Title: MORPHINAN DERIVATIVES OF ORGANIC AND INORGANIC ACIDS

Abstract: Novel 4,5-epoxy-14-substituted morphinan derivatives of organic and inorganic acids are disclosed. Pharmaceutical compositions containing the compounds and methods of their pharmaceutical uses and syntheses are also disclosed. The compounds disclosed are useful, inter alia, as modulators of opioid receptors.
MORPHINAN DERIVATIVES OF ORGANIC AND INORGANIC ACIDS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/047,996 filed April 25, 2008 and U.S. Provisional Application No. 61/055,155 filed on May 05, 2008, both of which are incorporated herein in their entireties.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0002] The present invention generally relates to novel 4,5-epoxy-morphinan derivatives of organic and inorganic acids, including in one embodiment 17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-carboxyalkoxy-morphinan-6-one, salts, including pharmaceutically acceptable salts thereof, and related neutral, acidic and basic forms thereof. The present invention also comprises synthetic methods for the preparation of these compounds, pharmaceutical preparations comprising the same, and methods for their use.

DESCRIPTION OF THE RELATED ART

[0003] Opioids are agents that bind to certain receptors, known as opioid receptors, principally found in the central nervous system and gastrointestinal tract. They typically exhibit opium or morphine-like properties. There are four broad classes of opioids: endogenous opioid peptides, produced in the body; opium alkaloids, such as morphine (the prototypical opioid) and codeine; semi-synthetic opioids such as heroin and oxycodone; and fully synthetic opioids such as pethidine and methadone that have structures unrelated to the opium alkaloids. Although used synonymously with the term "opiate," the term "opiate" is more correctly used to describe an opioid compound derived from a natural opium alkaloid or a semi-synthetic derivative of such a derived compound. Among the chemical classes of opioids with morphine-like activity are the purified alkaloids of opium consisting of phenanthrenes (morphine and codeine both share the phenanthrene or morphinan ring structure) and benzylisoquinolines, semi-synthetic derivatives of morphine, phenylpiperidine derivatives, morphinan derivatives, benzomorphan derivatives, diphenyl-heptane derivatives, and propionanilide derivatives.

[0004] Opioid receptors have been classified into at least four major classes: mu (mu-1, mu-2 and mu-3), kappa, delta and ORL 1 receptor. The nociceptin receptor or ORL 1
receptor has recently been identified. Each of these classes of receptors is believed to be distributed throughout the CNS and the periphery. All of these receptors have been hypothesized to be G-protein coupled receptors acting on GABAergic neurotransmission. Agonistic activation of these receptors activates K+ currents which increases K+ efflux, i.e., hyperpolarization, thereby reducing voltage-gated Ca2+ entry. Hyperpolarization of membrane potential by K+ currents and inhibition of the Ca2+ influx prevents neurotransmitter release and pain transmission in varying neuronal pathways. The pharmacological response to an opioid depends upon the receptor(s) it binds, its affinity for the receptor, and whether the opioid compound binds in a agonistic or antagonistic fashion. Activation of one receptor versus another may result in a distinct pharmacodynamic profile. For example, activation of the mu-1 receptor by the opioid agonist morphine may lead to supraspinal analgesia, while respiratory depression and physical dependence may be mediated by activation of the mu-2 receptor and spinal analgesia by the activation of the kappa-receptor.

[0005] Opioid compounds can be divided broadly into agonists and antagonists. The term "agonist" refers to a signaling molecule which binds to a receptor, inducing a conformational change that produces a response. The term "antagonist" broadly refers to a drug which attenuates the effect of the agonist.

[0006] Opioid compounds fall on a sliding scale of efficacy from a full agonist to an antagonist. For example, several morphinan derivatives having various substituents on the nitrogen atom have been found to exhibit narcotic antagonist as well as narcotic analgesic activity. Such compounds are referred to as agonist-antagonists. Pachter and Matossian, U.S. Pat. No. 3,393,197, disclose N-substituted-14-hydroxydihyronormorphines, including the N-cyclobutylmethyl derivative, commonly called nalbuphine. Monkovic and Thomas, U.S. Pat. No. 3,775,414, disclose N-cyclobutylmethyl-3,14-dihydroxymorphinan, commonly called butorphanol. Bentley et al., U.S. Pat. No. 3,433,791, disclose 17-(cyclopropylmethyl)-alpha-(1,1-dimethylcyclohexyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-alpha-methyl-6,14-ethenomorphinan-7-methanol, commonly called buprenorphine.

[0007] Opioid agonists are clinically used for a number of indications, including to produce analgesia and anesthesia, to suppress coughing, to alleviate diarrhea, to ameliorate the anxiety due to a shortness of breath (oxymorphone) and in the detoxification of an opioid antagonist overdose. Beyond their clinically useful effects, opioid agonists have also been reported to have a number of side effects, including constipation, dysphoria, respiratory depression, dizziness, nausea, dependency, and pruritus. Some of these side effects may be
associated with activation of peripheral rather than central receptors. For example, the administration of mu opioid agonists may result in intestinal dysfunction, such as constipation, due to the receptors in the wall of the gut.

[0008] Certain opioid analogs are known to act as opioid receptor binding antagonists, that is, the analogs bind to the opioid receptors and interfere with the expression of opioid activity at the receptor sites. Opioid antagonists reverse the major pharmacodynamic actions of the opioid narcotics, such as analgesia, sedation, respiratory depression and myosis. Antagonists generally may be segregated into two broad classes, "surmountable" or "insurmountable" (alternatively "unsurmountable"), on the basis of being competitive or non-competitive.

[0009] Mu opioid receptors, which have been classified as a G-protein coupled receptors (GPCR), have been suggested to have a constitutively active state that may be represented by mu* (μ*) (see, e.g., U.S. Patent No. 6,007,986). With no prior drug exposure (naive state) the activity of the mu* state is believed to be minimal. Compounds that exhibit antagonist activity at a particular GPCR having basal signaling activity, such as the mu-opioid receptor, have been classified as either neutral antagonists or inverse agonists based on the effect which they exhibit upon the basal signaling activity of the particular receptor for which they are a ligand following interaction. "Inverse antagonists," are agents which block the effects of an agonist at the target receptor and also suppress spontaneous receptor activity. By "neutral antagonist," it is meant the compound simply binds to the receptor without changing its activity. A null antagonist may bind selectively to the resting, drug-sensitive mu receptor state, or to the constitutively active mu receptor state, or to both states.

[0010] Several well-known N-substituted morphinan derivatives are pure narcotic antagonists with little or no agonist activity. Lewenstein, U.S. Pat. No. 3,254,088, discloses N-allyl-7,8-dihydro-14-hydroxynormorphinone, commonly known as naloxone. Pachter and Matossian, U.S. Pat. No. 3,332,950, disclose N-substituted- 14-hydroxy-dihydrormorphinones including the N-cyclopropylmethyl analog, commonly known as naltrexone. The compounds of these two patents are narcotic antagonists.

[0010] Naloxone and naltrexone are practically pure opioid antagonists devoid of analgesic activity (Bulberg, H.; Dayton, H.B. Narcotic Antagonists; Braude, M.C., Harris, L.S.; May, E.L.; Smith, J.P.; Villarrela, J.E., Ed.; Raven: New York, 1974; pp. 33 – 43). Competitive antagonists, such as naloxone and naltrexone, bind to the opioid receptors with higher affinity
than agonists but do not activate the receptors. This displaces the agonist, attenuating and/or reversing the agonist effects. This effectively blocks the receptor, preventing the body from making use of opioids and endorphins, endogenous proteins that naturally bind to the opioid receptors. On the other hand, nalorphine and nalbuphine, despite their potent mu-antagonistic activity, as indicated above, have been reported to possess analgesic activity of their own through agonism at the opioid kappa-receptor (Casy, A.F., Parfitt, R.T., *Opioid Analgesics, Chemistry and Receptors*; Plenum: New York, 1986; Chapter 4, pp. 153 - 214).

[0011] For many years, physical dependence or drug addiction caused by opioids have been treated by drug withdrawal through the administration of opioid antagonistic drugs, such as naltrexone and naloxone. Such treatment protocols may entail the substitution of another drug such as methadone, buprenorphine, or methadyl acetate for the opioid. Opioid overdose can also be rapidly reversed with an opioid antagonist.

[0012] More recently, there have been attempts to selectively antagonize opioid-induced side effects via the use of receptor antagonists, such as naloxone or nalmephene. However, the success may be said to be limited because these compounds may also reverse analgesia and induce opioid withdrawal (Yuan, C-S. *et al.*, J. Pharm. Exp. Ther. 300: 118-123 (2002)). For example, naloxone and naltrexone have been implicated as being useful in the treatment of gastrointestinal tract dysmotility (see, e.g., U.S. Pat. No. 4,987,126 and Kreek, M. J. Schaefer, R. A., Hahn, E. F., Fishman, J. Lancet, 1983, 1, 8319, 261 which disclose naloxone and other morphinan-based opioid antagonists (i.e., naloxone, naltrexone) for the treatment of idiopathic gastrointestinal dysmotility). Naloxone has also been reported to effectively treat non-opioid induced bowel obstruction, implying that the drug may act directly on the GI tract or in the brain (See, e.g., Schang, J. C , Devroede, G., Am. J. Gastroenerol., 1985, 80, 6, 407), and implicated as a therapy for paralytic ileus (Mack, D. J. Fulton, J. D., Br. J. Surg., 1989, 76, 10, 1101). However, it is well known that activity of naloxone and naltrexone is not limited to peripheral systems and may interfere with the analgesic effects of opioid narcotics.

[0013] A number of side-effects produced by opioid agonists are believed to be of central origin. In order to avoid such side effects, peripheral opioid agonists and antagonists that do not cross the blood-brain barrier into the central nervous system have been proposed and developed. One such peripheral opioid antagonist is a quaternary derivative of noroxymorphone, (R)-N-methylnaltrexone (WO 06127899 A3).
There is a need for other opioid compounds that do not have appreciable central activities and yet modulate opioid receptors, particularly mu-opioid receptors. There is a further need for opioid compounds that protect against peripheral opioid activity and/or allow for positive opioid effects, such as analgesia, while minimizing the peripheral side effects of opioid administration.

**SUMMARY OF THE INVENTION**

There is provided herein novel 4,5-epoxy-morphinan compounds that are derivatives of organic and inorganic acids and pharmaceutical compositions thereof. One embodiment of the invention is a 17-cyclopropylmethyl-4,5a-epoxy-3-hydroxy-14-carboxymethoxy-morphinan-6-one salt. In one embodiment, the compounds of the invention provide a method for modulating opioid receptors, including mu-receptors, kappa-receptors, and/or delta-receptors or any combination or sub-combination of these receptors. In another embodiment, the compounds of the invention modulate mu-receptors with little or no modulation of kappa- or delta-receptors. In yet another embodiment these compounds bind antagonistically to the mu-opioid receptor. In yet another embodiment, the compounds function as agonists on the mu-opioid receptor. In an embodiment the compounds of the invention have blood-brain barrier penetration with both central and peripheral effects on opioid receptors. In one embodiment, the compounds of the invention have limited or no blood-brain barrier penetration, and as such do not act centrally so as to cause significant central nervous system effects.

In one embodiment of the invention are disclosed compounds of formula I
and pharmaceutically acceptable salt forms, base forms, stereoisomers, N-oxides, polymorphs, and prodrugs thereof, wherein:

R_{i7} is selected from:

- unsubstituted or substituted: (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (cycloheteryl)alkyl, (cycloaryl)alkyl, (cycloalkyl)alkyl or (cycloalkenyl)alkyl,
- (cycloheteryl)alkyl, (cycloaryl)alkyl, linear or branched alkyl, alkenyl, or alkynyl;

R_{i6} is selected from none, H, OH, OR_{7}, NH_{2}, NHR_{7}, NR_{7}R_{8}, amino acids;

R_{i}, R_{g}, R_{i1} and R_{12} are independently H, OH, unsubstituted or substituted alkyl;

R_{i1} and R_{12} may form a substituted cyclic or heterocyclic ring, said ring to which Z may be attached at any position, consistent with valency requirements;

R_{io} is H, unsubstituted or substituted alkyl, halogen;

R_{6} is H, =0, =CH_{2}, or any unsubstituted cyclic ring, heterocycle, or forms a substituted cyclic or substituted heterocyclic ring with R_{7};

R_{s} is H, OH, unsubstituted or substituted alkyl, unsubstituted or unsubstituted alkoxy;

R_{3} is H, alkyl, aryl, alkylaryl, alkoxy, acyloxyalkyl, acyloxyaryl, aminoalkyl, aminoaaryl, amido, amidoalkyl, carboxamide, carboxyl, carboxylester, or forms a substituted cyclic or heterocyclic ring with R_{2}, any of the preceding groups being substituted or unsubstituted as valency allows.

R_{i} and R_{2} are independently H, halide, alkoxy, alkyl, aralkyl, or alkylaryl, the preceding groups being substituted or unsubstituted as valency allows;

Y is O, S, CH_{2}, NH or NH-(C=Z_{2})-NH-R_{i}, wherein when Y = NH, R_{6} is H, CH_{2}, or any unsubstituted cyclic ring or forms a substituted cyclic or substituted heterocyclic ring with R_{7};

Z is CH_{2}, CH_{2}OH, CHOH-R_{i}, C=O, S(=O)q, -(O)s-P(=O)(OH)r-, wherein q = 1-2, r = 0-2, S = O-I;

p = 0-6;
Z₂ is O, S; and

X⁻ is an anion.

[0017] Further included in the invention is the embodiment wherein Z = N, NH, O or S in the compounds of formula I.

[0018] In another embodiment are disclosed compounds having the formula I(a):

![Chemical Structure](image)

I(a)

and pharmaceutically acceptable salt forms, base forms, stereoisomers, N-oxides, polymorphs, and prodrugs thereof, wherein:

r₃ is H, C₁-C₄ alkyl, or C₁-C₃ acyl, the preceding groups being substituted or unsubstituted;

Z is CH₃, CH₂OH, CHOH-Ri, C=O, S(=O)q, -(O)s-P(=O)(OH)r, wherein q = 1-2, r = 0-2, s = 0-1;

Ri6 is selected from none, H, OH, OR₇, NH₂, NHR₇, NR₇R₈, amino acids;

p = 0-6; and

X⁻ is an anion.

[0019] In an additional embodiment are compounds having the formula I(b):
and pharmaceutically acceptable salt forms, stereoisomers, N-oxides, polymorphs, and prodrugs thereof, wherein:

$R_i$ is selected from:

- $C_4$-$C_{10}$ cycloalkylalkyl or cycloalkenylalkyl, cycloheterylalkyl, cycloarylalkyl;
- $C_4$-$C_{10}$ cycloalkylalkyl or cycloalkenylalkyl, cycloheterylalkyl, cycloarylalkyl linear or branched $C_1$-$C_3$ alkyl, halogenated $C_2$-$C_6$ alkenyl, or $C_3$ alkynyl, the preceding groups being optionally substituted or unsubstituted;

$R_{1,0}$ is $H$, unsubstituted or substituted alkyl, halogen;

$R_7$ and $R_8$ are $H$ or substituted or unsubstituted alkyl;

$R_6$ is $H$, $=0$, $=CH_2$, or any cyclic ring, or forms an unsubstituted or substituted cyclic or heterocyclic ring with $R_7$;

$R_5$ is $H$, OH, alkyl, alkoxy, or arylxy, the preceding groups being substituted or unsubstituted as valency allows;

$R_3$ is $H$, $C_1$-$C_4$ alkyl, or $C_1$-$C_3$ acyl, the preceding groups being substituted or unsubstituted;

$R_1$ and $R_2$ are independently $H$, halide, alkoxy, alkyl, or aryl, the preceding groups being substituted or unsubstituted as valency allows;

$p = 0$-$6$; and
X is an anion.

[0020] Also included, and as useful for the conditions discussed herein, are the free bases, base forms, anion forms, neutral forms, N-oxides, zwitterionic forms, prodrugs, salts, including pharmaceutically acceptable salts, stereoisomers when such can exist, radioisomers, polymorphs, hydrates, solvates, and acid hydrates of the compounds of the invention.

[0021] At a suitable pH, zwitterionic forms of the compounds of the invention may be obtained and such are an embodiment of the invention. In yet another example, at higher pH, the negatively charged chemical forms of the compounds of formula I may predominantly exist.

[0022] In embodiments of the invention are disclosed pharmaceutical compositions of compounds of the invention comprising parenteral, oral formulations, immediate release, enteric coated, and sustained release formulations. The pharmaceutical compositions may also comprise at least one opioid selected from the group consisting of alfentanil, anileridine, asimodiline, bremazocine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanil, sufentanil, tilidine, tramadoline, tramadol, and combinations thereof.

[0023] In embodiments of the invention are disclosed pharmaceutical compositions of the compounds of the invention and a pharmaceutically acceptable carrier.

[0024] In embodiments of the invention are also disclosed pharmaceutical formulations of the invention wherein the formulations are packaged unit dosages, wherein the packaged unit doses may be solutions.

[0025] Also, in embodiments of the invention, are disclosed pharmaceutical compositions of compounds of the invention further comprising an opioid and/or a compound that is not an opioid or an opioid antagonist. Such compounds may be, for example, a non-opioid analgesic/anti-pyretic, an antiviral agent, an anti-infective agent, an anticancer agent, an antispasmodic agent, an anti-muscarinic agent, an anti-inflammatory agent, a pro-motility agent, a 5HT agonist, a 5HT antagonist, a 5HT antagonist, a 5HT agonist, a bile salt sequestering agent, a bulk-forming agent, an alpha2-adrenergic agonist, a mineral oil, an antidepressant, a herbal medicine, an anti-emetic agent, an anti-diarrheal agent, a laxative, a stool softener, a fiber
or a hematopoietic stimulating agent. Examples of anti-inflammatory agents are non-steroidal anti-inflammatory drugs (NSAIDS), tumor necrosis factor inhibitors, basiliximab, daclizumab, infliximab, mycophenolate mofetil, azathioprine, tacrolimus, steroids, sulfasalazine, olsalazine, mesalamine, and combinations thereof.

[0026] In embodiments of the invention are disclosed methods for modulating mu-, kappa-, and/or delta-opioid receptors comprising administering to a patient in need thereof a composition of the invention in a modulation effective amount. The modulation may be consistent with an opioid agonist and/or an opioid antagonist. The administration can occur before, concurrently, or after a step of administering at least one opioid, the opioid selected from the group consisting of alfentanil, anileridine, asimodiline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenhydramine, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucuronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanil, sufentanil, tilidine, trimebutine, tramadol, and combinations thereof.

