selected R^6 groups;

each R^6 is independently selected from the group consisting of hydroxyl, halo, alkyl, haloalkyl, cyano, nitro, amino, alkylamino, dialkylamino, carboxy, alkoxy, carboxamido, and alkoxycarbonyl;

R^7 is H, hydroxyl, alkoxy, or alkyl;

R^{7a} and R^{7b} are, each independently, hydrogen or alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo;

Y is C=O or CH_2;

Z_a is C=O or CHR^8;

wherein R^8 is hydrogen, (C_{1-6})alkyl, or phenyl optionally substituted with 1, 2, or 3 independently selected R^6 groups,

provided that

i) when R^1 is hydroxyl, cyano, aminocarbonyl, or methoxy, and R^3 is hydroxyl, then R^4 and R^5 are the same; and

ii) when R^2 is alkyl substituted by an aryl group, then at least one of R^4 and R^5 is optionally-substituted alkyl;

further provided that

said compound is not any compound selected from the group consisting of

1) (4S,4b'R,8a'S,9'R)-8a'-hydroxy-3'-methoxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione;

2)(4S,4b'R,8a'S,9'R)-3',8a'-dihydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione;

3)(4S,4b'R,8a'S,9'R)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione;

4) (4S,4b'R,8a'S,9'R)-8a'-hydroxy-11'-isopentyl-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione;

5) (4S,4b'R,8a'S,9'R)-11'-ethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione;

6) (4S,4b'R,8a'S,9'R)-3',8a'-dihydroxy-11'-isopentyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione;

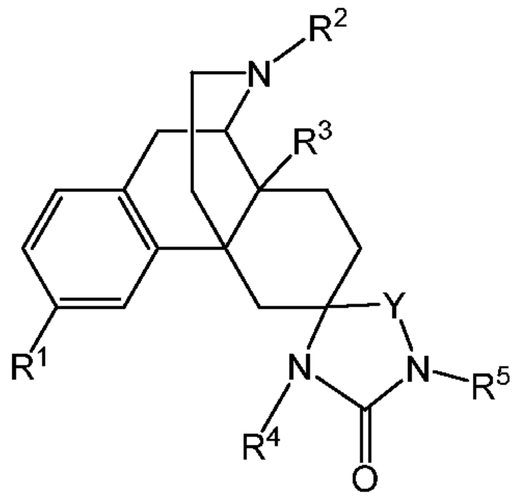
7) (4S,4b'R,8a'S,9'R)-11'-ethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione;

8) (4S,4b'R,8a'S,9'R)-1,3-diethyl-3',8a'-dihydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione; and

9) (4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-3',8a'-dihydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione.

2. The compound of claim 1, wherein Z_a is C=O or CH_2.

3. The compound of claim 1 or 2, having Formula **II**:

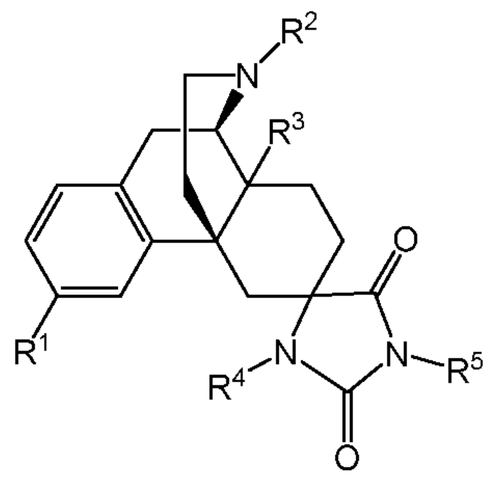


II

or a pharmaceutically acceptable salt or solvate thereof.

4. The compound of any one of claims 1 to 3, wherein Y is C=O.

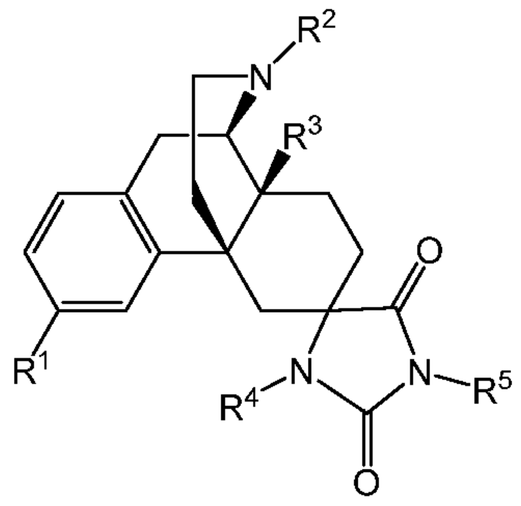
5. The compound of any one of claims 1 to 4, having Formula **III**:



III

or a pharmaceutically acceptable salt or solvate thereof.

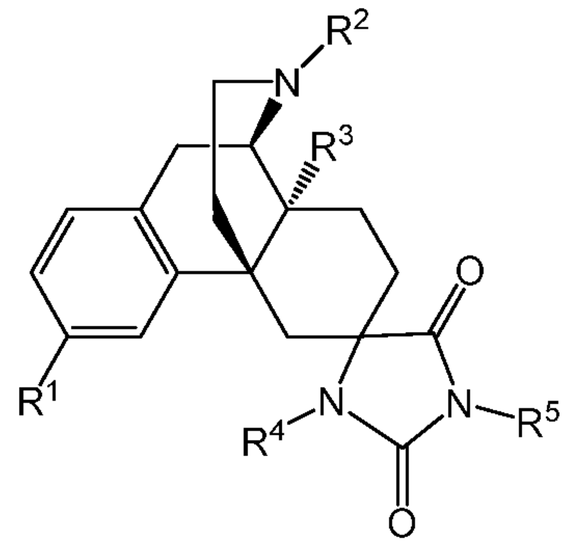
6. The compound of any one of claims 1 to 5, having Formula **IV**:



IV

or a pharmaceutically acceptable salt or solvate thereof.

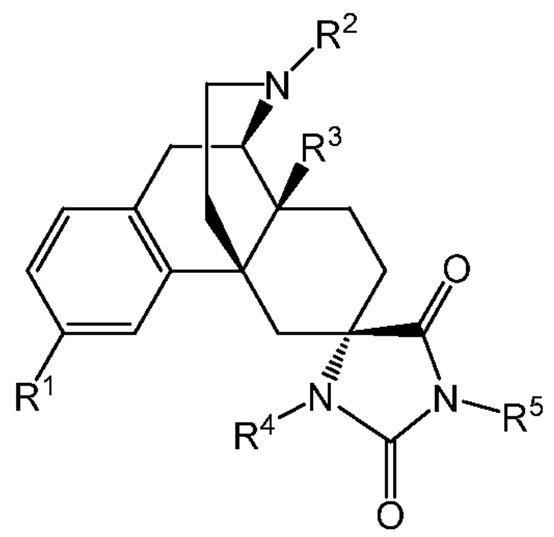
7. The compound of any one of claims 1 to 5, having Formula **V**:



V

or a pharmaceutically acceptable salt or solvate thereof.

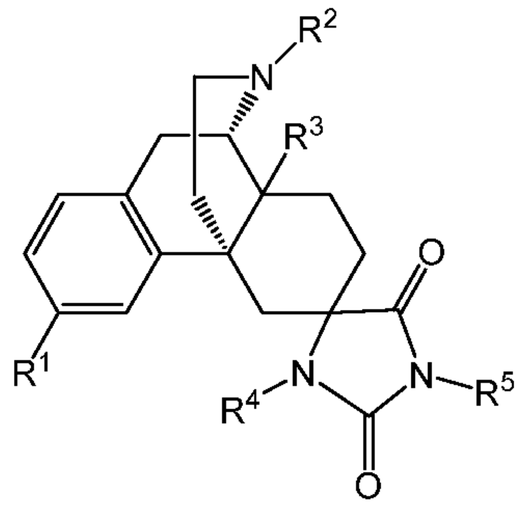
8. The compound of any one of claims 1 to 6, having Formula **VI**:



VI

or a pharmaceutically acceptable salt or solvate thereof.

9. The compound of any one of claims 1 to 4, having Formula **VII**:



VII

or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of any one of claims 1 to 9, wherein R^2 is hydrogen.

11. The compound of any one of claims 1 to 9, wherein R^2 is (C_{1-6})alkyl optionally substituted by hydroxyl, amino, alkylamino, dialkylamino, alkoxy, aryl, or alkoxycarbonyl.

12. The compound of any one of claims 1 to 9 and 11, wherein R^2 is unsubstituted (C_{1-6})alkyl.

13. The compound of any one of claims 1 to 9 and 11, wherein R^2 is (C_{1-6})alkyl substituted by amino, alkylamino, dialkylamino, or aryl.

14. The compound of claim 13, wherein R^2 is (C_{1-3})alkyl substituted by phenyl or di((C_{1-3})alkyl)amino.

15. The compound of any one of claims 1 to 14, wherein R^3 is hydrogen.

16. The compound of any one of claims 1 to 14, wherein R^3 is hydroxyl.

17. The compound of any one of claims 1 to 16, wherein R^4 and R^5 are, each independently, hydrogen or (C_{1-6})alkyl optionally substituted with a substituent selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo.

18. The compound of any one of claims 1 to 17, wherein one of R^4 and R^5 is hydrogen, the other is hydrogen or (C_{1-6})alkyl optionally substituted with a substituent selected from the

group consisting of hydroxyl, amino, ((C1-6)alkyl)amino, di((C1-6)alkyl)amino, carboxy, (C1-6)alkoxy, ((C1-6)alkoxy)carbonyl, carboxamido, (C3-8)cycloalkyl, and 5- to 6-membered heterocyclo.

19. The compound of any one of claims 1 to 17, wherein R^4 and R^5, each independently, are (C1-6)alkyl optionally substituted by (C3-8)cycloalkyl or 5- to 6-membered heterocyclo.

20. The compound of any one of claims 1 to 17 and 19, wherein R^4 and R^5, each independently, are unsubstituted (C1-6)alkyl.

21. The compound of any one of claims 1 to 17 and 19, wherein R^4 and R^5, each independently, are (C1-6)alkyl substituted by (C3-8)cycloalkyl or 5- to 6-membered heterocyclo.

22. The compound of any one of claims 1 to 17 and 19, wherein R^4 and R^5, each independently, are (C1-3)alkyl substituted by (C3-6)cycloalkyl.