[0027] In embodiments of the invention are disclosed methods of treating opioid-induced side effects by administering a pharmaceutical composition of the invention to a patient in need thereof. Examples of such side effects are constipation, dysphoria, respiratory depression, dizziness, nausea, dependence, pruritus, urinary retention, inhibition of intestinal motility, gastrointestinal dysfunction, bowel hypomotility, impaction, gastric hypomotility, GI sphincter constrictions, increased sphincter tone, inhibition of gastrointestinal motility, inhibition of gastric emptying, delayed gastric emptying, incomplete evacuation, emesis, cutaneous flushing, bloating, and abdominal distension.

[0028] In embodiments of the invention pharmaceutical compositions of compounds of the invention are administered, for example, orally, subcutaneously, buccally, rectally, and intravenously.

[0029] Prodrugs are known to enhance a number of desirable pharmaceutical qualities (e.g., solubility, bioavailability, manufacturing, etc.) and prodrugs of compounds of the invention are additionally embodiments. Prodrugs of the compounds of the invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound.
Non-limiting examples of prodrugs of compounds the invention would be phosphate esters, carbonate esters, 3-acylalkyl esters, 6-acylalkylesters, 3,6-diaeylalkyl esters or 3,6-diacylaryl esters, as well as esters formed by group substitution at the R₁₆ position in the compounds of formula I or I(a). Other such examples of prodrugs of compounds of the invention would be provided by the esterification of the carboxyl group of compounds of formula I(b) with sugar or amino acid groups, or similarly by attaching such groups to the chain pendant from the 14-oxo group in the compounds of formula I or I(a), or at other positions in the molecule.

[0030] Amino acid and sugar conjugates of compounds of the invention are embodiments of the invention that are expected to increase oral absorption of the parent compounds, by providing prodrug qualities to the compounds and/or facilitating transport of the compounds across the intestinal gut wall.

[0031] Further provided herein, as an aspect of formula I(b), is a composition of matter comprising 17-cyclopropylmethyl α-epoxy-3-hydroxy-14-carboxymethoxy-morphinan-6-one and its stereoisomers, and preferably a pharmaceutically acceptable acid salt thereof, the salt form described structurally as:

\[
\begin{align*}
&\text{wherein } X^- \text{ is an anion. In one embodiment, the anion is trifluoroacetate. As more generally} \\
&\text{stated above, it is understood that other salts of 17-cyclopropylmethyl-4,5-α-epoxy-3-hydroxy-} \\
&\text{14-carboxymethoxy-morphman-6-one may be formed by replacing the anion with other} \\
&\text{acceptable anions, and that other forms of the compound, as described above, are also disclosed} \\
&\text{as preferred embodiments.}
\end{align*}
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[0032] Also provided are the following compounds, their salts, including pharmaceutically acceptable salts, stereoisomers, bases, polymorphs and prodrugs thereof:
wherein \( X^- \) is an anion in each case.
Provided in embodiments herein are one or more compounds, their pharmaceutically acceptable salts, bases, N-oxides, polymorphs and prodrugs thereof, selected from the group comprising:

4-(3-(17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-6-oxo-morphinan-14-ylamino)-3-oxopropyl)benzoic acid;

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3-hydroxypropoxy)-morphinan-6-one;

4-(17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-6-oxo-morphinan-14-yloxy)-butanoic acid;

4-((17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-morphinan-14-yloxy)methyl)benzoic acid;

4-((17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-morphinan-14-yloxy)methyl) benzoic acid;

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-[(4’carboxybenzyl)oxy]morphinan;

(17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-morphinan-6-one-14-yloxy)-propionic acid;

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-6-oxo-14-(3’-hydroxypropyloxy)morphinan-N-oxide;

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(2’,3’-dihydroxy-3’-phenylpropyloxy)morphinan-6-one;

17-Cyclopropylmethyl-14-carboxymethoxy-4,5 α-epoxy-3-hydroxy-morphinan;
17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-[2'-{2H-tetrazol-5-yl}-ethoxy]-morphinan-6-one;

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(N-acetyl-3'-amino-3'-oxo-propoxy)- morphinan-6-one;

14-Butoxy-17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-morphinan;

and

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(3'-methanesulfonyl amino-3'-oxo-propoxy)-morphanin-6-one.

[0034] Provided in embodiments of the invention are methods for the synthesis of the compounds of the invention in addition to pharmaceutical compositions and uses thereof.

BRIEF DESCRIPTION OF FIGURES

[0035] Figure 1 illustrates the effect of peroral (PO) administration of a compound of the invention on morphine-induced decrease in gastrointestinal (GI) motility in a rat model. Direct comparisons are made to the mu-receptor antagonist, methylnaltrexone (MNTX), also administered PO.

DETAILED DESCRIPTION OF THE INVENTION

[0036] There is still a need for compounds that may be used in methods to modulate, agonize, or antagonize opioid receptors, particularly for use in preventing or treating the undesirable side effects associated with administering exogenous opioids. The present disclosure is directed to these desired compounds, as well as other important ends.

[0037] The compounds of the present invention may be used in methods to bind opioid receptors, including mu-, kappa-, and/or delta-opioid receptors. Such binding may be accomplished by contacting the receptor with an effective amount of the compound of the invention. Preferably, the contacting step is conducted in an aqueous medium, preferably at physiologically relevant ionic strength, pH, and the like.

[0038] In certain preferred embodiments, the compounds of the present invention bind mu and/or kappa opioid receptors, or combinations thereof. The opioid receptors may be
located in the central nervous system or located peripherally to the central nervous system or in both locations.

[0039] In certain other preferred embodiments, the compounds of the present invention bind kappa-opioid receptors.

[0040] In certain embodiments of methods for the binding opioid receptors in a patient in need thereof, the methods comprise the step of administering to the patient a composition comprising an effective amount of a compound of the invention. In certain embodiments, the patient is in need of prevention or treatment of a condition or disease caused by an opioid, wherein the opioid may be exogenous or endogenous. In certain preferred embodiments, the compound of the invention may be administered in combination with an effective amount of at least one opioid.

[0041] In preferred embodiments of the methods of the invention, the compounds of the invention antagonize the activity of the opioid receptors. In other preferred embodiments, the compounds prevent or treat a condition or disease caused by an opioid (either endogenous or exogenous). In certain embodiments of the method, particularly wherein the opioid is exogenous, the compounds of the invention do not substantially cross the blood-brain barrier.

[0042] The compounds of the present invention may be used in methods to antagonize mu-, kappa-, and/or delta-opioid receptors or any combinations or subcombinations of those opioid receptors, particularly where undesirable symptoms or conditions are side effects of administering exogenous opioids. Furthermore, the compounds of the invention may be used as to treat patients having disease states that are ameliorated by binding opioid receptors or in any treatment wherein temporary suppression of the mu-, kappa- or both types of opioid receptor systems is desired.

[0043] In one non-limiting embodiment of the present invention, there are disclosed compounds useful for modulating opioid receptor activity.

[0044] In one non-limiting embodiment of the present invention, there are disclosed compounds useful in methods to modulate opioid receptors, particularly the mu-opioid receptor, and more particularly to antagonize the mu-opioid receptor. Of particular interest are compounds that act peripherally, while exhibiting reduced and preferably no central nervous system (CNS) activity.
Opioid receptor binding activity may be adjudged using a receptor binding assay well known in the art. For example, a radioligand dose-displacement assay may be run using diprenorphine as the agent to be displaced. An unlabeled opioid antagonist, such as naloxone, can serve as a positive control. The assay may be performed in a well array with binding reactions terminated by rapid filtration and harvesting with a harvester.

Radioisomers of compounds of the invention, obtained by replacing one or more atoms of such by their radioactive counterparts, may themselves be used as radioligands, or for other purposes known to those of skill in the art.

Generally there are disclosed compounds of formula I, formula I(a), and formula I(b) as disclosed above. In another such exemplary embodiment, there is disclosed a mu-receptor binding 7,8-saturated-4,5-epoxy-morphinan acetic acid derivative having the structure of:

![Chemical Structure](image_url)

wherein X is an anion. The anion can be any ion, including a zwitterion. In one embodiment the anion is trifluoroacetic acid anion. Preferably the anion is pharmaceutically acceptable. Anions include halides, sulfates, phosphates, nitrates, EDTAs and related compounds, and anionic-charged organic species. The halide can be iodide, bromide, chloride, fluoride or a combination thereof. In one embodiment the halide is iodide. In another embodiment the halide is bromide. The anionic-charged organic species may be a sulfonate or carboxylate. The sulfonate may be mesylate, besylate, tosylate, or triflate. The carboxylate anion may be formate, acetate, citrate, an edetate, or fumarate.

The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" embraces an amine radical substituted with an acyl group. An examples of an
"acylamino" radical is acetylamine (CH$_2$C(=O)-NH-). The term "aryloxy" denotes a radical provided by the residue after removal of hydrido from a hydroxy-substituted aryl moiety (e.g., phenol).

[0049] As used herein, "alkanoyl" refers to a-C(=O)-alkyl group, wherein alkyl is as previously defined. Exemplary alkanoyl groups include acetyl (ethanoyl), n-propanoyl, n-butanoyl, 2-methylpropanoyl, n-pentanoyl, 2-methylbutanoyl, 3-methylbutanoyl, 2,2-dimethylpropanoyl, heptanoyl, decanoyl, and palmitoyl.

[0050] The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond and must contain at least two carbon atoms. For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term "lower alkylene" herein refers to those alkyene groups having from about 1 to about 6 carbon atoms. The term "alkenyl" includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkenyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkyl carbonylamino, aryl carbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arythio, thiacarbonyl, sulfates, alkyl sulfanyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0051] "Alkenylene", in general, refers to an alkyene group containing at least one carbon—carbon double bond. Exemplary alkenylene groups include, for example, ethenylene (-CH=CH-) and propenylene (-CH=CHCH$_2$-). Preferred alkenylene groups have from 2 to about 4 carbons.
[0052] The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialk oxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro chloro or bromo to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluromethoxy.

[0053] "Alkyl" in general, refers to an aliphatic hydrocarbon group which may be straight, branched or cyclic having from 1 to about 10 carbon atoms in the chain, and all combinations and subcombinations of ranges therein, e.g., a cycloalkyl, branched cycloalkylalkyl, a branched alkylcycloalky having 4-10 carbon atoms. The term "alkyl" includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the backbone. "Lower alkyl" refers to an alkyl group having 1 to about 6 carbon atoms. Alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, cyclopentyl, isopentyl, neopentyl, n-hexyl, isohexyl, cyclohexyl, cyclooctyl, adamantyl, 3-methylpentyl, 2-dimethylbutyl, and 2,3-dimethylbutyl, cyclopropylmethyl and cyclobutylmethyl. Alkyl substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, aroylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino (including alkyl carbonylamino, aryl carbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, phenylpropyl, and diphenethyl. The terms benzyl and phenylmethyl are interchangeable. The term "n-alkyl" means a straight chain (i.e. unbranched) unsubstituted alkyl group. "Branched" refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain.

[0054] An "alkylating agent" is a compound that can be reacted with a starting material to bind, typically covalently, an alkyl group to the starting material. The alkylating agent typically includes a leaving group that is separated from the alkyl group at the time of
attachment to the starting material. Leaving groups may be, for example, halogens, halogenated sulfonates or halogenated acetates. An example of an alkylating agent is cyclopropylmethyl iodide.

[0055] The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond and two carbon atoms. For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkynyl or cycloalkenyl substituted alkynyl groups.

[0056] The term "amido" when used by itself or with other terms such as "amidoalkyl", "N-monoalkylamido", "N-monoarylamido", "N,N-dialkylamido", "N-alkyl-N-arylamido", "N-alkyl-N-hydroxyamido" and "N-alkyl-N-hydroxyamidoalkyl", embraces a carbonyl radical substituted with an amino radical. The terms "N-alkylamido" and "N,N-dialkylamido" denote amido groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. The terms "N-monoarylamido" and "N-alkyl-N-arylamido" denote amido radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical. The term "N-alkyl-N-hydroxyamido" embraces amido radicals substituted with a hydroxyl radical and with an alkyl radical. The term "N-alkyl-N-hydroxyamidoalkyl" embraces alkyl radicals substituted with an N-alkyl-N-hydroxyamido radical. The term "amidoalkyl" embraces alkyl radicals substituted with amido radicals.

[0057] The term "aminoalkyl" embraces alkyl radicals substituted with amine radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "amidino" denotes an \(-\text{C}(=\text{NH})\text{NH}_2\) radical. The term "cyanoamidino" denotes an \(-\text{C}(=\text{N-CN})\text{NH}_2\) radical.

[0058] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

[0059] "Aryl-substituted alkyl", or aryalkyl, in general, refers to a linear alkyl group, preferably a lower alkyl group, substituted at a carbon with an optionally substituted aryl
group, preferably an optionally substituted phenyl ring. Exemplary aryl-substituted alkyl groups include, for example, phenylmethyl, phenylethyl and 3-(4-methylphenyl)propyl.

[0060] The term "carbocycle" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, \([3.3.0]bicyclooctane\), \([4.3.0]bicyclononane\), \([4.4.0]bicyclodecane\) (decalin), \([2.2.2]bicyclooctane\), fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Preferred "carbocycle" are cyclopentyl, cyclobutyl, cyclopentyl, and cyclohexyl.

(0061) The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0062] "Cycloalkyl-substituted alkyl", in general, refers to a linear alkyl group, preferably a lower alkyl group, substituted at a terminal carbon with a cycloalkyl group, preferably a C\(_3\) -Cg cycloalkyl group. Typical cycloalkyl-substituted alkyl groups include cyclohexylmethyl, cyclohexylethyl, cyclopenty lethyl, cyclopentylpropyl, cyclopropylmethyl and the like.

[0063] "Cycloalkenyl", in general, refers to an olefinically unsaturated cycloalkyl group having from about 4 to about 10 carbons, and all combinations and subcombinations of ranges therein. In some embodiments, the cycloalkenyl group is a C\(_5\) -Cs cycloalkenyl group, i.e., a cycloalkenyl group having from about 5 to about 8 carbons.

[0064] The phrase "does not substantially cross," as used herein, means that less than about 20% by weight of the compound employed in the present methods crosses the blood brain barrier, preferably less than about 15% by weight, more preferably less than about 10% by weight, even more preferably less than about 5% by weight and most preferably about 0% by weight of the compound crosses the blood-brain barrier.

[0065] The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and
polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

[0066] As used herein, the terms "heterocycle", "heterocyclic ring" or "cycloheteryl" are intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. Examples of saturated heterocyclic radicals include pyrrolidyl and morpholiny1.

[0067] The term "inorganic acid" denotes an inorganic compound with acidic properties and has its common ordinary meaning to those of skill in this art. Examples of common inorganic acids are phosphoric, nitric, and sulfuric acids. A morphinan derivative of an inorganic acid may be formed, for example, by replacing one or more of the acidic hydrogens of the inorganic acid group with a linkage to a morphinan structure.

[0068] "Organic solvent" has its common ordinary meaning to those of skill in this art. Exemplary organic solvents useful in the invention include, but are not limited to tetrahydrofuran (THF), acetone, hexane, ether, chloroform, acetic acid, acetonitrile, chloroform, dichloromethane (DCM), cyclohexane, methanol, and toluene. Anhydrous organic solvents are included.

[0069] The term "organic acid", denotes an organic compound with acidic properties, and has its common ordinary meaning to those of skill in this art. Examples of common organic acids are the carboxylic acids, such as ethanoic acid and propionic acid, whose acidity is associated with their carboxyl group -COOH. Amino acids, such as glycine, alanine, cysteine, arginine, and phenylalanine are also exemplary of the class. Organic sulfonic acids, containing the group -SO\(_2\)OH, another exemplary member of the class, are relatively stronger acids. Organic phosphoric acids, containing the group -\(\text{OP(OH)}_2\), are an additional example of the class. Other groups can also confer acidity, usually weakly, such as: -OH, -SH, enol group, and the phenol group. A morphinan derivative of an organic acid may be formed, for example, by replacing one or more C-H hydrogens of the organic acid group with a linkage to a morphinan structure. Alternatively, the attachment of the morphinan structure can occur via a linkage to an acidic hydrogen of the organic acid group.
The terms "N-alkylamino" and "N,N-dialkylamino" denote amine groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively.

As used herein, "patient" refers to animals, including mammals, preferably humans.

As used herein, "peripheral" or "peripherally-acting" refers to an agent that acts outside of the central nervous system. As used herein, "centrally-acting" refers to an agent that acts within the central nervous system (CNS). The term "peripheral" designates that the compound acts primarily on physiological systems and components external to the central nervous system. The phrase "substantially no CNS activity," as used herein, means that less than about 20% of the pharmacological activity of the compounds employed in the present methods is exhibited in the CNS, preferably less than about 15%, more preferably less than about 10%, even more preferably less than about 5% and most preferably about 0% of the pharmacological activity of the compounds employed in the present methods is exhibited in the CNS.

Hydrates are formed when water binds to the crystal structure of a compound in a fixed stoichiometric ratio, although generally this ratio will change depending on the surrounding humidity with which the hydrate is in equilibrium. Hydration is a more specific form of solvation. Solvates are crystalline solid adducts containing either stoichiometric or nonstoichiometric amounts of a solvent incorporated within the crystal structure. If the incorporated solvent is water, the solvates are also commonly known as hydrates. Hydrates and solvates are well known to those or ordinary skill in the art.

Pharmaceutical polymorphism is characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Polymorphism refers to the occurrence of different crystalline forms of the same drug substance. Polymorphs are well known to those of ordinary skill in the art.

Polymorphs or solvates of a pharmaceutical solid can have different chemical and physical properties such as melting point, chemical reactivity, apparent solubility, dissolution rate, optical and electrical properties, vapor pressure, and density. These properties can have a direct impact on the processing of drug substances and the quality or performance of drug products. Chemical and physical stability, dissolution, and bioavailability are some of these
qualities. A metastable pharmaceutical solid form may change crystalline structure or solvate or desolvate in response to changes in environmental conditions, processing, or over time. New, previously unknown polymorphs can develop spontaneously and unpredictably over time.

[0076] As used herein, "prodrug" refers to compounds specifically designed to maximize the amount of active species that reaches the desired site of reaction that are of themselves typically inactive or minimally active for the activity desired, but through biotransformation are converted into biologically active metabolites.

[0077] As used herein, "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio. As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

[0078] The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, laetic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, EDTA, isethionic, and the like. These physiologically acceptable salts are prepared by methods known in the art, e.g., by dissolving the free amine bases with an excess of the acid in aqueous alcohol, or neutralizing a free carboxylic acid with an alkali metal base such as a hydroxide, or with an amine.