23. The compound of any one of claims 1 to 22, wherein R^4 and R^5 are the same.

24. The compound of any one of claims 1 to 22, wherein R^4 and R^5 are different.

25. The compound of any one of claims 1 to 24, wherein R^1 is hydroxyl.

26. The compound of any one of claims 1 to 24, wherein R^1 is unsubstituted (C1-6)alkoxy.

27. The compound of claim 26, wherein R^1 is methoxy.

28. The compound of any one of claims 1 to 24, wherein R^1 is cyano.

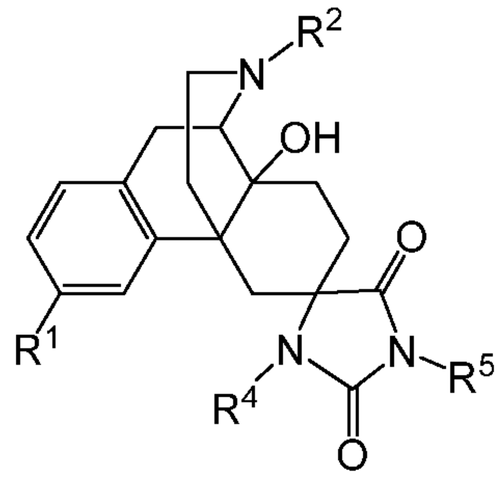
29. The compound of any one of claims 1 to 24, wherein R^1 is aminocarbonyl.

30. The compound of any one of claims 1 to 24, wherein R^1 is $-C(=NR^7)-NR^{7a}R^{7b}$.

31. The compound of claim 30, wherein R^7 is hydroxyl.

32. The compound of claim 30 or 31, wherein R^{7a} and R^{7b}, independently, are hydrogen or unsubstituted (C_{1-3})alkyl.

33. A compound of Formula **IA**, or a pharmaceutically acceptable salt or solvate thereof:



IA,

Wherein

R^1 is hydroxyl, cyano, aminocarbonyl, $-C(=NR^7)-NR^{7a}R^{7b}$, or alkoxy;

R^2 is hydrogen or alkyl optionally substituted with dialkylamino or aryl;

R^4 and R^5 are the same, which are hydrogen or alkyl optionally substituted with cycloalkyl;

R^7 is H, hydroxyl, or alkoxy; and

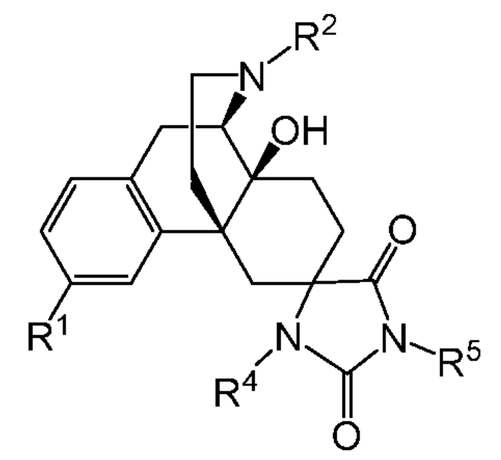
R^{7a} and R^{7b} are, each independently, hydrogen or alkyl;

Provided that

1) when R^2 is alkyl substituted with aryl, then R^4 and R^5 are alkyl optionally substituted with cycloalkyl; and

2) when R^2 is alkyl, then R^1 is cyano, aminocarbonyl, or $-C(=NR^7)-NR^{7a}R^{7b}$.

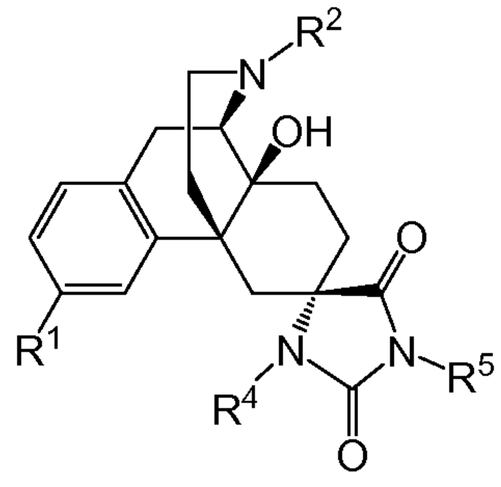
34. The compound of claim 33, wherein said compound is a compound of Formula **IB**:



IB

or a pharmaceutically acceptable salt or solvate thereof.

35. The compound of claim 33 or 34, wherein said compound is a compound of Formula **IC**:



IC

or a pharmaceutically acceptable salt or solvate thereof.

36. The compound of any one of claims 33 to 35, wherein R^2 is (C_{1-6})alkyl substituted by di(C_{1-3})alkylamino.

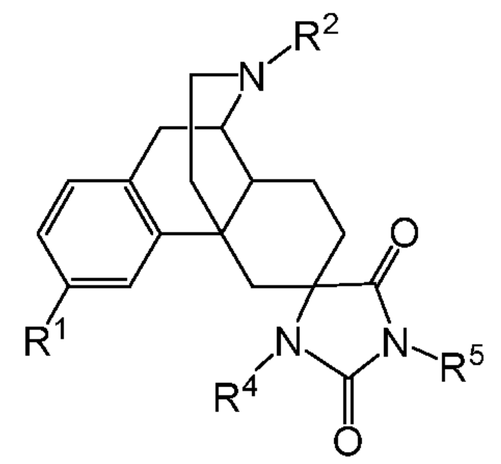
37. The compound of any one of claims 33 to 35, wherein R^2 is (C_{1-6})alkyl substituted by aryl.

38. The compound of any one of claims 33 to 37, wherein R^1 is hydroxyl or (C_{1-6})alkoxy.

39. The compound of any one of claims 33 to 35, wherein R^2 is (C_{1-6})alkyl.

40. The compound of claim 39, wherein R^1 is cyano, aminocarbonyl, or $-C(=N-OH)-NH_2$.

41. A compound of Formula **IIA**, or a pharmaceutically acceptable salt or solvate thereof:



IIA

Wherein

R^1 is hydroxyl, cyano, aminocarbonyl, $-C(=NR^7)-NR^{7a}R^{7b}$, or alkoxy;

R^2 is hydrogen or alkyl optionally substituted with 1, 2, or 3 substituents, each independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, aryl, and alkoxycarbonyl;

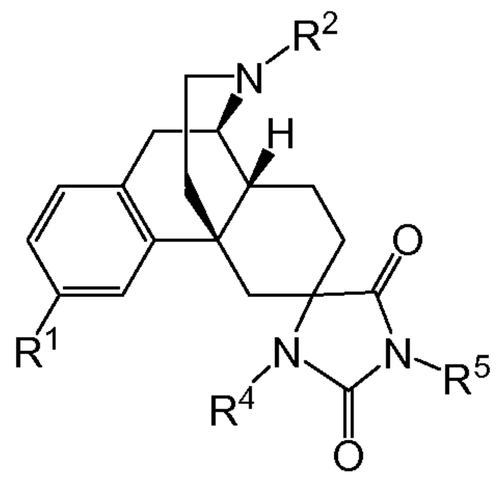
R^4 and R^5 are, each independently, hydrogen or alkyl, wherein said alkyl is optionally substituted with 1 or 2 substituents each independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo; wherein each of said cycloalkyl and said heterocyclo are optionally substituted with 1, 2, or 3 independently selected R^6 groups;

each R^6 is independently selected from the group consisting of hydroxyl, halo, alkyl, haloalkyl, cyano, nitro, amino, alkylamino, dialkylamino, carboxy, alkoxy, carboxamido, and alkoxycarbonyl;

R^7 is H, hydroxyl, alkoxy, alkyl, or cyano; and

R^{7a} and R^{7b} are, each independently, hydrogen or alkyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of hydroxyl, amino, alkylamino, dialkylamino, carboxy, alkoxy, alkoxycarbonyl, carboxamido, cycloalkyl, and heterocyclo.

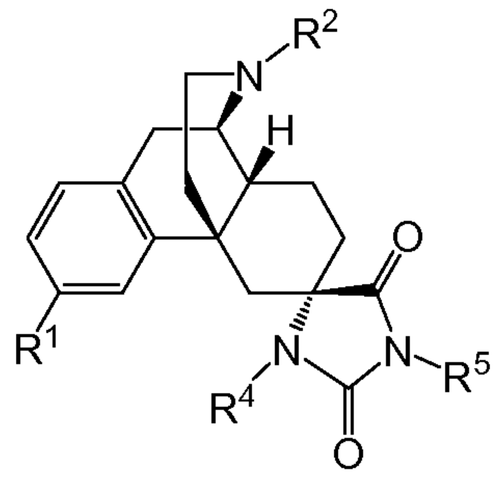
42. The compound of claim 41, wherein said compound is a compound of Formula **IIB**:



IIB

or a pharmaceutically acceptable salt or solvate thereof.

43. The compound of claim 41 or 42, wherein said compound is a compound of Formula **IIC**:



IIC

or a pharmaceutically acceptable salt or solvate thereof.

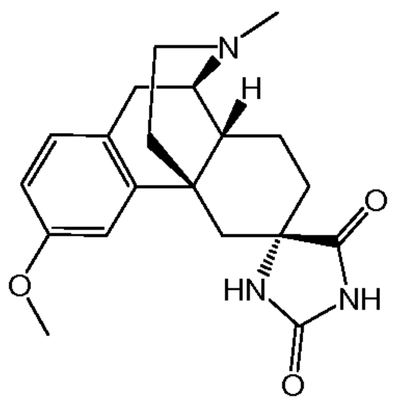
44. The compound of any one of claims 41 to 43, wherein R^2 is (C_{1-6})alkyl.

45. The compound of any one of claims 41 to 44, wherein R^1 is hydroxyl or (C_{1-6})alkoxy.

46. The compound of any one of claims 41 to 45, wherein R^4 and R^5, each independently, are hydrogen or (C_{1-6})alkyl.

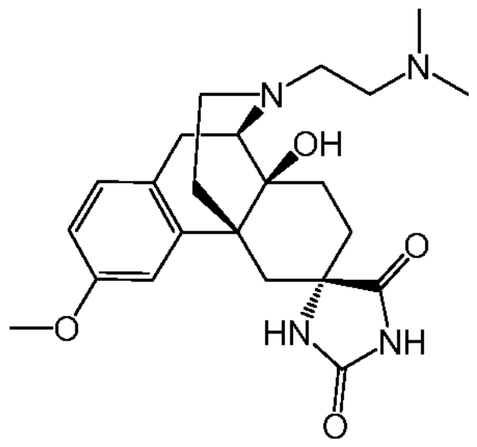
47. The compound of claim 1, selected from the group consisting of

1)



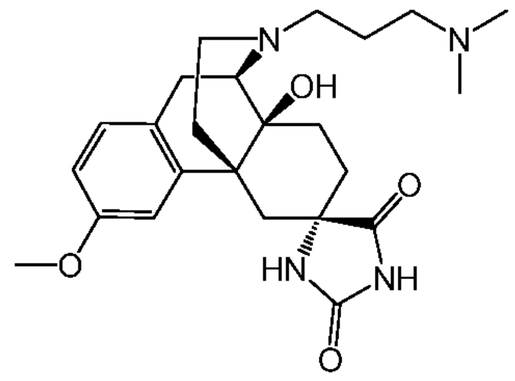
(4S,4b'S,8a'R,9'R)-3'-methoxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **2**);

2)