[0079] Certain acidic or basic compounds of the present invention may exist as zwitterions. All forms of the compounds, including free acid, free base and zwitterions, are contemplated to be within the scope of the present invention. It is well known in the art that compounds containing both amino and carboxyl groups often exist in equilibrium with their zwitterionic forms. Thus, any of the compounds described herein throughout that contain, for
example, both amino and carboxyl groups, also include reference to their corresponding zwitterions.

[0080] As used herein, the term "side effect" refers to a consequence other than the one (s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other then the one sought to be benefited by its administration.

[0081] As used herein, "stereoisomers" refers to compounds that have identical chemical constitution, but differ as regards the arrangement of the atoms or groups in space.

[0082] It should also be understood that when referring to compounds of the invention, it is meant to encompass radioisomers, stereoisomers, hydrates, solvates, N-oxides, and polymorphs of the same, as well as other acid-base forms connected by proton equilibria, such as zwitterionic forms, neutral forms, and cationic and anionic forms. For example, a neutral, zwitterionic form of a compound of formula I(b) would be represented by formula II(a), and a negatively charged carboxylate anion form of a compound of formula I(b) would be represented by formula II(b) (M⁺ is a cation).

![Formula II(a)](formula-II-a.png) ![Formula II(b)](formula-II-b.png)

[0083] The subjects to which the compounds of the present invention may be administered are vertebrates, in particular mammals. In one embodiment the mammal is a human, nonhuman primate, dog, cat, sheep, goat, horse, cow, pig and rodent. In one embodiment, the mammal is a human.

[0084] The pharmaceutical preparations of the invention, when used alone or in cocktails, are administered in therapeutically effective amounts. A therapeutically effective
amount will be determined by the parameters discussed below; but, in any event, is that amount which establishes a level of the drug(s) effective for treating a subject, such as a human subject, having, for example, one of the conditions described herein. An effective amount means that amount alone or with multiple doses, necessary to delay the onset of, lessen the severity of, or inhibit completely, lessen the progression of, or halt altogether the onset or progression of the condition being treated or a symptom associated therewith.

[0085] An effective amount of a pharmaceutical preparation of the invention having primarily opioid agonist activity, in particular, mu-opioid agonist activity, is an amount that prevents, treats, or manages at least one symptom of acute or chronic pain, hyperalgesia, or diarrhea, for example. The effective amount of the opioid agonist may provide antitussive, sedative, anesthetic, and/or anti-diarrheal activity.

[0086] An effective amount of a pharmaceutical preparation of the invention having primarily opioid antagonist activity, in particular, mu-opioid antagonist activity, is an amount that prevents, treats, or manages at least one opioid-induced side effect resulting from the action of endogenous or exogenous opioids, for example. Of particular interest are compounds which decrease the constipating effects of opioids without affecting centrally mediated analgesia.

[0087] The art defines constipation as (i) less than one bowel movement in the previous three days or (ii) less than three bowel movements in the previous week (see e.g., U.S. Patent 6,559,158). Functional constipation is a functional bowel disorder that presents as persistently difficult, infrequent, or seemingly incomplete defecation. Constipating medications, such as opioids and opioid agonists, and in particular extended use of opioids or opioid agonist are contributors to functional constipation. Recently, a Rome III diagnostic criteria was established for functional constipation (Longstreth, G.F. et ah, Gastroenterology Vol. 130, No. 5, 2006). Under this criteria, the diagnosis of functional constipation is made if the patient has 2 or more of the following symptoms for the last 3 months-with symptom onset at least 6 months prior to diagnosis: a) straining during at least 25% of defecation; b) lumpy or hard stools in at least 25% of defecations, c) sensation of incomplete evacuation for at least 25% of defecations, d) sensation of anorectal obstruction/blockage for at least 25% of defecations, e) manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor), f) fewer than 3 defecations per week.

[0088] In the case of constipation, an effective amount of an opioid antagonist, for example, is that amount which relieves at least one symptom of constipation, which induces a
bowel movement, which increases the frequency of bowel movements, or which decreases oral-cecal transit time. Effective amounts therefore can be those amounts necessary to establish or maintain regular bowel movements. In another embodiment, the effective amount treats or relieves two or more symptoms of constipation, for example, the amount is effective to reduce straining during defecation and improve stool consistency; stool consistency rated using the Bristol Stool scores. An improvement in stool consistency indicated by a change from a Type 1 at baseline to a Type 2, preferably a change to a Type 3, Type 4, or Type 5. In an embodiment, the effective amount provides 3 or more defecations per week and improves stool consistency.

[0089] In certain preferred embodiments, the compounds of the invention may be used in methods for preventing or treating gastrointestinal dysfunction, including, but not limited to, irritable bowel syndrome, opioid-bowel dysfunction, colitis, post-operative and opioid-induced emesis (nausea and vomiting), decreased gastric motility and emptying, inhibition of small and/or large intestinal propulsion, increased amplitude of non-propulsive segmental contractions, constriction of sphincter of Oddi, increased anal sphincter tone, impaired reflex relaxation with rectal distention, diminished gastric, biliary, pancreatic or intestinal secretions, increased absorption of water from bowel contents, gastro-esophageal reflux, gastroparesis, cramping, bloating, abdominal or epigastric pain and discomfort, constipation, and delayed absorption of orally administered medications or nutritive substances.

[0090] Certain patients that may particularly be amenable to treatment are patients having the symptoms of constipation and/or gastrointestinal immotility and who have failed to obtain relief or ceased to obtain relief or a consistent degree of relief of their symptoms using a laxative or a stool softener, either alone or in combination, or who are otherwise resistant to laxatives and/or stool softeners. Such patients are said to be refractory to the conventional laxatives and/or stool softeners. The constipation and/or gastrointestinal immotility may be induced or a consequence of one or more diverse conditions including, but not limited to, a disease condition, a physical condition, a drug-induced condition, a physiological imbalance, stress, anxiety, and the like. The conditions inducing constipation and/or gastrointestinal immotility may be acute conditions or chronic conditions.

[0091] Again with respect to an antagonist embodiment of the present invention, generally, an effective amount is the amount to relieve or diminish at least one symptom of a side effect of opioid administration to a patient or a symptom of endogenous opioids. Such symptoms, conditions or diseases include the complete or partial antagonism of opioid-induced sedation, confusion, respiratory depression, euphoria, dysphoria, hallucinations, pruritus
(itching), increased biliary tone, increased biliary colic, and urinary retention, ileus, emesis, and addiction liability or impulse control disorders; prevention or treatment of opioid and cocaine dependence; rapid opioid detoxification; treatment of alcoholism; treatment of alcoholic conia; detection of opioid use or abuse (pupil lest); treatment of eating disorders; treatment of obesity; treatment of post-concussional syndrome; adjunctive therapy in septic, hypovolemic or endotoxin-induced shock; potentiation of opioid analgesia (especially at ultra-low doses); reversal or prevention of opioid tolerance and physical dependence (especially at ultra-low doses); prevention of sudden infant death syndrome; treatment of psychosis (especially wherein the symptoms are associated with schizophrenia, schizophreniform disorder, schizoaffective disorder, unipolar disorder, bipolar disorder, psychotic depression, Alzheimer's disease, Parkinson's disease, compulsive disorders, and other psychiatric or neurologic disorders with psychosis as symptoms); treatment of dyskinesia, treatment of autism; treatment of the endocrine system (including increased release of leutinizing hormone, treatment of infertility, increasing number of multiple births in animal husbandry, and male and female sexual behavior): treatment of the immune system and cancers associated with binding of the opioid receptors; treatment of anxiolysis; treatment of diuresis; treatment and regulation of blood pressure; treatment of tinnitus or impaired hearing; treatment of epilepsy; treatment of cachexia; treatment of general cognitive dysfunctions; and treatment of kleptomania.

[0092] The compounds of the present invention may be used in methods of treatment of a disorder mediated by opioid receptor activity in a subject comprising administering to the subject a composition comprising an effective amount of the compound of the present invention, wherein the disorder is selected from the group consisting of cancer, cancer involving angiogenesis, an inflammatory disorder, immune suppression, a cardiovascular disorder, chronic inflammation, chronic pain, sickle cell anemia, a vascular wound, retinopathy, decreased biliary secretion, decreased pancreatic secretion, biliary spasm, and increased gastroesophageal reflux.

[0093] The compounds of the present invention may also be used as cytostatic agents, as antimigraine agents, as immunomodulators, as immunosuppressives, as antiarthritic agents, as antiallergic agents, as \iricides. to treat diarrhea, antipsychotics, antischizophrenies, as antidepressants, as uropathic agents, as antitussives, as antiadditive agents, as antismoking agents, to treat alcoholism, as hypotensive agents, to treat and or prevent paralysis resulting from traumatic ischemia, general neuroprotection against ischemic trauma, as adjuncts to nerve growth factor treatment of hyperalgesia and nerve grafts, as antiuretics, as stimulants, as anti-
cumulants, or to treat obesity. Additionally, the present compounds may be used in the
treatment of Parkinson’s disease as an adjunct to L-dopa for treatment of dyskinesia associated
with the L-dopa treatment.

[0094] Patients may use opioids chronically for weeks, months, and even years
depending on the underlying disease/condition. These patients may include, for example, late
stage cancer patients, terminally-ill patients, elderly patients with osteoarthritic changes,
methadone maintenance patients, neuropathic pain and chronic back pain patients. Treatment of
these patients, using a compound of the present invention, is important from a quality of life
standpoint, as well as to reduce complications arising from chronic constipation, such as
hemorrhoids, appetite suppression, mucosal breakdown, sepsis, colon cancer risk, and
myocardial infarction.

[0095] Patients receiving treatment using the compounds of the present invention
may concurrently or sequentially be receiving opioids. Compounds disclosed herein may be
mixed with a conventional opioid compound. Conventional opioids include those selected from
the group consisting of alfentanil, anileridine, asimadoline, bremazocine, buprenorphine,
butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate,
fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl
acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-
glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram,
propoxyphene, remifentanil, sufentanil, tildidine, trimebutine, and tramadol. Optionally, an non-
opioid anesthetic/antipyretic such as acetaminophen may be admixed with the opioid, in
particular with oxycodone. The opioid also may be moved together with the compounds
disclosed herein and provided in any of the forms described herein.

[0096] Dosage may be adjusted appropriately to achieve desired drug levels, local
or systemic, depending on the mode of administration. In the event that the response in a patient
is insufficient at such doses, even higher doses (or effectively higher dosage by a different, more
localized delivery route) may be employed to the extent that the patient tolerance permits.
Multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.
Appropriate systemic levels can be determined by, for example, measurement of the patient's
peak or sustained plasma level of the drug. "Dose" and "dosage" are used interchangeably
herein.
A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular combination of drugs selected, the severity of the condition being treated, or prevented, the condition of the patient, and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, topical, transdermal, sublingual, intravenous infusion, pulmonary, intra-arterial, intra-adipose tissue, intra-lymphatic, intramuscular, intracavity, aerosol, aural (e.g., via eardrops), intranasal, inhalation, intra-articular, needleless injection, subcutaneous or intradermal (e.g., transdermal) delivery. For continuous infusion, a patient-controlled analgesia (PCA) device or an implantable drug delivery device may be employed. Oral, rectal, or topical administration may be important for prophylactic or long-term treatment. Preferred rectal modes of delivery include administration as a suppository or enema wash.

The pharmaceutical preparations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the compounds of the invention into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds of the invention into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

When administered, the pharmaceutical preparations of the invention are applied in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, lubricants, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention.

Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, EDTA, salicylic, p-toluenesulfonic, trifluoroacetic, tartaric, citric, methanesulfonic, formic, succinic, naphthalene-2-sulfonic, pamoic, 3-hydroxy-2-naphthalenecarboxylic, and benzene sulfonic.
Also, such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following bases: sodium and potassium hydroxide, NH₄OH, Na₂HPO₄, NaHCO₃, and Ca(OH)₂.

It should be understood that when referring to compounds of the invention, it is meant to encompass salts and bases of the same. Such are of a variety well known to those or ordinary skill in the art. When used in pharmaceutical preparations, the salts preferably are pharmaceutically-acceptable for use in humans. Bromide is an example of one such salt. Sodium is an example of another when the compound is negatively charged at a suitable pH.

The pharmaceutical preparations of the present invention may include or be diluted into a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid fillers, diluents or encapsulating substances which are suitable for administration to a human or other mammal such as non-human primate, a dog, cat, horse, cow, sheep, pig, or goat. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The carriers are capable of being commingled with the preparations of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy or stability. Carrier formulations suitable for oral administration, for suppositories, and for parenteral administration, etc., can be found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa.

Formulations may include a chelating agent, a buffering agent, an antioxidant and, optionally, an isotonicity agent, preferably pH adjusted, and a permeation/penetration enhancer. Examples of such formulations are described in co-pending U.S. Application Serial No. 10/821,811, entitled "Pharmaceutical Formulation" and in WO 2008/019115 A2, entitled "Formulations for Parenteral Delivery of Compounds and Uses thereof. Chelating agents may include, but are not limited to, for example, ethylenediaminetetraacetic acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, sodium desoxycholate and derivatives thereof, and L-glutamic acid, N, N-diaceitic acid and derivatives thereof. EDTA derivatives include dipotassium edetate, disodium edetate, calcium disodium edetate, sodium edetate, trisodium edetate, and potassium edetate.
Buffering agents may include, but are not limited to those selected from the group comprising citric acid, sodium citrate, sodium acetate, acetic acid, sodium phosphate and phosphoric acid, sodium ascorbate, tartaric acid, maleic acid, glycine, sodium lactate, lactic acid, ascorbic acid, imidazole, sodium bicarbonate and carbonic acid, sodium succinate and succinic acid, histidine, and sodium benzoate and benzoic acid, or combinations thereof.

Antioxidants may include, but are not limited to those selected from the group comprising an ascorbic acid derivative, butylated hydroxy anisole, butylated hydroxy toluene, alkyl gallate, sodium meta-bisulfite, sodium bisulfite, sodium dithionite, sodium thioglycollate acid, sodium formaldehyde sulfoxylate, tocopherol and derivatives thereof, monothioglycerol, and sodium sulfate. The preferred antioxidant is monothioglycerol.

Isotonicity agents may include, but are not limited to those selected from the group comprising sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol.

Preservatives that can be used with the present compositions include, but are not limited to benzyl alcohol, parabens, thimerosal, chlorobutanol and preferably benzalkonium chloride. Typically, the preservative will be present in a composition in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

The compounds of the invention can be prepared in lyophilized compositions, preferably in the presence of a cryoprotecting agent such as mannitol, or lactose, sucrose, polyethylene glycol, and polyvinyl pyrrolidines. Cryoprotecting agents which result in a reconstitution pH of 6.0 or less are preferred. The invention therefore provides a lyophilized preparation of therapeutic agent(s) of the invention. The preparation can contain a cryoprotecting agent, such as mannitol or lactose, which is preferably neutral or acidic in water.

Oral, parenteral and suppository formulations of agents are well known and commercially available. The therapeutic agent(s) of the invention can be added to such well known formulations. The therapeutic agent(s) of the invention can be mixed together in solution or semi-solid solution in such formulations, can be provided in a suspension within such formulations or could be contained in particles within such formulations.

A product containing therapeutic agent(s) of the invention and, optionally, one or more other active agents can be configured as an oral dosage. The oral dosage may be a tablet, a capsule, a liquid, a semisolid or a solid. An opioid may optionally be included in the
oral dosage. The oral dosage may be configured to release the therapeutic agent(s) of the invention before, after or simultaneously with the other agent (and/or the opioid). The oral dosage may be configured to have the therapeutic agent(s) of the invention and the other agents release completely in the stomach, release partially in the stomach and partially in the intestine, in the intestine, in the colon, partially in the stomach, or wholly in the colon. The oral dosage also may be configured whereby the release of the therapeutic agent(s) of the invention is confined to the stomach or intestine while the release of the other active agent is not so confined or is confined differently from the therapeutic agent(s) of the invention. For example, the therapeutic agent(s) of the invention may be an enterically coated core or pellets contained within a tablet or capsule that releases the other agent first and releases the therapeutic agent(s) of the invention only after the therapeutic agent(s) of the invention passes through the stomach and into the intestine. The therapeutic agent(s) of the invention also can be in a sustained release material, whereby the therapeutic agent(s) of the invention is released throughout the gastrointestinal tract and the other agent is released on the same or a different schedule. The same objective for therapeutic agent(s) of the invention release can be achieved with immediate release of therapeutic agent(s) of the invention combined with enteric coated therapeutic agent(s) of the invention. In these instances, the other agent could be released immediately in the stomach, throughout the gastrointestinal tract or only in the intestine.

[0112] The materials useful for achieving these different release profiles are well known to those of ordinary skill in the art. Immediate release is obtainable by conventional tablets with binders which dissolve in the stomach. Coatings which dissolve at the pH of the stomach or which dissolve at elevated temperatures will achieve the same purpose. Release only in the intestine is achieved using conventional enteric coatings such as pH sensitive coatings which dissolve in the pH environment of the intestine (but not the stomach) or coatings which dissolve over time. Release throughout the gastrointestinal tract is achieved by using sustained-release materials and/or combinations of the immediate release systems and sustained and/or delayed intentional release systems (e.g., pellets which dissolve at different pHs).

[0113] To improve oral bioavailability of the compounds of the present invention, excipients may be used that increase intestinal membrane permeability (Aungst, BJ. (2000) J. Pharm. Set., vol. 89, issue 5, pp. 429-442). Permeation enhancers may include surfactants, fatty acids, medium chain glycerides, steroidal detergents, acyl carnitine and alkanoylcholines, N-acetylated alpha amino acids and N-acetylated non-alpha amino acids, and chitosans, and other mucoadhesive polymers. Specific examples include: cholate, glycocholate,

[0114] In the event that it is desirable to release the therapeutic agent(s) of the invention first, the therapeutic agent(s) of the invention could be coated on the surface of the controlled release formulation in any pharmaceutically acceptable carrier suitable for such coatings and for permitting the release of the therapeutic agent(s) of the invention, such as in a temperature sensitive pharmaceutically acceptable carrier used for controlled release routinely. Other coatings which dissolve when placed in the body are well known to those of ordinary skill in the art.