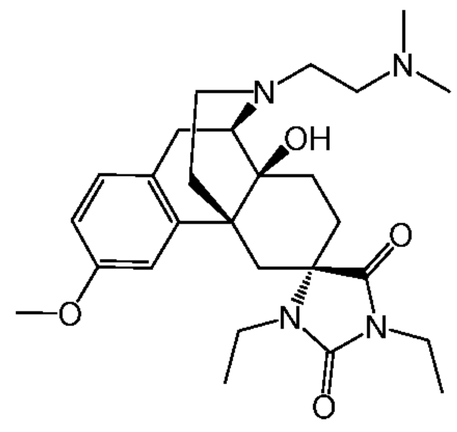
(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **3**);

3)



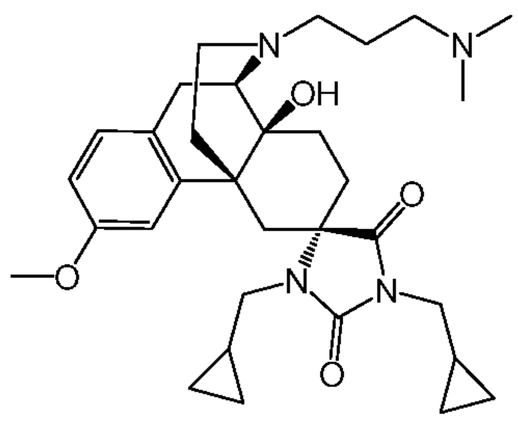
(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **4**);

4)



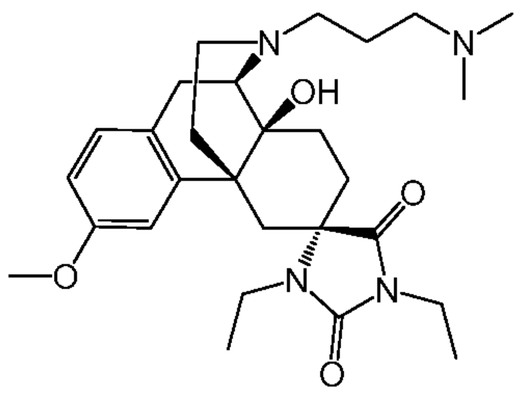
(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione (Compound **8**);

5)



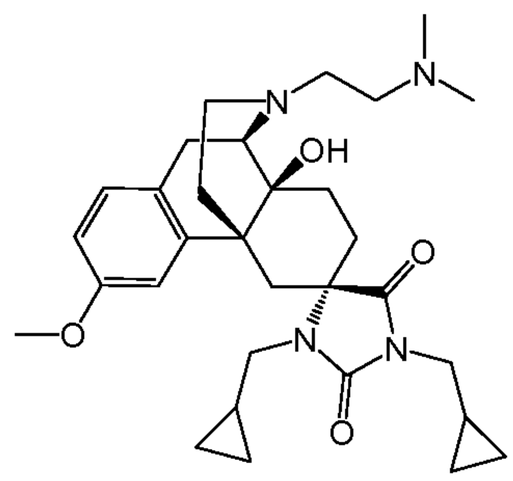
(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(3-(dimethylamino)-propyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione (Compound **13**);

6)



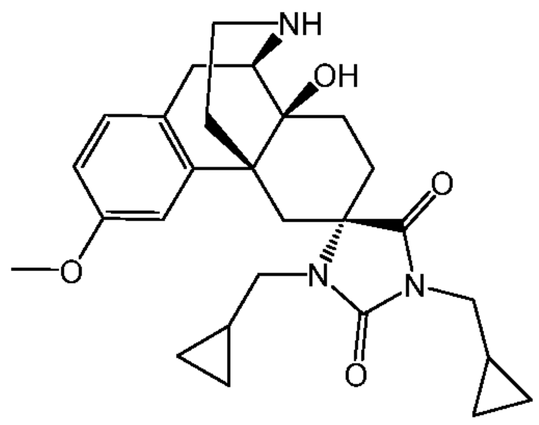
(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione (Compound **14**);

7)



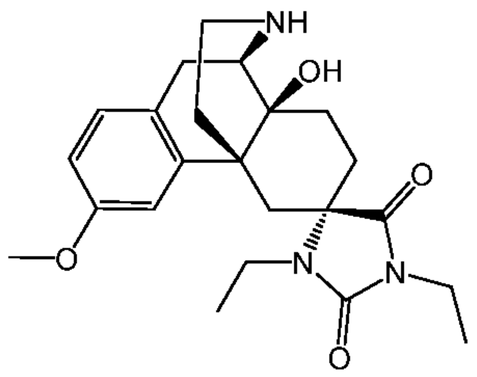
(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(2-(dimethylamino)ethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)phenanthrene]-2,5-dione (Compound **15**);

8)



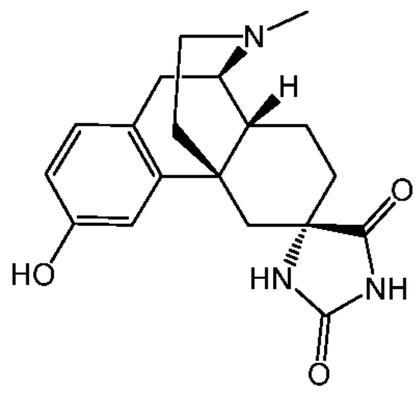
(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **17**);

9)



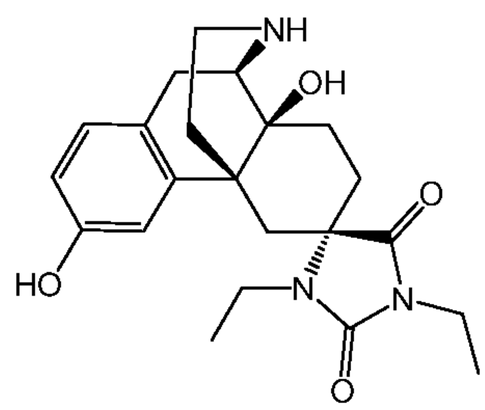
(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-3'-methoxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **18**);