[0115] The therapeutic agent(s) of the invention also may be mixed throughout a controlled release formulation, whereby it is released before, after or simultaneously with another agent. The therapeutic agent(s) of the invention may be free, that is, solubilized within the material of the formulation. The therapeutic agent(s) of the invention also may be in the form of vesicles, such as wax coated micropellets dispersed throughout the material of the formulation. The coated pellets can be fashioned to immediately release the therapeutic agent(s) of the invention based on temperature, pH or the like. The pellets also can be configured so as to delay the release of the therapeutic agent(s) of the invention, allowing the other agent a period of time to act before the therapeutic agent(s) of the invention exerts its effects. The therapeutic agent(s) of the invention pellets also can be configured to release the therapeutic agent(s) of the invention in virtually any sustained release pattern, including patterns exhibiting first order release kinetics or sigmoidal order release kinetics using materials of the prior art and well known to those of ordinary skill in the art.

[0116] The therapeutic agent(s) of the invention also can be contained within a core within the controlled release formulation. The core may have any one or any combination of the properties described above in connection with the pellets. The therapeutic agent(s) of the invention may be, for example, in a core coated with a material, dispersed throughout a material, coated onto a material or adsorbed into or throughout a material.

[0117] It should be understood that the pellets or core may be of virtually any type. They may be drug coated with a release material, drug interspersed throughout material, drug adsorbed into a material, and so on. The material may be erodible or nonerodible.
[018] The therapeutic agent(s) of the invention, may be provided in particles. Particles as used herein means nano or microparticles (or in some instances larger) which can consist in whole or in part of the therapeutic agent(s) of the inventions or the other agents as described herein. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, including, but not limited to, an enteric coating. The therapeutic agent(s) also may be dispersed throughout the particles. The therapeutic agent(s) also may be adsorbed into the particles. The particles may be of any order release kinetics, including zero order release, first order release, second order release, delayed release, sustained release, immediate release, and any combination thereof, etc. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, but not limited to, erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the antagonist in a solution or in a semi-solid state. The particles may be of virtually any shape.

[0119] Both non-biodegradable and biodegradable polymeric materials can be used in the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels described by H.S. Sawhney, CP. Pathak and J.A. Hubell in *Macromolecules*, (1993) 26:581-587, the teachings of which are incorporated herein. These include polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

[0120] The therapeutic agent(s) may be contained in controlled release systems. The term "controlled release" is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are controlled. This refers to immediate as well as nonimmediate release formulations, with nonimmediate release formulations including but not limited to sustained release and delayed release formulations. The term "sustained release" (also referred to as "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is used in its
conventional sense to refer to a drug formulation in which there is a time delay between administration of the formulation and the release of the drug therefrom. "Delayed release" may or may not involve gradual release of drug over an extended period of time, and thus may or may not be "sustained release." These formulations may be for any mode of administration.

[0121] Delivery systems specific for the gastrointestinal tract are roughly divided into three types: the first is a delayed release system designed to release a drug in response to, for example, a change in pH; the second is a timed-release system designed to release a drug after a predetermined time; and the third is a microflora enzyme system making use of the abundant enterobacteria in the lower part of the gastrointestinal tract (e.g., in a colonic site-directed release formulation).

[0122] An example of a delayed release system is one that uses, for example, an acrylic or cellulosic coating material and dissolves on pH change. Because of ease of preparation, many reports on such "enteric coatings" have been made. In general, an enteric coating is one which passes through the stomach without releasing substantial amounts of drug in the stomach (i.e., less than 10% release, 5% release and even 1% release in the stomach) and sufficiently disintegrating in the intestinal tract (by contact with approximately neutral or alkaline intestine juices) to allow the transport (active or passive) of the active agent through the walls of the intestinal tract.

[0123] Various in vitro tests for determining whether or not a coating is classified as an enteric coating have been published in the pharmacopoeia of various countries. A coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38 °C and thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH₂PO₄ buffered solution of pH 6.8 is one example. One such well known system is EUDRAGIT material, commercially available and reported on by Behringer, Manchester University, Saale Co., and the like. Enteric coatings are discussed further, below.

[0124] A timed release system is represented by Time Erosion System (TES) by Fujisawa Pharmaceutical Co., Ltd. and Pulsincap by R. P. Scherer. According to these systems, the site of drug release is decided by the time of transit of a preparation in the gastrointestinal tract. Since the transit of a preparation in the gastrointestinal tract is largely influenced by the gastric emptying time, some time release systems are also enterically coated.
[0125] Systems making use of the enterobacteria can be classified into those utilizing degradation of azoaromatic polymers by an azo reductase produced from enterobacteria as reported by the group of Ohio University (M. Saffran, et al, Science, Vol. 233: 1081 (1986)) and the group of Utah University (J. Kopecek, et al, Pharmaceutical Research, 9(12), 1540-1545 (1992)); and those utilizing degradation of polysaccharides by beta-galactosidase of enterobacteria as reported by the group of Hebrew University (unexamined published Japanese patent application No. 5-50863 based on a PCT application) and the group of Freiberg University (K. H. Bauer et al, Pharmaceutical Research, 10(10), S218 (1993)). In addition, the system using chitosan degradable by chitosanase by Teikoku Seiyaku K. K. (unexamined published Japanese patent application No. 4-217924 and unexamined published Japanese patent application No. 4-225922) is also included.

[0126] The enteric coating is typically, although not necessarily, a polymeric material. Preferred enteric coating materials comprise bioerodible, gradually hydrolyzable and/or gradually water-soluble polymers. The "coating weight," or relative amount of coating material per capsule, generally dictates the time interval between ingestion and drug release. Any coating should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention. The selection of the specific enteric coating material will depend on the following properties: resistance to dissolution and disintegration in the stomach; impermeability to gastric fluids and drug/carrier/enzyme while in the stomach; ability to dissolve or disintegrate rapidly at the target intestine site; physical and chemical stability during storage; non-toxicity; ease of application as a coating (substrate friendly); and economical practicality.

[0127] Suitable enteric coating materials include, but are not limited to: cellulose polymers such as cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose succinate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ammonium methacrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate (e.g., those copolymers sold under the trade name EUDRAGIT); vinyl polymers and copolymers such as polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; and shellac (purified lac). Combinations of different coating materials may also be used. Well known enteric coating
material for use herein are those acrylic acid polymers and copolymers available under the trade name EUDRAGIT from Rohm Pharma (Germany). The EUDRAGIT series E, L, S, RL, RS and NE copolymers are available as solubilized in organic solvent, as an aqueous dispersion, or as a dry powder. The EUDRAGIT series RL, NE, and RS copolymers are insoluble in the gastrointestinal tract but are permeable and are used primarily for extended release. The EUDRAGIT series E copolymers dissolve in the stomach. The EUDRAGIT series L, L-30D and S copolymers are insoluble in stomach and dissolve in the intestine, and are thus most preferred herein.

[0128] A particular methacrylic copolymer is EUDRAGIT L, particularly L-30D and EUDRAGIT L 100-55. In EUDRAGIT L-30D, the ratio of free carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH generally present in the fluid of lower gastrointestinal tract. Another particular methacrylic acid polymer is EUDRAGIT S, which differs from EUDRAGIT L-30D in that the ratio of free carboxyl groups to ester groups is approximately 1:2. EUDRAGIT S is insoluble at pH below 5.5, but unlike EUDRAGIT L-30D, is poorly soluble in gastrointestinal fluids having a pH in the range of 5.5 to 7.0, such as in the small intestine. This copolymer is soluble at pH 7.0 and above, i.e., the pH generally found in the colon. EUDRAGIT S can be used alone as a coating to provide drug delivery in the large intestine. Alternatively, EUDRAGIT S, being poorly soluble in intestinal fluids below pH 7, can be used in combination with EUDRAGIT L-30D, soluble in intestinal fluids above pH 5.5, in order to provide a delayed release composition which can be formulated to deliver the active agent to various segments of the intestinal tract. The more EUDRAGIT L-30D used, the more proximal release and delivery begins, and the more EUDRAGIT S used, the more distal release and delivery begins. It will be appreciated by those skilled in the art that both EUDRAGIT L-30D and EUDRAGIT S can be replaced with other pharmaceutically acceptable polymers having similar pH solubility characteristics. In certain embodiments of the invention, the preferred enteric coating is ACRL-EZE™ (methacrylic acid co-polymer type C; Colorcon, West Point, PA).

[0129] The enteric coating provides for controlled release of the active agent, such that drug release can be accomplished at some generally predictable location. The enteric coating also prevents exposure of the therapeutic agent and carrier to the epithelial and mucosal tissue of the buccal cavity, pharynx, esophagus, and stomach, and to the enzymes associated with
these tissues. The enteric coating therefore helps to protect the active agent, carrier and a patient's internal tissue from any adverse event prior to drug release at the desired site of delivery. Furthermore, the coated material of the present invention allows optimization of drug absorption, active agent protection, and safety. Multiple enteric coatings targeted to release the active agent at various regions in the gastrointestinal tract would enable even more effective and sustained improved delivery throughout the gastrointestinal tract.

[0130] The coating can, and usually does, contain a plasticizer to prevent the formation of pores and cracks that would permit the penetration of the gastric fluids. Suitable plasticizers include, but are not limited to, triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflex A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, a coating comprised of an anionic carboxylic acrylic polymer will usually contain approximately 10% to 25% by weight of a plasticizer, particularly dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. The coating can also contain other coating excipients such as detackifiers, antifoaming agents, lubricants (e.g., magnesium stearate), and stabilizers (e.g., hydroxypropylcellulose, acids and bases) to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[0131] The coating can be applied to particles of the therapeutic agent(s), tablets of the therapeutic agent(s), capsules containing the therapeutic agent(s) and the like, using conventional coating methods and equipment. For example, an enteric coating can be applied to a capsule using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like. Detailed information concerning materials, equipment and processes for preparing coated dosage forms may be found in Pharmaceutical Dosage Forms: Tablets, eds. Lieberman et al. (New York: Marcel Dekker, Inc., 1989), and in Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed. (Media, PA: Williams & Wilkins, 1995). The coating thickness, as noted above, must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the lower intestinal tract is reached.

[0132] In another embodiment, drug dosage forms are provided that comprise an enterically coated, osmotically activated device housing a formulation of the invention. In this embodiment, the drug-containing formulation is encapsulated in a semipermeable membrane or barrier containing a small orifice. As known in the art with respect to so-called "osmotic pump" drug delivery devices, the semipermeable membrane allows passage of water in either direction, but not drug. Therefore, when the device is exposed to aqueous fluids, water will flow into the
device due to the osmotic pressure differential between the interior and exterior of the device. As water flows into the device, the drug-containing formulation in the interior will be "pumped" out through the orifice. The rate of drug release will be equivalent to the inflow rate of water times the drug concentration. The rate of water influx and drug efflux can be controlled by the composition and size of the orifice of the device. Suitable materials for the semipermeable membrane include, but are not limited to, polyvinyl alcohol, polyvinyl chloride, semipermeable polyethylene glycols, semipermeable polyurethanes, semipermeable polyamides, semipermeable sulfonated polystyrenes and polystyrene derivatives; semipermeable poly(sodium styrenesulfonate), semipermeable poly(vinylbenzyltrimethylammonium chloride), and cellulosic polymers such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose trivalerate, cellulose trilate, cellulose tripalmitate, cellulose trioctanoate, cellulose tripropionate, cellulose disuccinate, cellulose dipalmitate, cellulose dicylate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate heptanate, cellulose acetaldehyde dimethyl acetal, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose dimethylaminoacetate and ethylcellulose.

[0133] In another embodiment, drug dosage forms are provided that comprise a sustained release coated device housing a formulation of the invention. In this embodiment, the drug-containing formulation is encapsulated in a sustained release membrane or film. The membrane may be semipermeable, as described above. A semipermeable membrane allows for the passage of water inside the coated device to dissolve the drug. The dissolved drug solution diffuses out through the semipermeable membrane. The rate of drug release depends upon the thickness of the coated film and the release of drug can begin in any part of the GI tract. Suitable membrane materials for such a membrane include ethylcellulose.

[0134] In another embodiment, drug dosage forms are provided that comprise a sustained release device housing a formulation of the invention. In this embodiment, the drug-containing formulation is uniformly mixed with a sustained release polymer. These sustained release polymers are high molecular weight water-soluble polymers, which when in contact with water, swell and create channels for water to diffuse inside and dissolve the drug. As the polymers swell and dissolve in water, more of drug is exposed to water for dissolution. Such a system is generally referred to as sustained release matrix. Suitable materials for such a device include hydropropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose and methyl cellulose.
In another embodiment, drug dosage forms are provided that comprise an enteric coated device housing a sustained release formulation of the invention. In this embodiment, the drug containing product described above is coated with an enteric polymer. Such a device would not release any drug in the stomach and when the device reaches the intestine, the enteric polymer is first dissolved and only then would the drug release begin. The drug release would take place in a sustained release fashion.

Enterically coated, osmotically activated devices can be manufactured using conventional materials, methods and equipment. For example, osmotically activated devices may be made by first encapsulating, in a pharmaceutically acceptable soft capsule, a liquid or semi-solid formulation of the compounds of the invention as described previously. This interior capsule is then coated with a semipermeable membrane composition (comprising, for example, cellulose acetate and polyethylene glycol 4000 in a suitable solvent such as a methylene chloride-methanol admixture), for example using an air suspension machine, until a sufficiently thick laminate is formed, e.g., around 0.05 mm. The semipermeable laminated capsule is then dried using conventional techniques. Then, an orifice having a desired diameter (e.g., about 0.99 mm) is provided through the semipermeable laminated capsule wall, using, for example, mechanical drilling, laser drilling, mechanical rupturing, or erosion of an erodible element such as a gelatin plug. The osmotically activated device may then be enterically coated as previously described. For osmotically activated devices containing a solid carrier rather than a liquid or semi-solid carrier, the interior capsule is optional; that is, the semipermeable membrane may be formed directly around the carrier-drug composition. However, preferred carriers for use in the drug-containing formulation of the osmotically activated device are solutions, suspensions, liquids, immiscible liquids, emulsions, sols, colloids, and oils. Particularly preferred carriers include, but are not limited to, those used for enterically coated capsules containing liquid or semisolid drug formulations.

Cellulose coatings include those of cellulose acetate phthalate and trimellitate; methacrylic acid copolymers, e.g. copolymers derived from methylacrylic acid and esters thereof, containing at least 40% methylacrylic acid; and especially hydroxypropyl methylcellulose phthalate. Methylacrylates include those of molecular weight above 100,000 daltons based on, e.g. methylacrylate and methyl or ethyl methylacrylate in a ratio of about 1:1. Typical products include Endragit L, e.g. L 100-55, marketed by Rohm GmbH, Darmstadt, Germany. Typical cellulose acetate phthalates have an acetyl content of 17-26% and a phthalate content of from 30-40% with a viscosity of ca. 45-90 cP. Typical cellulose acetate trimellitates
have an acetyl content of 17-26%, a trimellityl content from 25-35% with a viscosity of ca. 15-20 cS. An example of a cellulose acetate trimellitate is the marketed product CAT (Eastman Kodak Company, USA). Hydroxypropyl methylcellulose phthalates typically have a molecular weight of from 20,000 to 130,000 daltons, a hydroxypropyl content of from 5 to 10%, a methoxy content of from 18 to 24% and a phthalyl content from 21 to 35%. An example of a cellulose acetate phthalate is the marketed product CAP (Eastman Kodak, Rochester N.Y., USA). Examples of hydroxypropyl methylcellulose phthalates are the marketed products having a hydroxypropyl content of from 6-10%, a methoxy content of from 20-24%, a phthalyl content of from 21-27%, a molecular weight of about 84,000 daltons, sold under the trademark HP50 and available from Shin-Etsu Chemical Co. Ltd., Tokyo, Japan, and having a hydroxypropyl content, a methoxyl content, and a phthalyl content of 5-9%, 18-22% and 27-35%, respectively, and a molecular weight of 78,000 daltons, known under the trademark HP55 and available from the same supplier.

[0138] The therapeutic agents may be provided in capsules, coated or not. The capsule material may be either hard or soft, and as will be appreciated by those skilled in the art, typically comprises a tasteless, easily administered and water soluble compound such as gelatin, starch or a cellulosic material. The capsules are preferably sealed, such as with gelatin bands or the like. See, for example, Remington: The Science and Practice of Pharmacy, Nineteenth Edition (Easton, Pa.: Mack Publishing Co., 1995), which describes materials and methods for preparing encapsulated pharmaceuticals.

[0139] A product containing therapeutic agent(s) of the invention can be configured as a suppository. The therapeutic agent(s) of the invention can be placed anywhere within or on the suppository to favorably affect the relative release of the therapeutic agent(s). The nature of the release can be zero order, first order, or sigmoidal, as desired.

[0140] Suppositories are solid dosage forms of medicine intended for administration via the rectum. Suppositories are compounded so as to melt, soften, or dissolve in the body cavity (around 98.6 °F) thereby releasing the medication contained therein. Suppository bases should be stable, nonirritating, chemically inert, and physiologically inert. Many commercially available suppositories contain oily or fatty base materials, such as cocoa butter, coconut oil, palm kernel oil, and palm oil, which often melt or deform at room temperature necessitating cool storage or other storage limitations. U.S. Patent No. 4,837,214 to Tanaka et al. describes a suppository base comprised of 80 to 99 percent by weight of a lauric-type fat having a hydroxyl value of 20 or smaller and containing glycerides of fatty acids having
8 to 18 carbon atoms combined with 1 to 20 percent by weight diglycerides of fatty acids (which erucic acid is an example of). The shelf life of these type of suppositories is limited due to degradation. Other suppository bases contain alcohols, surfactants, and the like which raise the melting temperature but also can lead to poor absorption of the medicine and side effects due to irritation of the local mucous membranes (see for example, U.S. Patent No. 6,099,853 to Hartelendy et al., U.S. Patent No. 4,999,342 to Ahmad et al., and U.S. Patent No. 4,765,978 to Abidi et al.).

[0141] The base used in the pharmaceutical suppository composition of this invention includes, in general, oils and fats comprising triglycerides as main components such as cacao butter, palm fat, palm kernel oil, coconut oil, fractionated coconut oil, lard and WITEPSOL®, waxes such as lanolin and reduced lanolin; hydrocarbons such as VASELINE®, squalene, squalane and liquid paraffin; long to medium chain fatty acids such as caprylic acid, lauric acid, stearic acid and oleic acid; higher alcohols such as lauryl alcohol, cetanol and stearyl alcohol; fatty acid esters such as butyl stearate and dilauryl malonate; medium to long chain carboxylic acid esters of glycerin such as triolein and tristearin; glycerin-substituted carboxylic acid esters such as glycerin acetoacetate; and polyethylene glycols and its derivatives such as macrogols and cetomacrogol. They may be used either singly or in combination of two or more. If desired, the composition of this invention may further include a surface-active agent, a coloring agent, etc., which are ordinarily used in suppositories.

[0142] The pharmaceutical composition of this invention may be prepared by uniformly mixing predetermined amounts of the active ingredient, the absorption aid and optionally the base, etc. in a stirrer or a grinding mill, if required at an elevated temperature. The resulting composition, may be formed into a suppository in unit dosage form by, for example, casting the mixture in a mold, or by forming it into a gelatin capsule using a capsule filling machine.

[0143] The compositions according to the present invention also can be administered as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. The administration of a composition can also include using a nasal tampon or a nasal sponge containing a composition of the present invention.

[0144] The nasal delivery systems that can be used with the present invention can take various forms including aqueous preparations, non-aqueous preparations and combinations thereof. Aqueous preparations include, for example, aqueous gels, aqueous suspensions,
aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof. Non-aqueous preparations include, for example, non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof. The various forms of the nasal delivery systems can include a buffer to maintain pH, a pharmaceutically acceptable thickening agent and a humectant. The pH of the buffer can be selected to optimize the absorption of the therapeutic agent(s) across the nasal mucosa.

[0145] With respect to the non-aqueous nasal formulations, suitable forms of buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa. In the present invention, the pH of the compositions may be maintained from about 2.0 to about 6.0. It is desirable that the pH of the compositions is one which does not cause significant irritation to the nasal mucosa of a recipient upon administration.

[0146] The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening agents that can be used in accordance with the present invention include methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired. Such agents can also be used in a powder formulation discussed above.

[0147] The compositions of the present invention can also include a humectant to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable humectants that can be used in the present invention include sorbitol, mineral oil, vegetable oil and glycerol; soothing agents; membrane conditioners; sweeteners; and combinations thereof. The concentration of the humectant in the present compositions will vary depending upon the agent selected.

[0148] One or more therapeutic agents may be incorporated into the nasal delivery system or any other delivery system described herein.

[0149] A composition formulated for topical administration may be liquid or semi-solid (including, for example, a gel, lotion, emulsion, cream, ointment, spray or aerosol) or may be provided in combination with a "finite" carrier, for example, a non-spreading material that
retains its form, including, for example, a patch, bioadhesive, dressing or bandage. It may be aqueous or non-aqueous; it may be formulated as a solution, emulsion, dispersion, a suspension or any other mixture.

[0150] Important modes of administration include topical application to the skin, eyes or mucosa. Thus, typical vehicles are those suitable for pharmaceutical or cosmetic application to body surfaces. The compositions provided herein may be applied topically or locally to various areas in the body of a patient. As noted above, topical application is intended to refer to application to the tissue of an accessible body surface, such as, for example, the skin (the outer integument or covering) and the mucosa (the mucous-producing, secreting and/or containing surfaces). Exemplary mucosal surfaces include the mucosal surfaces of the eyes, mouth (such as the lips, tongue, gums, cheeks, sublingual and roof of the mouth), larynx, esophagus, bronchial, nasal passages, vagina and rectum/anus; in some embodiments, preferably the mouth, larynx, esophagus, vagina and rectum/anus; in other embodiments, preferably the eyes, larynx, esophagus, bronchial, nasal passages, and vagina and rectum/anus. As noted above, local application herein refers to application to a discrete internal area of the body, such as, for example, a joint, soft tissue area (such as muscle, tendon, ligaments, intraocular or other fleshy internal areas), or other internal area of the body. Thus, as used herein, local application refers to applications to discrete areas of the body.

[0151] Also in certain embodiments, including embodiments that involve aqueous vehicles, the compositions may also contain a glycol, that is, a compound containing two or more hydroxy groups. A glycol which may be particularly useful for use in the compositions is propylene glycol. The glycol may be included in the compositions in a concentration of from greater than 0 to about 5 wt. %. based on the total weight of the composition.

[0152] For local internal administration, such as intra-articular administration, the compositions are preferably formulated as a solution or a suspension in an aqueous-based medium, such as isotropically buffered saline or are combined with a biocompatible support or bioadhesive intended for internal administration.

[0153] Lotions, which, for example, may be in the form of a suspension, dispersion or emulsion, contain an effective concentration of one or more of the compounds. The effective concentration is preferably to deliver an effective amount. For example, the compound of the present invention may find use at a concentration of between about 0.1-50% [by weight] or more of one or more of the compounds provided herein.
The lotions may contain, for example, [by weight] from 1% to 50% of an emollient and the balance water, a suitable buffer, and other agents as described above. Any emollients known to those of skill in the art as suitable for application to human skin may be used. These include, but are not limited to, the following: (a) hydrocarbon oils and waxes, including mineral oil, petrolatum, paraffin, ceresin, ozokerite, microcrystalline wax, polyethylene, and perhydrosqualene; b) silicone oils, including dimethyldichlorosilanes, methylphenylpolysiloxanes, water-soluble and alcohol-soluble silicone-glycol copolymers; (c) triglyceride fats and oils, including those derived from vegetable, animal and marine sources. Examples include, but are not limited to, castor oil, safflower oil, cotton seed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil, and soybean oil; (d) acetoglyceride esters, such as acetyl monoglycerides; (e) ethoxylated glycerides, such as ethoxylated glyceryl monostearate.

Other emollients include but are not limited to (f) alkyl esters of fatty acids having 10 to 20 carbon atoms. Methyl, isopropyl and butyl esters of fatty acids are useful herein. Examples include, but are not limited to, hexyl laurate, isoHexyl laurate, isohexyl palmitate, isopropyl palmitate, isopropyl myristate, decyl oleate, isodecyl oleate, hexadecyl stearate, decyl stearate, isopropyl istearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate; (g) alkenyl esters of fatty acids having 10 to 20 carbon atoms. Examples thereof include, but are not limited to, oleyl myristate, oleyl stearate, and oleyl oleate; (h) fatty acids having 9 to 22 carbon atoms. Suitable examples include, but are not limited to, pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidonic, behenic, and erucic acids. (i) fatty alcohols having 10 to 22 carbon atoms, such as, but not limited to, lauryl, myristyl, cetyl, hexadecyl, stearyl, isostearyl, hydroxystearyl, oleyl, ricinoleyl, behenyl, erucyl, and 2-ocetyl dodecyl alcohols; (j) fatty alcohol ethers, including, but not limited to ethoxylated fatty alcohols of 10 to 20 carbon atoms, such as, but are not limited to, the lauryl, cetyl, stearyl, isostearyl, oleyl, and cholesterol alcohols having attached thereto from 1 to 50 ethylene oxide groups or 1 to 50 propylene oxide groups or mixtures thereof; (k) ether-esters, such as fatty acid esters of ethoxylated fatty alcohols.

Still other emollients include but are not limited to (1) lanolin and derivatives, including, but not limited to, lanolin, lanolin oil, lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate, ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxylated cholesterol, propoxylated lanolin alcohols, acetylated lanolin, acetylated lanolin
alcohols, lanolin alcohols linoleate, lanolin alcohols ricinoleate, acetate of lanolin alcohols ricinoleate, acetate of ethoxylated alcohols-esters, hydrogenolysis of lanolin, ethoxylated hydrogenated lanolin, ethoxylated sorbitol lanolin, and liquid and semisolid lanolin absorption bases; (m) polyhydric alcohols and polyether derivatives, including, but not limited to, propylene glycol, dipropylene glycol, polypropylene glycol [M.W. 2000-4000], polyoxyethylene polyoxypropylene glycols, polyoxypropylene polyoxyethylene glycols, glycerol, ethoxylated glycerol, propoxylated glycerol, sorbitol, ethoxylated sorbitol, hydroxypropyl sorbitol, polyethylene glycol [M.W. 200-6000], methoxy polyethylene glycols 350, 550, 750, 2000, 5000, poly(ethylene oxide) homopolymers [M.W. 100,000-5,000,000], polyalkylene glycols and derivatives, hexylene glycol (2-methyl-2,4-pentanediol), 1,3-butylene glycol, 1,2,6-hexanetriol, ethohexadiol USP (2-ethyl-1,3-hexanediol), C_{15} -C_{18} vicinal glycol and polyoxypropylene derivatives of trimethylolpropane.

[0157] Still other emollients include but are not limited to (n) polyhydric alcohol esters, including, but not limited to, ethylene glycol mono- and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol [M.W. 200-6000], mono- and di-fatty esters, propylene glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty acid esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters; (o) wax esters, including, but not limited to, beeswax, spermaceti, myristyl myristate, and stearyl stearate and beeswax derivatives, including, but not limited to, polyoxyethylene sorbitol beeswax, which are reaction products of beeswax with ethoxylated sorbitol of varying ethylene oxide content that form a mixture of ether-esters; (p) vegetable waxes, including, but not limited to, carnauba and candelilla waxes; (q) phospholipids, such as lecithin and derivatives; (r) sterols, including, but not limited to, cholesterol and cholesterol fatty acid esters; (s) amides, such as fatty acid amides, ethoxylated fatty acid amides, and solid fatty acid alkanolamides.

[0158] The lotions further preferably contain [by weight] from 1% to 10%, more preferably from 2% to 5%, of an emulsifier. The emulsifiers can be nonionic, anionic or cationic. Examples of satisfactory nonionic emulsifiers include, but are not limited to, fatty alcohols having 10 to 20 carbon atoms, fatty alcohols having 10 to 20 carbon atoms condensed with 2 to 20 moles of ethylene oxide or propylene oxide, alkyl phenols with 6 to 12 carbon atoms in the alkyl chain condensed with 2 to 20 moles of ethylene oxide, mono- and di-fatty acid esters
of ethylene oxide, mono- and di-fatty acid esters of ethylene glycol where the fatty acid moiety contains from 10 to 20 carbon atoms, diethylene glycol, polyethylene glycols of molecular weight 200 to 6000, propylene glycols of molecular weight 200 to 3000, glycerol, sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan and hydrophilic wax esters.

[0159] Suitable anionic emulsifiers include, but are not limited to, the fatty acid soaps, e.g., sodium, potassium and triethanolamine soaps, where the fatty acid moiety contains from 10 to 20 carbon atoms. Other suitable anionic emulsifiers include, but are not limited to, the alkali metal, ammonium or substituted ammonium alkyl sulfates, alkyl arylsulfonates, and alkyl ethoxy ether sulfonates having 10 to 30 carbon atoms in the alkyl moiety. The alkyl ethoxy ether sulfonates contain from 1 to 50 ethylene oxide units. Among satisfactory cationic emulsifiers are quaternary ammonium, morpholinium and pyridinium compounds. Certain of the emollients described in preceding paragraphs also have emulsifying properties. When a lotion is formulated containing such an emollient, an additional emulsifier is not needed, though it can be included in the composition.

[0160] The balance of the lotion is water or a C₂ or C₃ alcohol, or a mixture of water and the alcohol. The lotions are formulated by simply admixing all of the components together. Preferably the compound is dissolved, suspended or otherwise uniformly dispersed in the mixture.

[0161] Other conventional components of such lotions may be included. One such additive is a thickening agent at a level from 1% to 10% by weight of the composition. Examples of suitable thickening agents include, but are not limited to: cross-linked carboxypolymethylene polymers, ethyl cellulose, polyethylene glycols, gum tragacanth, gum kharaya, xanthan gums and bentonite, hydroxyethyl cellulose, and hydroxypropyl cellulose.

[0162] Creams can be formulated to contain a concentration effective to deliver an effective amount of therapeutic agent(s) of the invention to the treated tissue, typically at between about 0.1%, preferably at greater than 1% up to and greater than 50%, preferably between about 3% and 50%, more preferably between about 5% and 15% therapeutic agent(s) of the invention. The creams also contain from 5% to 50%, preferably from 10% to 25%, of an emollient and the remainder is water or other suitable non-toxic carrier, such as an isotonic buffer. The emollients, as described above for the lotions, can also be used in the cream compositions. The cream may also contain a suitable emulsifier, as described above. The emulsifier is included in the composition at a level from 3% to 50%, preferably from 5% to 20%.
These compositions that are formulated as solutions or suspensions may be applied to the skin, or, may be formulated as an aerosol or foam and applied to the skin as a spray-on. The aerosol compositions typically contain [by weight] from 25% to 80%, preferably from 30% to 50%, of a suitable propellant. Examples of such propellants are the chlorinated, fluorinated and chlorofluorinated lower molecular weight hydrocarbons. Nitrous oxide, carbon dioxide, butane, and propane are also used as propellant gases. These propellants are used as understood in the art in a quantity and under a pressure suitable to expel the contents of the container.

Suitably prepared solutions and suspensions may also be topically applied to the eyes and mucosa. Solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts, and preferably containing one or more of the compounds herein at a concentration of about 0.1%, preferably greater than 1%, up to 50% or more. Suitable ophthalmic solutions are known [see, e.g., U.S. Pat. No. 5,168,668, which describes typical compositions of ophthalmic irrigation solutions and solutions for topical application]. Such solutions, which have a pH adjusted to about 7.4, contain, for example, 90-100 mM sodium chloride, 4-6 mM dibasic potassium phosphate, 4-6 mM dibasic sodium phosphate, 8-12 mM sodium citrate, 0.5-1.5 mM magnesium chloride, 1.5-2.5 mM calcium chloride, 15-25 mM sodium acetate, 10-20 mM D.L.-sodium, β-hydroxybutyrate and 5-5.5 mM glucose.

Gel compositions can be formulated by simply admixing a suitable thickening agent to the previously described solution or suspension compositions. Examples of suitable thickening agents have been previously described with respect to the lotions.

The gelled compositions contain an effective amount of therapeutic agent(s) of the invention, typically at a concentration of between about 0.1-50% by weight or more of one or more of the compounds provided herein; from 5% to 75%, preferably from 10% to 50%, of an organic solvent as previously described; from 0.5% to 20%, preferably from 1% to 10% of the thickening agent; the balance being water or other aqueous or non-aqueous carrier, such as, for example, an organic liquid, or a mixture of carriers.

The formulations can be constructed and arranged to create steady state plasma levels. Steady state plasma concentrations can be measured using HPLC techniques, as are known to those of skill in the art. Steady state is achieved when the rate of drug availability is equal to the rate of drug elimination from the circulation. In typical therapeutic settings, the
therapeutic agent(s) of the invention will be administered to patients either on a periodic dosing regimen or with a constant infusion regimen. The concentration of drug in the plasma will tend to rise immediately after the onset of administration and will tend to fall over time as the drug is eliminated from the circulation by means of distribution into cells and tissues, by metabolism, or by excretion. Steady state will be obtained when the mean drug concentration remains constant over time. In the case of intermittent dosing, the pattern of the drug concentration cycle is repeated identically in each interval between doses with the mean concentration remaining constant. In the case of constant infusion, the mean drug concentration will remain constant with very little oscillation. The achievement of steady state is determined by means of measuring the concentration of drug in plasma over at least one cycle of dosing such that one can verify that the cycle is being repeated identically from dose to dose. Typically, in an intermittent dosing regimen, maintenance of steady state can be verified by determining drug concentrations at the consecutive troughs of a cycle, just prior to administration of another dose. In a constant infusion regimen where oscillation in the concentration is low, steady state can be verified by any two consecutive measurements of drug concentration.

[01681] Included within embodiments, is a kit which includes a container containing a compound of the present disclosure. The kit may additionally contain a second therapeutic agent such as a container containing an opioid formulation. The kit may include a pharmaceutical preparation vial, and a pharmaceutical preparation diluents vial. The diluents vial may, for example, contain diluents such as physiological saline for diluting what could be a concentrated solution or lyophilized powder of the compound. The instructions can include instructions for mixing a particular amount of the diluents with a particular amount of the concentrated pharmaceutical preparation, whereby a final formulation for injection or infusion is prepared. The instructions may include instructions for treating a patient with an effective amount of the compound. It also will be understood that the containers containing the preparations, whether the container is a bottle, a vial with a septum, an ampoule with a septum, an infusion bag, and the like, can contain additional indicia such as conventional markings which change color when the preparation has been autoclaved or otherwise sterilized.

Examples of Functional Assays

[0169] The following are abbreviations known to those skilled in the art: "DAMGO", D-Ala²-N-Me-Phe⁴,Gly-ol²-enkephalin; "cAMP", cyclic adenosine monophosphate; "CTOP", D-Phe-Cys-Tyr-D-Try-Orn-Thr-Pen-Thr-NH₂; "EIA", enzyme immunoassay; "CHO", Chinese hamster ovary
Specificity of Receptor Binding of Morphinans.

[0170] Radioligand binding assays may be conducted to determine the binding specificity of a morphinan of the invention for mu-, kappa-, and delta-opiate receptors using methods adapted from scientific literature (Simonin, F et al. 1994, Mol. Pharmacol 46:1015-1021; Maguire, P. et al 1992, Ew: J. Pharmacol. 213:219-225; Simonin, F. et al PNAS USA 92(15):1431-1437; Wang, JB 1994,. FEBS Lett. 338:217-222). For example, a membrane may be associated with human opioid receptor material. Diprenorphine, which has an affinity for these three opioid receptors, can be used as a competitive challenge to the test compound. Membranes can then be separated, and the binding of the test compounds to the receptor material can be determined by scintillation counting. A control, such as naltrexone, can be used to determine relative binding affinity.

Exemplar Test for Agonist Activity.

10171] Tissues, for example an isolated segment of guinea pig ileum, may be exposed to a submaximal concentration of the reference agonist DAMGO, D-Ala²-N-Me-Phe⁴,Gly-ol²-enkephalin (0.1 μM), to verify responsiveness and to obtain a control response. Following extensive washings and recovery of the control twitch contractions, the tissues may be exposed to increasing concentrations of the morphinan of the present invention or the same reference agonist. The different concentrations may be added cumulatively and each left in contact with the tissues until a stable response is obtained or for a maximum of 15 min. If an agonist-like response (inhibition of twitch contractions) is obtained, the reference antagonist naloxone (0.1 μM) may be tested against the highest concentration of the morphinan used to confirm the involvement of the mu-receptors in the response.

Exemplar Test for Antagonist Activity.

[0172] The tissues may be exposed to a submaximal concentration of the reference agonist DAMGO (0.1 μM) to obtain a control response. After stabilization of the DAMGO-induced response, increasing concentrations of a morphinan of the present invention or the reference antagonist naloxone may be added cumulatively. Each concentration may be left in contact with the tissues until a stable response is obtained or for a maximum time, such as 15 min. The maximum change in the amplitude of the electrically-evoked twitch contractions induced by each compound concentration may be measured. Results may be expressed as a percent of the control response to DAMGO (mean values). The EC50 value (concentration
producing a half-maximum response) or $IC_{50}$ value (concentration causing a half-maximum inhibition of the response to DAMGO) may be determined by linear regression analysis of the concentration-response curves. Inhibition of the DAMGO-induced response by a morphinan of the present invention may indicate an antagonist activity at the mu-receptors.