10)



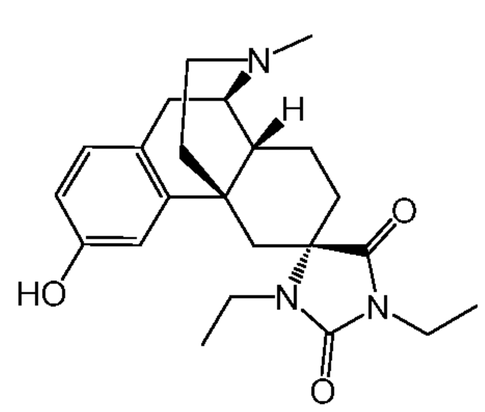
(4S,4b'S,8a'R,9'R)-3'-hydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **19**);

11)



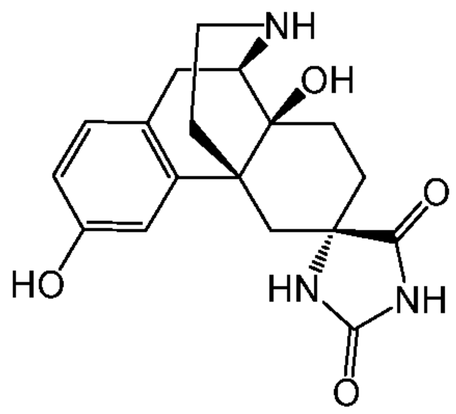
(4S,4b'R,8a'S,9'R)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **20**);

12)



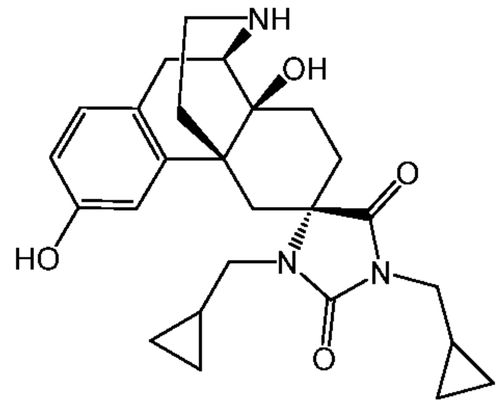
(4S,4b'S,8a'R,9'R)-1,3-diethyl-3'-hydroxy-11'-methyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **21**);

13)



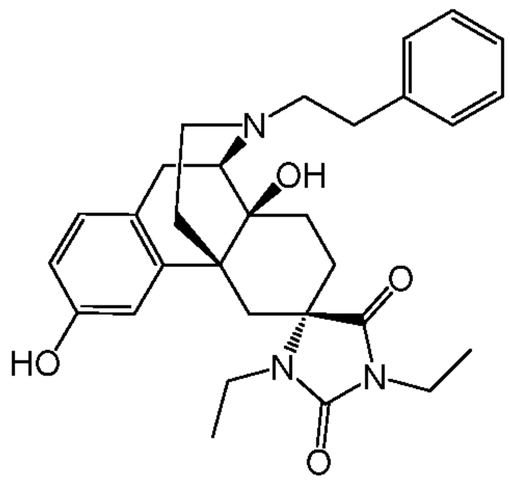
(4S,4b'R,8a'S,9'R)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **22**);

14)



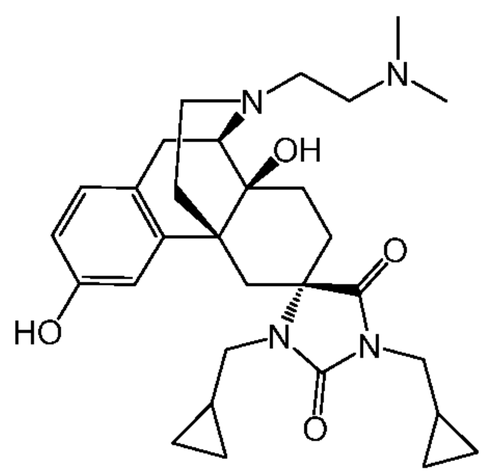
(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **23**);

15)



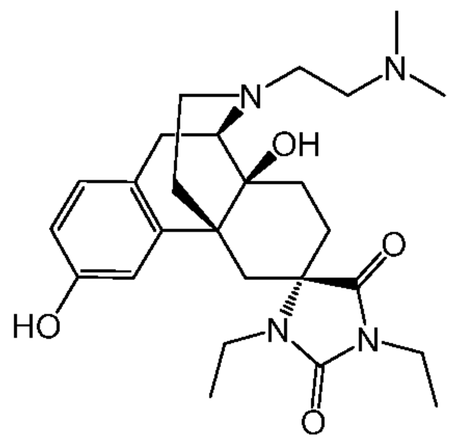
(4S,4b'R,8a'S,9'R)-1,3-diethyl-3',8a'-dihydroxy-11'-phenethyl-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **24**);

16)



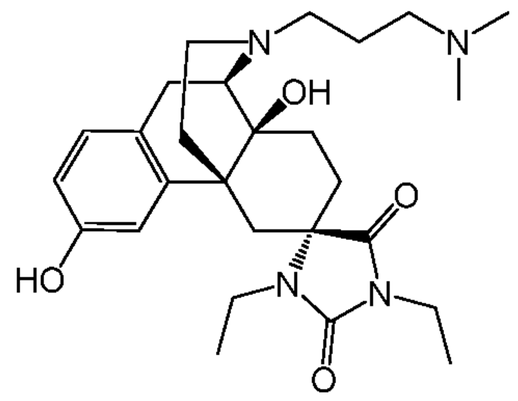
(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(2-(dimethylamino)ethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **25**);