**Test of Gastrointestinal Transit in Rats.**


**Tests for Anti-Diarrheal Activity.**

[0174] Tests for antidiarrheal activity may also be run for morphinans of the present invention. For example, the castor oil tests described in Niemegeers *et al.* (1972) *Arzneim. Forsch.* 22:516-518; U.S. Pat. Nos. 4,867,979; 4,990,521; 4,824,853 may be used. In such tests, rats or mice may be fasted overnight. Each animal is treated intravenously with the desired dose of the compound to be tested. A period of time thereafter, the animal receives a dose of oil, such as castor oil or ricino oil, orally. Each animal is kept in an individual cage. A period of time after the castor oil treatment, each animal is assessed for the presence or absence of diarrhea. The $ED_{50}$ value is determined as that dose in mg/kg body weight at which no diarrhea is present in 50% of the tested animals.

[0175] Anti-diarrheal activity can also be determined by assessing the effects of a compound as an antagonist of PGE$_2$-induced diarrhea in mice [see, *e.g.*, Dajani *et al.* 1975] *European Jour. Pharmacol.* 34:105-113; and Dajani *et al.* (1977) *J. Pharmacol. Exp. Ther.* 203:512-526; *see, e.g.*, U.S. Pat. No. 4,870,084]. This method reliably elicits diarrhea in otherwise untreated mice within 15 minutes.

**Methods for Determining Analgesic Activity**

[0176] The following pain models are useful in determining the analgesic activity of a morphinan of the present invention:
Acetic Acid Writhing assay in Mice.

[0177] Mice (CD-I, male) are weighed and placed in individual squares. The test or control article are administered and after the appropriate absorption time, acetic acid solution are administered intraperitoneally. Ten minutes after the i.p. injection of acetic acid, the number of writhes are recorded for a period of 5 minutes.

[0178] The total number of writhes for each mouse are recorded. The mean number of writhes for the control and each test article group are compared using an ANOVA followed by a relevant multiple comparison test and percent inhibition calculated.

Phenylquinone (PPQ) Writhing Assay.

[0179] Mice (CD-I, male) are weighed and placed in individual squares. The test or control article are administered and after the appropriate absorption time, the PPQ solution (0.02% aqueous solution) is administered intraperitoneally. Each animal is observed closely for ten minutes for exhibition of writhing.

[0180] The total number of writhes for each mouse are recorded. The mean number of writhes for the control and each test article group are compared using an ANOVA followed by a relevant multiple comparison test and percent inhibition calculated.

Randall-Selitto Assay in Rats.

[0181] The purpose of this assay is to determine the effect of test articles upon the pain threshold of rats.

[0182] Following an overnight fast, rats are placed in groups of ten. Twenty rats are used as vehicle controls. The rats are then sequentially injected with a 20% Brewer's yeast suspension into the plantar surface of the left hind paw. Two hours later the rats are administered the test article, reference drug, or control vehicle. One hour after dose administration, the pain threshold of the inflamed and non-inflamed paw is measured by a "Analgesia Meter" that exerts a force which increases at a constant rate along a linear scale.

[0183] The control group threshold and standard deviation for the inflamed paw and non-inflamed paw are calculated. Rats in the test article group and reference group are considered protected if the individual pain threshold exceeds the control group mean threshold by two standard deviations of the means.
Hot Plate Analgesia Assay.

[0184] Each mouse (CD-I, male) serves as its own control throughout the experiment. The mice are placed sequentially on a Hot Plate Analgesia Meter (set for 55°C ± 2°C). The mice react characteristically to the heat stimulus by:

1. Licking the forepaw
2. Rapid fanning of the hind paw
3. A sudden jump off the hot plate

[0185] Any of the three types of reactions are taken as an end point to the heat stimulus. The mouse is removed from the hot plate immediately upon displaying the end point. The reaction time is measured quantitatively by the number of seconds that elapse between the placing of the mouse on the hot plate and the display of a definitive end point. Elapsed time is measured by a stop watch accurate to at least 1/5 of a second. Only mice whose control reaction time is 10.0 seconds or less are used. At 15, 30, 60 and 120 minutes (± 1 to 5 minutes) after test or control article administration, reaction times will be obtained and recorded for the group sequentially.

[0186] Analgesic response is an increase in reaction time of the mouse to the heat stimulus. Percent analgesia is calculated from the average response of the group of ten mice per dose level at a specified time interval:

\[
\text{\% analgesia} = 100 \times \frac{\text{average response time in seconds (test article treated)}}{\text{average response time in seconds (control)}} - 1.00
\]

An ANOVA with appropriate Multiple Comparison Test is then performed.

Rat Tail Radiant Heat Test (Tail Flick).

[0187] This methodology allows evaluation of the potential ability of a test article to produce an analgesic response to thermal stimulation in rats. Following an overnight fast, rats are weighed and placed in groups of ten. The test or vehicle control articles are administered. A Tail Flick Analgesia Meter is used. Sixty minutes following oral administration (or as recommended by the Sponsor), the tail of each rat is exposed to a specific intensity of heat stimulus and the time required to elicit a response (a characteristic tail flick) is recorded.
Percent analgesia is calculated using the mean control response compared to the mean test article response.

Identification of Compounds for Use as Peripheral Anti-Hyperalgesics.

In general, the methods described above, are also useful for assessing peripheral anti-hyperalgesic activities of test compounds. Most preferred among the methods for assessing anti-hyperalgesic activity are those described in Niemegeers et al. (1974) Drug Res. 24:1633-1636.

Assessment of Ratio \( [C] \) of the \( ED_{50} \) Value \( [A] \) in a Test for Anti-diarrheal Activity, Such as the Castor Oil Test, to the \( ED_{50} \) Value \( [B] \) in a Test of CNS Effects, Such as the Tail Withdrawal Test.

The agents intended for use in the methods and compositions can be identified by their activity as anti-diarrheals, and their lack of CNS effects. In particular, the selected compound exhibits anti-hyperalgesic activity in any of the standard models, discussed above, and, preferably, either (a) the ratio of these activities \( [B/A] \), as measured in standard assays, is substantially greater or equal to [at least equal to, more preferably at least about 2-fold greater] than the ratio of such activities for diphenoxylate; or (b) the activity of the compound in an assay that measures CNS activity is substantially less [at least two-fold, preferably 3-fold or more] than diphenoxylate.

In Vitro Pharmacology cAMP Assay in CHO Cells Expressing Human \( \mu \), MOP) Receptor.

The mu-opioid receptor is \( G_{i} \) coupled, and works when activated by inhibiting a cAMP increase. Thus, changes in cAMP can be used to determine agonist/antagonist activity at the \( \mu \) receptor. Cellular cAMP may be increased by addition of forskolin. Prior addition of DAMGO, or similar agonists, e.g. endomorphin-1, fentanyl, or morphine, inhibit this forskolin-induced increase. The absence of agonist effect produces a result equivalent to forskolin alone. Therefore, increasing agonist concentration decreases cAMP levels.

Antagonists, such as CTOP (D-Phe-Cys-Tyr-D-Try-Orn-Thr-Pen-Thr-NH\(_2\)), naloxone and ciprodime inhibit the cAMP inhibition. By adding the test compound, then
DAMGO, then forskolin, one can determine if the test compound has antagonistic activity. Increasing antagonist concentration increases cAMP.

[0193] Extracted cAMP level may be determined via competitive EIA assay utilizing alkaline phosphatase. Additional experimental conditions are as described, for example, in Toll L., J Pharmacol Exp Ther. (1995) 273(2): 721-727.

Determining Oral Bioavailability in a Rat Model

[0194] Jugular-cannulated Sprague-Dawley Rats (3/group) were dosed typically with 5 mg/kg of a test compound through oral gavage. Water was used as a formulation vehicle. Blood was drawn at 0.5, 1, 2 and 4 hours and the resulting plasma was subsequently analyzed by a LC/MS assay and a pharmacokinetic analysis conducted.

Determining Brain Permeability

[0195] One group of rats (3/group) was dosed typically with 5 mg/kg of a test compound through LV. injection. One hour after administration, blood was collected through cardiac puncture and the brains were harvested. Following a quick rinse, brains were homogenated with the appropriate volume of water. Both brain homogenates and the plasma were analyzed by LC/MS methods. The blood-to-brain ratio was then reported as a ratio of the corresponding concentrations.

Synthetic Examples

[0196] The following are abbreviations known to those skilled in the art: "DCM", dichloromethane; "DMF", dimethyl formamide; "EtOAc", ethyl acetate; HATU, O-(7-azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; "HPLC", high performance liquid chromatography; Oxone®, potassium peroxymonosulfate; "PrO", propoxy; "THF", tetrahydrofuran; TFA trifluoroacetic acid; NMO, N-morpholine-N-Oxide.
Example 1

\(^\text{-Cyclopropylmethyl-}^\alpha\text{-epoxy-}^\text{-hydroxy-H-earboxymethoxy-morphinan-}^\delta\text{-one} \)

**Trifluoroacetic acid salt**

(i) 17-Cyclopropylmethyl-4,5-\(\alpha\)-epoxy-3,14-dihydroxy-6,6-dimethoxymorphinan (2)

[0197] To a solution of naltrexone hydrochloride (1-HCl, 2.2 g, 1 eq.) in methanol (30 mL) was added trimethylorthoformate (2.04 g, 3.3 eq.) and HCl in ether (2M, 3.2 mL, 1.1 eq.) and the mixture was stirred at room temperature for 3h. The reaction mixture was diluted with water (150 mL) and basified using \(\text{NH}_4\text{OH} \) and extracted with dichloromethane (2X200 mL). The combined organics were dried over \(\text{MgSO}_4 \) and concentrated to get the crude 17-cyclopropylmethyl-4,5-\(\alpha\)-epoxy-3,14-dihydroxy-6,6-dimethoxymorphinan 2 as a white foam.
[0198] $^1$H NMR (301 MHz, CHLOROFORMS) $\delta$ ppm 6.68 (d, J=8.3 Hz, 1 H), 6.51 (d, J=8.0 Hz, 1 H), 5.18 (br. s., 1 H), 4.58 (s, 1 H), 3.36 (s, 3 H), 3.10 (s, 4 H), 2.99 (d, J=1.5 Hz, 1 H), 2.51 - 2.71 (m, 2 H), 2.35 (dd, J=6.6, 1.4 Hz, 2 H), 2.24 - 2.33 (m, 1 H), 2.06 - 2.21 (m, 1 H), 1.83 - 1.97 (m, 1 H), 1.34 - 1.60 (m, 4 H), 0.75 - 0.92 (m, 1 H), 0.41 - 0.59 (m, 1 H), 0.08 - 0.21 (m, 2 H); APCI [M+H] 388.1.

(ii) 3-Benzylxoy-17-cyclopropylmethyl-4,6$\alpha$-epoxy-14-hydroxy- 6,8-dimethoxymorphinan (3)

[0199] To a solution of 2 (2.1 g, 1 eq.) in DMF under N$_2$ was added K$_2$CO$_3$ (1.72 g, 2.2 eq.) followed by benzyl bromide (1.1 g, 1.2 eq.). The mixture was stirred for 20 h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organics were dried over MgSO$_4$ and the solvent concentrated to get the crude product which was purified on a silica column using hexane and ethyl acetate as eluent to get 2.41 g of the title compound 3 (with small amount of DMF as impurity) as a highly viscous liquid.

[0200] $^1$H NMR (301 MHz, CHLOROFORMS) $\delta$ ppm 7.27 - 7.53 (m, 5 H), 6.71 (d, J=8.3 Hz, 1 H), 6.49 (d, J=8.0 Hz, 1 H), 5.24 (dd, J=32.5, 12.1 Hz, 3 H), 4.61 (s, 1 H), 3.39 (s, 3 H), 3.09 (d, J=5.5 Hz, 1 H), 3.06 (s, 4 H), 2.99 (d, J=18.2 Hz, 1 H), 2.50 - 2.70 (m, 2 H), 2.35 (d, J=6.6 Hz, 2 H), 2.23 - 2.32 (m, 1 H), 2.15 (dd, J=11.8, 3.6 Hz, 1 H), 1.81 - 2.01 (m, 1 H), 1.59 - 1.70 (m, 1 H), 1.45 - 1.52 (m, 2 H), 1.32 - 1.43 (m, 1 H), 0.43 - 0.56 (m, 2 H), 0.06 - 0.17 (m, 2 H); APCI [M+H] 478.2.

(iii) 17-Cyclopropylmethyl-4,5 $\alpha$-epoxy-3-benzylxoy-14-cinnamyloxymorphinan-6-one dimethyl ketal (4a) and 17-cyclopropylmethyl-4,6$\alpha$-epoxy-S-benzylxoy-M-cinnamyloxy- 6-methoxy-6,7-didehydromorphinan (4b)

[0201] Compound 3 (2.88 g, 6.04 mmol) was dissolved in anhydrous DMF (40 mL) and stirred under N$_2$. NaH (0.73 g, 60% in mineral oil, 18.12 mmol) was added. After 20 min cinnamyl bromide (2.38 g, 12.08 mmol) was added. The resulting mixture was stirred at room temperature for 1.5 h. Mass spectrometry showed little reaction. More NaH (0.56 g, 60% in mineral oil, 13.90 mmol) and cinnamyl bromide (1.22 g, 6.19 mmol) were added. Stirring was continued for another hour. Mass spectrometry showed a 5 to 4 ratio of product to the starting material. EtOAc (150 mL) was added. The solution was washed with water (3X 70 mL) and brine (70 mL), dried over Na$_2$SO$_4$ and filtered. The filtrate was evaporated and the yellow oily
residue was purified by column (eluens: 5 - 50% EtOAc in hexanes) to give 4a (1.38 g, 39%) as a yellow solid and 4b (0.76 g, 22%) as a yellow gum.

[0202] 4a: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.19 - 7.49 (m, 10 H), 6.72 (d, J=8.0 Hz, 1H), 6.66 (d, J=16.0 Hz, 1H), 6.50 (d, J=8.3 Hz, 1H), 6.34 - 6.46 (m, 1H), 5.16 - 5.36 (m, 2H), 4.70 (s, 1H), 4.33 - 4.43 (m, 1H), 3.95 - 4.04 (m, 1H), 3.49 (d, J=4.4 Hz, 1H), 3.40 (s, 3H), 3.11 (d, 2J=17.6 Hz, 1H), 2.99 (s, 3H), 2.55 - 2.76 (m, 2H), 2.27 - 2.45 (m, 3H), 1.90 - 2.16 (m, 2H), 1.63 - 1.75 (m, 2H), 1.12 - 1.42 (m, 2H), 0.82 - 0.96 (m, 1H), 0.45 - 0.56 (m, 2H), 0.08 - 0.20 (m, 2H), MS [M+H]: 594.3.

[0203] 4b: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.16 - 7.46 (m, 10 H), 6.70 (d, J=8.0 Hz, 1H), 6.64 (d, J=16.0 Hz, 1H), 6.52 (d, J=8.3 Hz, 1H), 6.32 - 6.44 (m, 1H), 5.13 - 5.25 (m, 2H), 4.96 (d, J=1.1 Hz, 1H), 4.58 (dd, J=6.6, 1.9 Hz, 1H), 4.37 - 4.46 (m, 1H), 4.32 - 4.37 (m, 1H), 4.03 - 4.12 (m, 1H), 3.60 (d, J=6.1 Hz, 1H), 3.54 (s, 3H), 3.14 (d, J=18.4 Hz, 1H), 2.54 - 2.75 (m, 2H), 2.39 - 2.50 (m, 2H), 2.26 - 2.38 (m, 1H), 2.12 - 2.25 (m, 1H), 1.80 - 1.90 (m, 1H), 1.49 - 1.57 (m, 1H), 0.84 - 0.96 (m, 1H), 0.49 - 0.57 (m, 2H), 0.12 - 0.19 (m, 2H). MS [M+H]: 562.3.

(iv) 17-Cyd opropylmethyl-4,5α-epoxy-S-benzyloxy-M-ciimamyloxy-morphinan-6-one (5)

[0204] Compound 4b (737 mg, 1.31 mmol) was dissolved in THF (10 mL) and aqueous HCl (5 mL, 3 N) was added. The resulting solution was stirred at 60°C for 4 h. This was basified with aqueous Na$_2$CO$_3$ (10 mL, 2 M) and THF was removed. The aqueous residue was extracted with DCM (2X 50 mL). The DCM extracts were combined, dried over Na$_2$SO$_4$ and filtered. The filtrate was evaporated and the brown solid residue was purified by column (eluens: 5-12% MeOH in DCM) to give 5 (304 mg, 42%) as a yellow gum. MS [M+H]: 548.3.

(v) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-(2',3'-dihydroxy-3'phenyl)pyrroloxy-morphiian-6-one (6)

[0205] Compound 5 (303 mg, 0.554 mmol) was dissolved in THF (10 mL) and OsO$_4$ (0.1 mL, 2.5 wt % in t-BuOH, 0.008 mmol) was added. The resulting solution was stirred at room temperature for 10 min. Aqueous NaIO$_4$ (10 mL, 1.4 M, 1.4 mmol) was added. After 1 h a lot of precipitates appeared and stirring became difficult. More THF (10 mL) and water (10 mL) were added. The resulting mixture was stirred for 16 h. Water (40 mL) was added, followed by aqueous Na$_2$CO$_3$ (10 mL, 2 M). This was extracted with DCM (3X50 mL). The DCM extracts were combined, dried over Na$_2$SO$_4$ and filtered. The filtrate was evaporated and the black oily
residue was purified by column (eluent: 20-100 % EtOAc in hexanes) to give 6 (135 mg, 42 %) as a brown gum.

[0206] $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.28 - 7.48 (m, 10 H), 6.72 (d, /=8.3 Hz, 1 H), 6.56 (d, /=8.3 Hz, 1 H), 5.18 - 5.31 (m, 2 H), 4.69 (s, 1 H), 4.51 (d, /=4.7 Hz, 1 H), 4.06 - 4.10 (m, 1 H), 3.53 - 3.63 (m, 3 H), 3.17 (d, /=8.7 Hz, 1 H), 2.90 - 3.00 (m, 1 H), 2.61 - 2.79 (m, 2 H), 2.37 - 2.57 (m, 2 H), 2.18 - 2.31 (m, 2 H), 1.93 - 2.04 (m, 2 H), 1.46 - 1.55 (m, 1 H), 0.89 - 1.05 (m, 1 H), 0.58 (d, /=7.4 Hz, 1 H), 0.16 (d, /=4.7 Hz, 2 H). MS [M+H]: 582.3.

(vi) 17-Cyclopropylmethyl-$^\alpha$-epoxy-S-benzyloxy-M-carboxymethoxy-morphinan-6-one (7)

[0207] Compound 6 (135 mg, 0.232 mmol) was dissolved in DCM (10 mL) and stirred at room temperature. NaIO$_4$ (74 mg, 0.347 mmol) in water (5 mL) was added dropwise. Mass spectrometry after 90 min showed complete disappearance of 3. Aqueous Na$_2$CO$_3$ (1 mL, 2 M) was added and the DCM layer was separated. The aqueous layer was extracted with DCM (10 mL). The DCM extract was combined with the DCM layer and stirred at room temperature. Oxone (380 mg, 0.464 mmol) in water (10 mL) was added dropwise. After two hours the DCM layer was separated and the aqueous layer was extracted with DCM (10 mL). The DCM extract was combined with the DCM layer, dried over Na$_2$SO$_4$ and filtered. The filtrate was evaporated to give 7 (200 mg with solvent, 100 %) as a yellow gum. This was used in the next reaction without purification. MS [M+H]: 490.2.

(vii) 17-Cyclopropylmethyl-4,S$\alpha$-epoxy-S-hydroxy-M-carboxymethoxy-morphinan-6-one trifluoroacetic acid salt (8)

[0208] Compound 7 (200 mg, from the above reaction) was dissolved in a mixture of MeOH (8 mL) and DCM (8 mL). Pd/C (0.126 g, 10%, wet, 0.17 mmol) was added. The resulting mixture was stirred at room temperature under a H$_2$ balloon. Mass spectrometry after 1.5 h showed complete conversion of the starting material to the product. The reaction solution was filtered. The filtrate was evaporated and the residue was purified by semi-prep HPLC (mobile phase containing 0.1% TFA) to give 8 (31 mg, TFA salt, 26 % for 2 steps from 6) as a white foam.

[0209] $^1$H NMR (300 MHz, DMSO-d$_6$) δ ppm 6.71 (d, /=8.3 Hz, 1 H), 6.65 (d, /=8.3 Hz, 1 H), 4.88 (s, 1 H), 4.26 - 4.55 (m, 2 H), 4.23 (d, /=5.2 Hz, 1 H), 3.45 - 3.56 (m, 1 H), 3.40 (d, /=20.4 Hz, 2 H), 3.14 - 3.25 (m, 1 H), 2.84 - 3.09 (m, 2 H), 2.64 - 2.83 (m, 2 H), 2.42 -
2.62 (m, 1 H), 2.23 - 2.36 (m, 1 H), 2.06 - 2.21 (m, 1 H), 1.56 - 1.68 (m, 1 H), 1.37 - 1.54 (m, 1 H), 1.02 - 1.22 (m, 1 H), 0.69 (d, J=6.9 Hz, 2 H), 0.37 - 0.51 (m, 2 H). HPLC purity: 100%. M_S [M+H]: 400.2.

**Example 2**

**14-Butoxy-l 7-evelopropyImethyl-4,5 α-epoxy-3-hydroxy-6-morpholino-morphinan salt (9)**

[Diagram showing the reaction process]

(numbering in scheme refers to section directly below)

[0210] Compound (1) was prepared from naltrexone HCl using methods demonstrated in Example 8 (compound 3).

(i) **Synthesis of 3-benzyloxy-17-cyclopropymethyl-6-(l',3'-dioxolan-2'yI)-14-proxy-4,5α-epoxymorphinan (2)**

[0211] 1 (3.21 g, 6.8 mmol, 1 eq.) was taken up in anhydrous DMF. Sodium hydride (0.81 g of a 60% dispersion in mineral oil, 20.2 mmol, 3 eq.) was added, and the reaction mixture stirred for 30 minutes. Di-M-propyl sulfate (2.72 mL, 16.9 mmol, 2.5 eq.) was added and the reaction mixture was stirred at room temperature for 24 hours. The presence of starting material was detected by TLC, and so an additional three equivalents of NaH and two equivalents of (n-PrO^SOa were added. Stirring was continued for an additional 48 hours. The reaction was quenched by the addition of water and the crude product was extracted into ethyl acetate. Pure product was obtained by chromatography on silica gel using a 0 to 30% ethyl acetate/hexanes gradient containing 1% triethylamine. Yield: 2.75 g (78%) as a white foam.

[0212] H NMR (300 MHz, chloroform-d) δ (ppm): 7.26-7.48 (m, 5H), 6.75 (d, J=8.2 Hz, 1H), 6.54 (d, J=8.0 Hz, 1H), 5.15 (q, J=13.2 Hz, 2H), 4.61 (s, 1H), 4.18 (q, J=6.4 Hz,
IH), 4.07 (q, J=6.4 Hz, IH), 3.89 (q, J=6.5 Hz, IH), 3.78 (q, J=6.1 Hz, IH), 3.54 (q, J=7.0 Hz, IH), 3.42 (d, J=4.7 Hz, IH), 3.18 (q, J=6.9 Hz, IH), 3.08 (d, J=18 Hz, IH), 2.51-2.72 (m, 2H), 2.24-2.43 (m, 3H), 1.99-2.33 (m, 2H), 1.77 (br d, J=14 Hz, IH), 1.55-1.68 (m, 2H), 1.24-1.47 (m, 3H), 0.98 (t, J=7.4 Hz, 3H), 0.78-0.90 (m, IH), 0.48 (br d, J=7.7 Hz, 2H), 0.08-1.60 (m, 2H). APCI(+) m/z = 518 amu.

(ii) 3-Benzoyloxy-1 7-cyclopropylmethyl-1 4-propoxy-4,5 α-epoxymorphinan-6-one (3)

[0213] 2 (1.85 g, 35.7 mmol, 1 eq.) was taken up in 8 mL 4:1 MeOH:H₂O and an equal volume of 2N HCl (aq.) was added. After refluxing overnight, the reaction mixture was made basic with NaHCO₃ (aq, sat), and the crude product was extracted into ethyl acetate. The combined organic fractions were washed with brine, dried (MgSO₄), stripped and used in the next step without purification. Yield: 1.69 g (quant.) as a gel.

[0214] ¹H NMR (300 MHz, chloroform-d): δ (ppm): 7.26-7.48 (m, 5H), 6.68 (d, J=8.2 Hz, IH), 6.53 (d, J=8.0 Hz, IH), 5.23 (q, J=9.6 Hz, 2H), 4.67 (s, IH), 3.60-3.75 (m, IH), 3.51 (d, J=5.0 Hz, IH), 3.29 (q, J=6.9 Hz, IH), 3.10 (d, J=18 Hz, IH), 2.62-2.90 (m, 3H), 2.25-2.40 (m, 3H), 2.17 (dt, J=14.6, 3.0 Hz, IH), 2.00-2.12 (m, 2H), 1.60-1.72 (m, 2H), 1.38-1.50 (m, 2H), 1.01 (t, J=7.4 Hz, 3H), 0.80-0.94 (m, IH), 0.47-0.55 (m, 2H), 0.10-0.17 (m, 2H). APCI(+) m/z = 474 amu.

(iii) 3-Benzoyloxy-1 7-cyclopropylmethyl-4,5α-epoxy-6-morpholino-1 4-propoxy-6,7-di-dehydro-morphinan (4)

[0215] 3 (0.75 g, 1.6 mmol, 1 eq.) was taken up in toluene (50 mL), and morpholine (1.5 mL, 17.3 mmol, 11 eq.) was added. The reaction mixture was refluxed overnight with a Soxhlet apparatus containing 4A molecular sieves. The volatiles were removed under vacuum to give 0.76 g (88%) of crude product. It was used in the next step without purification.

[0216] ¹H NMR (300 MHz, chloroform-d): δ (ppm): 7.10-7.45 (m, 5H), 6.69 (d, J=8.0 Hz, IH), 6.50 (d, J=8.2 Hz, IH), 5.16 (s, 1.6H), 5.09 (s, IH), 4.55 (d, J=5.0 Hz, IH), 3.48-3.78 (m, 8H), 2.85-3.21 (m, 7H), 2.11-2.72 (m, 9.5H), 1.76 (d, J=17H, IH), 1.44-1.61 (m, 3H), 0.80-1.00 (m, 5H), 0.45-0.52 (m, 2H), 0.05-0.16 (m, 8H). APCI(+) m/z = 543 amu.
(iv) IT-Cyclopropylmethyl^-^ α-epoxy-S-hydroxy-6-morpholino-M-propoxy-6,7-di-dehydro-morphinan (5)

[0217] 4 (0.45 g, 0.83 mmol, 1 eq.) was taken up in methanol (20 mL). The solution was degassed and 10% palladium on carbon added under nitrogen. The atmosphere was replaced with hydrogen, and the reaction was allowed to proceed overnight under 1 atm. H₂. The catalyst was removed by filtration and the filtrate evaporated to give a brown gum which was used in the next step without purification. Yield: 0.24 g (64%).

[0218] ¹H NMR (300 MHz, chloroform-d): δ (ppm): 6.66 (d, J=8.0 Hz, IH), 6.50 (d, J=8.0 Hz, IH), 5.09 (s, IH), 4.6-4.72 (m, 1.4H), 3.45-3.90 (m, 10H), 3.05-3.25 (m, 3H), 2.78-3.00 (m, 5H), 2.00-2.65 (m, 10H), 1.22-1.90 (m, 8H), 0.80-1.10 (m, 8H), 0.45-0.52 (m, 3.7H), 0.10-0.22 (m, 4H). APCI(+) m/z = 453 amu.

(v) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroy-6-iV-morpholino-1 4-propoxy morphinan trifluoroacetic acid salt (9)

[0219] 5 (0.240 g, 0.53 mmol, 1 eq.) was taken up in dichloroethane (4 mL) containing 0.03 mL (1 eq.) acetic acid. Sodium triacetoxyborohydride (0.169 g, 0.80 mmol, 1.5 eq.) was added and the reaction mixture stirred under nitrogen at room temperature overnight. The reaction mixture was quenched by the addition of IN NaOH (aq) and the product was extracted into 5% methanol in dichloromethane to give 0.20 g of crude material. Half of this material was purified by semi-prep HPLC using 25% methanol in water containing 0.1% TFA as eluent. Yield: 32 mg (13%) as a white solid, mp 118-122°C. TLC R_f = 0.61 (10% MeOH/CHCl₃).

[0220] ¹H NMR (300 MHz, methanol-d₃): δ (ppm): 6.81 (s, 2H), 5.10 (d, J=7.4 Hz, IH), 4.57 (d, J=5.8 Hz, IH), 3.97 (br s, 3H), 3.40-3.60 (m, 7H), 3.05-3.20 (m, 3H), 2.60-2.88 (m, 3H), 2.34 (br d, J=1 3.2 Hz, IH), 1.95-2.06 (m, IH), 1.76-1.90 (m, 3H), 1.69 (br d, J=13 Hz, IH), 1.42 (br t, J=14 Hz, IH), 1.08-1.20 (m, IH), 1.04 (t, J=7.4 Hz, 3H), 0.85-0.94 (m, IH), 0.72-0.80 (m, IH), 0.48-0.58 (m, 2H). APCI(+) m/z = 455 amu. HPLC showed 95%, purity.

Example 3

17-evelopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(4'-carboxyphenethyl amido)-morphinan-6-one trifluoroacetic acid salt (10)

[0221] The following reaction sequence was used for the preparation of 10.
(numbering in scheme refers to section directly below)

(i) Preparation of cycloadduct 3

To a suspension of sodium periodate (0.91 g, 0.0042 mole) and sodium acetate (0.584 g, 0.0071 mole) in water (15 ml) was added N-(cyclopropylmethyl)northebaine (1) (1.0 g, 0.0028 mole) in ethyl acetate (30 ml) at 0°C. To this resulting two phase solution was added, portion-wise, hydroxamic acid (2) (0.715 g, 0.0043 mole). The mixture was stirred at the same temperature for additional 1 h then made alkaline by addition of saturated aqueous sodium hydrogen carbonate (20 ml). The ethyl acetate phase was separated and the aqueous phase was extracted with ethyl acetate (2 X 20 ml). The combined organic phases were washed with 5% aqueous sodium thiosulphate (10 ml), brine (20 ml) and dried (Na₂SO₄). Evaporation of the
solvent gave the crude cycloadduct, which was purified by column chromatography using 50% ethyl acetate in hexane and provided the cycloadduct. Isolated yield = 1.4 g (quantitative).

[0223] ¹H NMR (300 MHz, CDCl₃): δ 7.22-7.43 (m, 5H), 6.67 (d, J = 8.26 Hz, IH), 6.53 (d, J = 8.26 Hz, IH), 6.01-6.06 (m, 2H), 5.04-5.18 (m, 2H), 4.55 (s, IH), 3.79 (s, 3H), 3.47 (s, 3H), 3.24 (d, J = 18.71 Hz, IH), 2.79 (td, J = 12.38, 4.13 Hz, 2H), 2.37-2.54 (m, 3H), 2.01-2.12 (m, IH), 1.9 (d, J = 10.18 Hz, IH), 1.64-1.72 (m, IH), 0.92-0.94 (m, IH), 0.42-0.47 (m, 2H), 0.07-0.09 (m, 2H). (APCI⁺): 517 (M+1).

ii) Preparation of 17-cyclopropylmethyl-4,5-α-epoxy-3-methoxy-14-amino morphinan-6-one (4)

[0224] A mixture of cycloadduct 3 (0.1 g, 0.19 mmol) and Pd/C (10%) in MeOH (5 ml) was hydrogenated at 30 psi for 3 h. The catalyst was filtered and the solvent was evaporated to give crude product. Purification of this crude product by column chromatography using 5% MeOH in DCM gave 18 mg (25%) of the pure desired product.

[0225] ¹H NMR (300 MHz, CDCl₃): δ 6.68 (d, J = 8.26 Hz, IH), 6.60 (d, J = 8.26 Hz, IH), 4.71 (s, IH), 3.86 (s, 3H), 2.97-3.08 (m, 3H), 2.68-2.79 (m, 2H), 2.25-2.54 (m, 5H), 2.10 (dd, J = 3.58, 12.1 Hz, IH), 2.04 (s, IH), 1.66-1.79 (m, 2H), 1.54 (dd, J = 2.19, 12.9 Hz, IH), 0.82-0.88 (m, IH), 0.49-0.56 (m, 2H), 0.11-0.15 (m, 2H). (APCI⁺): 355 (M+1).

(iii) 17-Cyclopropylmethyl-4,5-α-epoxy-3-methoxy-14-(4′-carboxymethyl phenethylamido)-morphinan-6-one (6)

[0226] To a mixture of amine 4 (0.215 g, 0.6 mmol), acid 5 (0.189 g, 0.9 mmol) and diisopropylethylamine (0.316 ml, 1.8 mmol) in DCM (5 ml) was added HATU (0.346 g, 0.9 mmol) portionwise at RT and the resulting reaction mixture stirred for 21 h. The solvent was evaporated and the residue was dissolved in EtOAc (30 ml) and washed with water (2X5ml), brine (2X5ml) and dried (Na₂SO₄). The solvent was evaporated and the residue purified twice by column chromatography (eluent for the first column: 10% MeOH in DCM; eluent for the second column: 2%MeOH+2%NH₄OH+EtOAc) to provide compound 6 (0.218 g, 66%).

[0227] ¹H NMR (300 MHz, CDCl₃): δ 7.96 (d, J = 8.26 Hz, 2H), 7.3 (d, J = 8.26 Hz, 2H), 6.82 (bs, IH), 6.68 (d, J = 8.26 Hz, IH), 6.60 (d, J = 8.26 Hz, IH), 4.77 (s, IH), 3.88 (s, 3H), 3.84 (s, 3H), 2.98-3.14 (m, 4H), 2.82-2.89 (m, 4H), 2.57-2.65 (m, 3H), 2.44-2.52 (m, 3H), 2.36 (dd, J₁ = 12.66 Hz, J₂ = 6.33 Hz, IH), 2.24 (dd, J₁ = 12.66 Hz, J₂ = 6.88 Hz, IH), 1.98-2.05
(m, 2H), 1.86-1.92 (m, IH), 1.68-1.79 (m, IH), 1.52-1.58 (m, IH), 1.36 (dd, J1 = 16.24 Hz, J2 = 3.03 Hz, IH), 0.73-0.79 (m, IH), 0.5-0.57 (m, 2H), 0.1-0.14 (m, 2H).

(iv) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(4′-carboxymethyl phenethylamido)-morphinan-6-one (7)

[0228] To a solution of compound 6 (0.195 g, 0.36 mmol) in DCM (5 ml) was added BBr3 (2.15 ml of 1M solution in DCM, 2.2 mmol) at -20 °C and the resulting reaction mixture stirred for 3 h. The reaction was quenched by adding MeOH at the same temperature and then basified by adding ammonia in MeOH (7M). The solvent was evaporated to provide a residue which was dissolved in MeOH and pre-adsorbed on silica gel. Purification was performed twice by column chromatography (eluent for the first column: 5% MeOH in DCM; eluent for the second column: 2%MeOH+2%NH4OH+EtOAc) and gave pure compound 7 (0.117 g, 67%).

[0229] 1H NMR (300 MHz, CDCl3): δ 7.94 (d, J = 7.98 Hz, 2H), 7.31 (d, J = 7.98 Hz, 2H), 6.88 (bs, IH), 6.70 (d, J = 7.98 Hz, IH), 6.55 (d, J = 7.98 Hz, IH), 5.52 (bs, IH), 4.80 (s, IH), 3.88 (s, 3H), 2.80-3.13 (m, 5H), 2.63 (t, J = 6.6 Hz, 2H), 2.44-2.56 (m, 2H), 2.36 (dd, J1 = 12.66 Hz, J2 = 6.33 Hz, IH), 2.24 (dd, J1 = 12.66 Hz, J2 = 6.88 Hz, IH), 2.05-2.12 (m, 2H), 1.68-1.92 (m, 2H), 1.54-1.64 (m, IH), 1.34 (dd, J1 = 16.24 Hz, J2 = 3.03 Hz, IH), 0.71-0.79 (m, IH), 0.49-0.59 (m, 2H), 0.09-0.14 (m, 2H). (APCI+): 531 (M+l).