17)



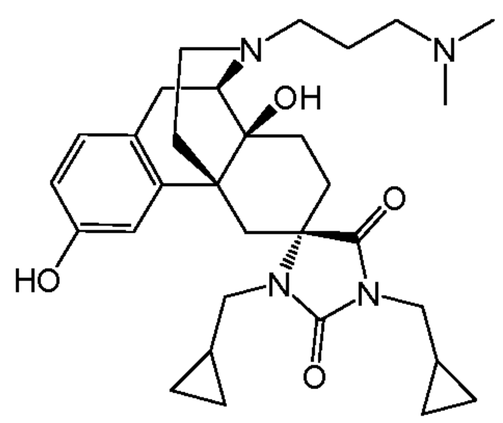
(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **26**);

18)



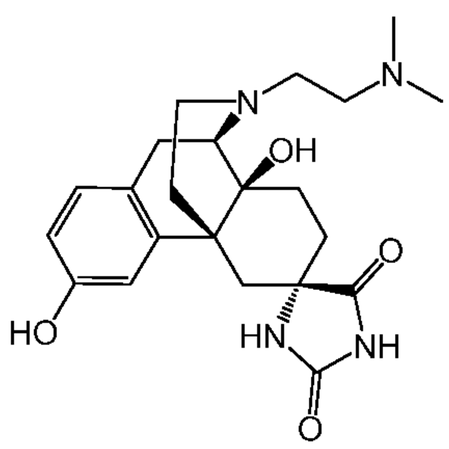
(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-1,3-diethyl-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b]-(epiminoethano)-phenanthrene]-2,5-dione (Compound **27**);

19)



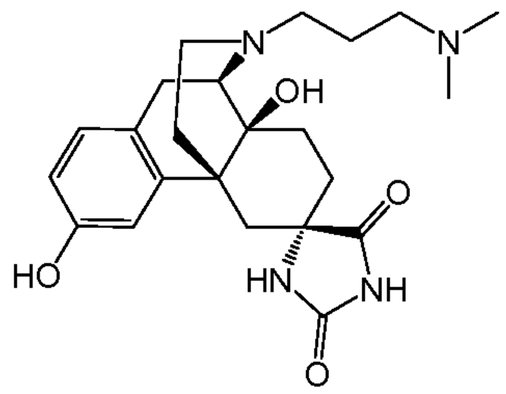
(4S,4b'R,8a'S,9'R)-1,3-bis(cyclopropylmethyl)-11'-(3-(dimethylamino)-propyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **28**);

20)



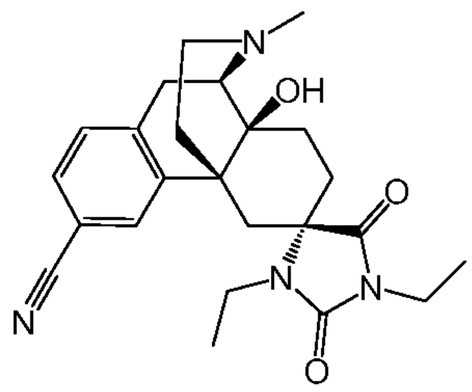
(4S,4b'R,8a'S,9'R)-11'-(2-(dimethylamino)ethyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-2,5-dione (Compound **29**);

21)



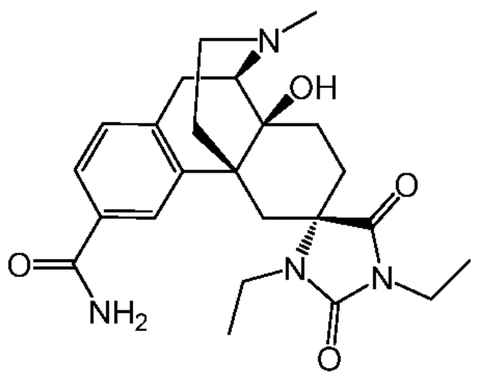
(4S,4b'R,8a'S,9'R)-11'-(3-(dimethylamino)propyl)-3',8a'-dihydroxy-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-2,5-dione (Compound **30**);

22)



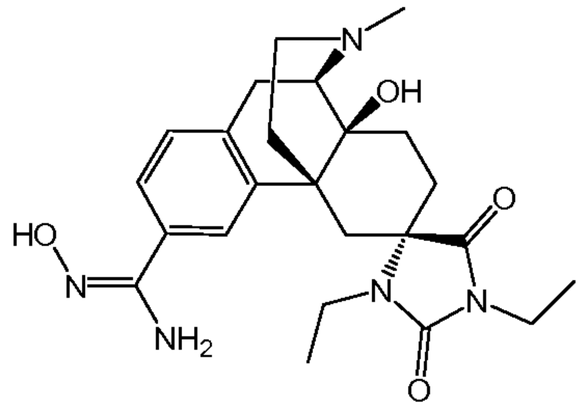
(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-3'-carbonitrile (Compound **32**);

23)



(4S,4b'R,8a'S,9'R)-1,3-diethyl-8a'-hydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)phenanthrene]-3'-carboxamide (Compound **33**); and

24)



(4S,4b'R,8a'S,9'R,E)-1,3-diethyl-N',8a'-dihydroxy-11'-methyl-2,5-dioxo-8',8a',9',10'-tetrahydro-5'H,7'H-spiro[imidazolidine-4,6'-[9,4b](epiminoethano)-phenanthrene]-3'-carboximidamide (Compound **34**);

and a pharmaceutically acceptable salt and solvate thereof.

48. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-47, or a pharmaceutically acceptable salt or solvate thereof, and one or more pharmaceutically acceptable carriers.

49. A method of treating or preventing a disorder responsive to modulation of one or more opioid receptors in a patient identified as in need of such treatment or prevention, comprising administering to said patient an effective amount of a compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt or solvate thereof.

50. The method of claim 49, wherein the disorder is responsive to modulation of μ-opioid receptor or κ-opioid receptor, or to modulation of a combination thereof.

51. The method of claim 49 or 50, wherein the disorder is responsive to modulation of the κ-opioid receptor.

52. The method of any one of claims 49 to 51, wherein the disorder is pain.

53. A method of treating or preventing pain, constipation, diarrhea, pruritis, an addictive disorder, withdrawal from alcohol addiction or withdrawal from drug addiction in a patient identified as in need of such treatment or prevention, comprising administering to said patient an effective amount of a compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt or solvate thereof.

54. The method of claim 53, wherein the method is for treating pain.

55. The method of claim 53 or 54, wherein said pain is acute pain, chronic pain or surgical pain.

56 The method of any one of claims 53 to 55, wherein said pain is chronic pain.

57. The method of claim 55 or 56, wherein said chronic pain is neuropathic pain, postoperative pain, or inflammatory pain.

58. A method of modulating one or more opioid receptors in a subject, comprising administering to the subject an effective amount of a compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt or solvate thereof.

59. The method of claim 58, wherein μ- or κ-opioid receptor is modulated, or both the μ- and κ-opioid receptors are modulated in said subject.

60. A compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt or solvate thereof, for use in treatment or prevention of a disorder responsive to modulation of one or more opioid receptors in a patient.

61. The compound of claim 60, wherein the disorder is responsive to modulation of μ-opioid receptor or κ-opioid receptor, or to modulation of a combination thereof.

62. The compound of claim 60 or 61, wherein the disorder is responsive to the modulation of the κ-opioid receptor.

63. The compound of any one of claims 60 to 62, wherein the disorder is pain.

64. A compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt or solvate thereof, for use in treatment or prevention of pain, constipation, diarrhea, pruritis, an addictive disorder, withdrawal from alcohol addiction or withdrawal from drug addiction in a patient.

65. The compound of claim 64, wherein said use is for the treatment or prevention of pain.

66. The compound of claim 64 or 65, wherein said pain is acute pain, chronic pain or surgical pain.

67. The compound of claim 66, wherein said chronic pain is neuropathic pain, postoperative pain, or inflammatory pain.

68. Use of a compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating or preventing a disorder responsive to the modulation of one or more opioid receptors.

69. The use of claim 68, wherein the disorder is responsive to modulation of μ-opioid receptor or κ-opioid receptor, or both the μ-opioid and the κ-opioid receptors.

70. The use of claim 68 or 69, wherein the disorder is responsive to modulation of the κ-opioid receptor.

71. The use of any one of claims 68 to 70, wherein the disorder is pain.

72. The use of claim 71, wherein said pain is acute pain, chronic pain or surgical pain.

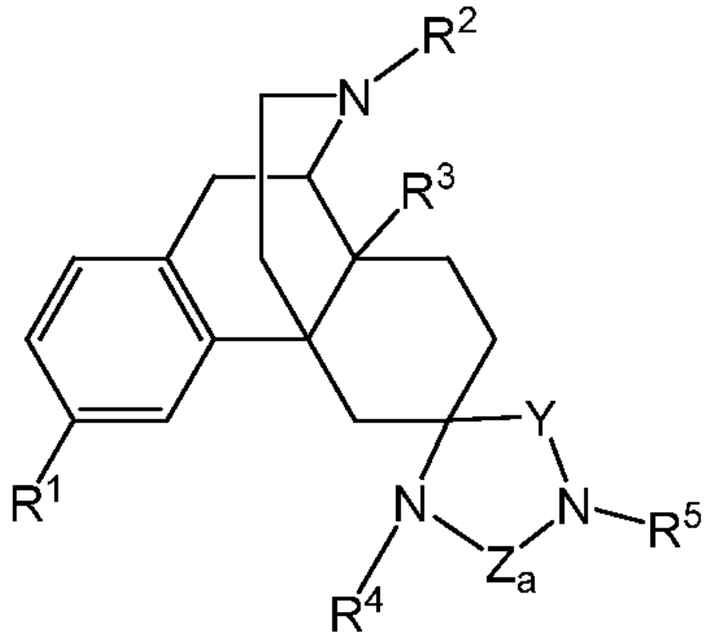
73. The use of claim 72, wherein said chronic pain is neuropathic pain, postoperative pain, or inflammatory pain.

74. A compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is ^{3}H, ^{11}C, or ^{14}C radiolabeled.

75. A method of screening a candidate compound for the ability to bind to an opioid receptor using a radiolabeled compound of claim 74, comprising a) introducing a fixed concentration of the radiolabeled compound to the receptor to form a complex; b) titrating the complex with a candidate compound; and c) determining the binding of the candidate compound to said receptor.

76. A method of preparing a pharmaceutical composition, comprising admixing a therapeutically effective amount of a compound of any one of claims 1-47, or a pharmaceutically acceptable salt or solvate thereof, with a pharmaceutically acceptable carrier.

77. A kit, comprising a sterile container containing an effective amount of the compound of any one of claims 1 to 47, or a pharmaceutically acceptable salt or solvate thereof, and instructions for therapeutic use.



(I)