(v) 17-Cyclopropylmethyl-4,5 α-hydroxy-3-hydroxy-14-(4′-carboxy phenethylamido)-morphinan-6-one trifluoroacetic acid salt (10)

[0230] To compound 7 (0.106 g, 0.2 mmol) in MeOH (3 ml) was added lithium hydroxide monohydrate (0.018 g, 0.44 mmol) in water (2 ml) dropwise and the resulting reaction mixture stirred 22 h at rt. The solvent was evaporated and the residue acidified to pH 2 using TFA. The solid thus obtained was collected and purified by semi-prep HPLC using a Phenomenex column (eluent: water/pMeOH = 50:50 with 0.1% TFA) to provide 29 mg (23%) of pure compound 10 as its TFA salt.

[0231] m. p. = 184-189 °C. 1H NMR (300 MHz, D2O): δ 7.87 (d, J = 7.14 Hz, 2H), 7.36 (d, J = 7.14 Hz, 2H), 6.75-6.79 (m, 2H), 5.47 (d, J = 4.95 Hz, lH), 4.95 (s, IH), 3.22-3.34 (m, 2H), 2.70-3.11 (m, 9H), 2.45-2.55 (m, IH), 2.18-2.22 (m, IH), 1.74 (t, J = 12.93 Hz, IH), 1.34-1.57 (m, 2H), 0.84-0.94 (m, IH), 0.7-0.8 (m, IH), 0.6-0.7 (m, IH), 0.35-0.45 (m, IH), 0.26-0.34 (m, IH). (APCI+): 517 (M+l).
Example 4

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3-hydroxypropoxy)-morphinan-6-one salt (11)

(i) 14-AHyloxy-3-benzyloxy-17-cyclopropylmethyl-6-(1',3'-dioxolan-2'-yl)-4,5 α-epoxymorphinan (2)

[0232] Compound 1 (1.45 g, 3.05 mmol, prepared as described in the synthesis of intermediate 3 from naltrexone HCl in Example 8 was dissolved in DMF (30 mL, anhydrous) under N₂ and NaH (0.81 g, 20.2 mmol, 60% suspension in mineral oil) was added. The resulting solution was stirred at room temperature for 30 min. Allyl bromide (1.1 mL, 12.2 mmol) was added and the resulting mixture was stirred overnight at room temperature. EtOAc (150 mL) was added. The solution was washed with water (3X 70 mL) and brine (70 mL), dried over Na₂SO₄ and filtered. The filtrate was evaporated and the yellow oily residue was purified by column (eluent: 5—50 % EtOAc in hexanes) to give 2 (1.24 g, 79 %) as a yellow gum.

[0233] ¹H NMR (300 MHz, CDCl₃) δ ppm 7.28 - 7.48 (m, 5H), 6.76 (d, J = 8.3 Hz, IH), 6.55 (d, J = 8.3 Hz, IH), 5.91 - 6.1 1 (m, OH), 5.28 - 5.41 (m, IH), 5.07 - 5.26 (m, 3H), 4.64 (s, IH), 4.00 - 4.28 (m, 4H), 3.71 - 3.97 (m, 3H), 3.46 (d, J = 4.7 Hz, IH), 3.10 (d, J = 18.2 Hz, IH), 2.53 - 2.71 (m, 2H), 2.30 - 2.44 (m, 3H), 2.06 - 2.25 (m, 2H), 1.72 - 1.83 (m, IH), 1.29 -
1.49 (m, 3H), 0.78 - 0.91 (m, IH), 0.43 - 0.53 (m, 2H), 0.12 (d, J = 5.0 Hz, 2H). MS [M+H]: 516.2.

(ii) 3-Benzyl-oxy-17-cyelopropylmethyl-6-(63'-dioxoIan-2'-yl)-4,5 α-epoxy-14-(3'-(hydroxypropyloxy) morphinan (3)

[0234] Compound 2 (258 mg, 0.50 mmol) was dissolved in THF (6 mL, anhydrous) under N₂ and BH₃ (1.0 mL, 1.0 M in THF, 1.0 mmol) was added. The resulting solution was stirred at room temperature for 1 h. Aqueous NaOH (2.2 mL, 3 M, 6.6 mmol) was added, followed by H₂O₂ (0.62 mL, 30 wt% in H₂O). After 1 h H₂O (20 mL) was added. The resulting mixture was extracted with DCM (2X30 mL). The DCM extracts were combined, dried over Na₂SO₄, and filtered. The filtrate was evaporated and the opaque gel was purified by column (eluent: 1-2% MeOH in DCM) to give 3 (62 mg, 23 %) as an opaque gel.

[0235] ¹H NMR (300 MHz, CDCl₃) δ ppm 7.29 - 7.47 (m, 5H), 6.77 (d, J = 8.3 Hz, IH), 6.56 (d, J = 8.3 Hz, IH), 5.07 - 5.24 (m, 2H), 4.64 (s, IH), 4.15 - 4.24 (m, IH), 3.55 - 4.13 (m, 7H), 3.36 - 3.50 (m, IH), 3.13 (d, J = 19.0 Hz, IH), 2.34 - 2.75 (m, 5H), 1.97 - 2.12 (m, 2H), 1.75 - 1.93 (m, 2H), 1.34 - 1.52 (m, 4H), 1.12 (d, J = 6.3 Hz, IH), 0.90 - 1.02 (m, IH), 0.49 - 0.61 (m, 2H), 0.12 - 0.24 (m, 2H). MS [M+H]: 534.3.

(iii) ω-CyclopropylmethylωS α-epoxy-θ-hydroxy-H-P'-hydroxypropyloxyJ-morphinan-6-one trifluoroacetic acid salt (11)

[0236] Compound 3 (60 mg, 0.11 mmol) was mixed with HCl (5 mL, 3 N) and heated at reflux for 2 h. After cooled to room temperature the reaction solution was evaporated and the brown solid residue was purified by semi-prep HPLC (eluent: 75% H₂O (with 0.1% TFA)/25% MeOH (with 0.1% TFA)) to give 11 (38 mg, TFA salt, 67 %) as a white foam.

[0237] ¹H NMR (300 MHz, D₂O) δ ppm 6.69 - 6.81 (m, 2H), 5.01 (s, IH), 4.60 (d, J = 5.8 Hz, IH), 3.60 - 3.90 (m, 4H), 3.28 - 3.45 (m, 2H), 2.85 - 3.20 (m, 3H), 2.75 (d, J = 8.8 Hz, 3H), 2.32 - 2.44 (m, IH), 2.18 - 2.30 (m, IH), 1.88 - 2.03 (m, 2H), 1.66 (d, J = 10.2 Hz, IH), 1.45 - 1.61 (m, IH), 0.98 - 1.10 (m, IH), 0.65 - 0.81 (m, 2H), 0.34 - 0.46 (m, 2H). HPLC purity: 100%. MS [M+H]: 400.2.
Example 5

4-(17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-6-oxo-morphinan-14yloxy)-butanoic acid salt (12)

![Chemical structures](image)

(numbering in scheme refers to section directly below)

(i) 3-Benzylxy-17-cyclopropylmethyl-6-([3'-dioxolan-2'-yl]-4,5 α-epoxy-14-(3'-methylsulfonyloxypropyloxy)morphinan (2)

[0238] Compound 1 (0.38 g, 0.71 mmol, prepared as described in the synthesis of compound 3 in Example 4, above, was dissolved in DCM (10 mL, anhydrous) under N₂ and EtN(iPr)₂ (0.50 mL, 2.8 mmol) was added, followed by MsCl (0.11 mL, 1.4 mmol). The resulting solution was stirred at room temperature for 2 h. Aqueous Na₂CO₃ (20 mL, 2 M) was added and the resulting mixture was extracted with DCM (2X25 mL). The DCM extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated and the opaque gel was purified by column (eluent: 1-2 % MeOH in DCM) to give 3 (62 mg, 23 %) as an opaque gel. The solution was washed with water (3X 70 mL) and brine (70 mL), dried over Na₂SO₄ and filtered. The filtrate was evaporated to give 2 (511 mg) as a brown solid. This crude product was used in the next reaction without purification.

[0239] ¹H NMR (300 MHz, CDCl₃) δ ppm 7.29 - 7.48 (m, 5H), 6.76 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 5.15 (d, J = 12.1 Hz, 2H), 4.61 - 4.68 (m, 1H), 4.59 (s, 1H), 4.44 -
4.52 (m, III), 3.62 - 4.30 (m, 6H), 3.34 - 3.48 (m, 2H), 3.04 (s, 3H), 2.58 - 2.72 (m, IH), 2.24 - 2.55 (m, 5H), 1.99 - 2.13 (m, 3H), 1.71 - 1.81 (m, IH), 1.20 - 1.52 (m, 3H), 0.76 - 0.90 (m, IH), 0.51 (d, J = 8.3 Hz, 2H), 0.07 - 0.16 (m, 2H). MS [M+H]: 612.1.

(ii) 3-Benzoyloxy-14-(3'-cyanopropyloxy)-17-cyclopropylmethyl-6-(1',3'-dioxolan-2'-yl)-4,5α-epoxy-morphinan (3)

[0240] Compound 2 (51.1 mg, crude product from the above reaction) was dissolved in DMF (15 mL, anhydrous) under N₂ and NaCN (81 mg 1.65 mmol) was added. The resulting solution was stirred at 100 °C for 2 h. After cooled to room temperature the reaction solution was diluted with EtOAc (100 mL) and washed with water (3X 60 mL) and brine (60 mL). It was dried over Na₂SO₄ and filtered. The filtrate was evaporated and the yellow oily residue was purified by column (eluent: 50 – 100% EtOAc in hexanes) to give 3 (122 mg, 32% for 2 steps from 1) as a yellow oil.

[0241] ¹H NMR (300 MHz, CDCl₃) δ ppm 7.29 - 7.48 (m, 5H), 6.77 (d, J = 8.3 Hz, IH), 6.55 (d, J = 8.3 Hz, IH), 5.05 - 5.24 (m, 2H), 4.60 (s, IH), 3.99 - 4.26 (m, 3H), 3.74 - 3.97 (m, 2H), 3.60 - 3.72 (m, IH), 3.34 - 3.46 (m, 2H), 3.11 (d, J = 17.9 Hz, IH), 2.69 - 2.78 (m, IH), 2.65 (t, J = 7.2 Hz, 2H), 2.16 - 2.54 (m, 3H), 1.92 - 2.13 (m, 3H), 1.65 - 1.81 (m, IH), 1.31 - 1.51 (m, 4H), 0.77 - 0.92 (m, IH), 0.44 - 0.57 (m, 2H), 0.05 - 0.15 (m, 2H). MS [M+H]: 543.2.

(iii) 14-(3'-Carboxypropyloxy)-17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-morphinan-6-one trifluoroacetic acid salt (12)

[0242] Compound 3 (114 mg, 0.21 mmol) was mixed with HCl (6 mL, 3 N) and heated at reflux for 28 h. After cooled to room temperature the reaction solution was evaporated and the brown solid residue was purified by semi-prep HPLC (eluient: 75% H₂O (with 0.1% TFA)/25% MeOH (with 0.1% TFA)) to give 12 (81 mg, TFA salt, 71%) as a white foam.

[0243] ¹H NMR (300 MHz, DMSO-d₆) δ ppm 9.53 (br. s., IH), 7.88 (br. s., IH), 6.60 - 6.74 (m, 2H), 4.94 (s, IH), 4.50 (d, J = 5.8 Hz, IH), 3.49 - 3.68 (m, 4H), 3.44 (d, J = 19.5 Hz, IH), 3.08 (d, J = 9.1 Hz, IH), 2.87 - 3.01 (m, IH), 2.69 - 2.86 (m, OH), 2.57 - 2.66 (m, 2H), 2.25 - 2.43 (m, 5H), 2.06 - 2.18 (m, 2H), 1.88 - 2.01 (m, IH), 1.51 (d, J = 10.5 Hz, IH), 1.27 - 1.43 (m, IH), 1.00 - 1.15 (m, IH), 0.67 - 0.81 (m, IH), 0.51 - 0.66 (m, 2H), 0.38 - 0.50 (m, IH). HPLC purity: 100%. MS [M+H]: 409.1.
Example 6

4-((17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-niropinan-14-yloxy)methyl) benzoic acid salt (13)

(i) 3-Benzyl-7-cyclopropylmethyl-4,5 α-epoxy-14-hydroxymorphinan (3):

[0244] To a solution of naltrexone hydrochloride (1.HCl, 10 g, 1 eq.) in diethyleneglycol (55 mL) was added hydrazine hydrate (98 %, 8 mL) and potassium hydroxide (28 g, 30 eq.) and the mixture was heated at 100 °C for 1h and 165 °C for for 3 h. The reaction mixture was cooled and diluted with water (150 mL) and acidified to pH 6 with cone.HCl and then to pH 10 with solid NaHCO3 and extracted with methanol : dichloromethane (1:9) (2X200 mL). The combined organics were dried over MgSO4 and concentrated to provide a brownish residue. Purification of the crude material by column chromatography using hexanes/ethyl acetate/triethylamine: 50/45/5 afforded 4.5 g (35%) of the 17-cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxymorphinan 2 as a white solid.

[0245] 1H NMR (301 MHz, CHLOROFORM-d) δ ppm 6.69 (d, J=8.0 Hz, 1H), 6.51 - 6.62 (d, J=8.0 Hz, 1H), 5.13 (br. S., 1H), 4.73 (t, J=8.22 Hz, 1H), 2.95 - 3.08 (m, 2H), 2.54 - 2.70 (m, 2H), 2.31 - 2.41 (m, 2H), 2.06 - 2.27 (m, 2H), 1.77 (tt, J=12.9, 3.0 Hz, 1H), 1.35 - 1.57 (m, 2H), 1.13 - 1.35 (m, 2H), 0.74 - 0.94 (m, 1H), 0.45 - 0.59 (m, 2H), 0.41 - 0.70 (m, 2H), 0.07 - 0.23 (m, 2H); APCI [M+H] 328.2.
[0246] A solution of 2 (0.991 g, 1 eq.) in DMF (10 mL) under N₂ was treated with K₂C₂H and benzyl bromide as described in the general procedure. The mixture was stirred for 20 h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organics were dried over MgSO₄ and the solvent concentrated to provide 1.2 g (95%) of the title compound 3 which was used for the next step without further purification.

[0247] ¹H NMR (301 MHz, CHLOROFORM-d) δ ppm 7.29 - 7.47 (m, 5 H), 6.75 (d, J=8.3 Hz, 1 H), 6.56 (d, J=8.0 Hz, 1 H), 5.17 (dd, J=26.4, 12.4 Hz, 2 H), 5.08 (s, 1 H), 4.73 (t, J=8.0 Hz, 1 H), 2.94 - 3.12 (m, 2 H), 2.51 - 2.73 (m, 2 H), 2.36 (d, J=6.6 Hz, 2 H), 2.03 - 2.28 (m, 3 H), 1.67 - 1.99 (m, 1 H), 1.10 - 1.65 (m, 5 H), 0.72 - 0.92 (m, 1 H), 0.53 (d, J=7.7 Hz, 2 H), 0.00 - 0.26 (m, 2 H); APCI [M+H] 418.3.

(ii) 17-Cyclopropylmethyl-4,5-α-epoxy-3-benzyloxy-14-(4'-bromo benzyloxy)morphinan (4)

[0248] To a solution of compound 3 (790 mg, 1.89 mmol) in anhydrous DMF (15 mL) under N₂ was added NaH (60%, 110 mg, 4.20 mmol) and the resulting reaction mixture was stirred at RT for 1h. 1-bromo-4-(bromomethyl)benzene (2.36 g, 9.45 mmol) was then added and the reaction mixture was stirred at RT for 24h. The contents of the flask were poured onto water and the aqueous phase was extracted with EtOAc. The organic phase was washed with water, brine and dried (Na₂SO₄). EtOAc was removed under reduced pressure and the resulting residue was purified by flash chromatography with 5-25% EtOAc / hexanes to isolate the required product 4 (770 mg, 26%) as a colorless oil.

[0249] ¹H NMR (300 MHz, CDCl₃): δ 7.25-7.85 (m, 9H), 6.77 (d, J = 8.0 Hz, IH), 6.52 (d, J = 8.0 Hz, IH), 5.30 (m, 2H), 4.70 (m, 2H), 4.28 (d, J = 10.5 Hz, IH), 3.60 (d, J = 4.7 Hz, IH), 3.17 (d, J = 17.9 Hz, IH), 2.75 (m, IH), 2.10-2.70 (m, 5H), 1.78 (m, 2H), 1.10-1.215 (m, 4H), 0.79-0.85 (m, IH), 0.47-0.44 (m, 2H), 0.093-0.05 (m, 2H). APCI+ = 586, 588.

(iii) IT-CyclopropylmethylM, 5α-epoxy-3-benzyloxy-14-(4'-cyanobenzyl oxy)morphinan (5)

[0250] To a solution of compound 4 (770 mg, 1.31 mmol) in anhydrous DMF (10 mL) under N₂ was added Zn(CN)₂ (461 mg, 3.93 mmol) followed by Pd(PPh₃)₄. The reaction mixture was heated at 80 °C for 24h. The contents of the flask were poured onto water and the aqueous phase was extracted with EtOAc. The organic phase was washed with water, brine and dried (Na₂SO₄). EtOAc was removed under reduced pressure and the resulting residue was purified by flash chromatography with 5-25% EtOAc / hexanes to isolate the required product 5 (404 mg, 58%) as a brown oil.
\( ^1H \text{ NMR} (300 \text{ MHz, CDCl}_3): \delta 7.25-7.85 (m, 9H), 6.77 (d, J = 8.0 \text{ Hz, IH}), 6.52 (d, J = 8.0 \text{ Hz, IH}), 5.30 (m, 2H), 4.70 (m, 2H), 4.28 (d, J = 10.5 \text{ Hz, IH}), 3.60 (d, J = 4.7 \text{ Hz, IH}), 3.17 (d, J = 17.9 \text{ Hz, IH}), 2.75 (m, IH), 2.10-2.70 (m, 5H), 1.78 (m, 2H), 1.10-1.215 (m, 4H), 0.79-0.85 (m, IH), 0.47-0.44 (m, 2H), 0.093-0.05 (m, 2H). APCI^+ = 533. \)

(iv) 17-Cyclopropylmethyl-4,5 \( \alpha \)-epoxy-3-benzyloxy-14-[(4’carboxy benzyl)oxy] morphinanum hydrochloride (6)

\[ ^1H \text{ NMR} (300 \text{ MHz, CDCl}_3): \delta 7.75-7.85 (m, 9H), 6.77 (d, J = 8.0 \text{ Hz, IH}), 6.52 (d, J = 8.0 \text{ Hz, IH}), 5.30 (m, 2H), 4.70 (m, 2H), 4.28 (d, J = 10.5 \text{ Hz, IH}), 3.60 (d, J = 4.7 \text{ Hz, IH}), 3.17 (d, J = 17.9 \text{ Hz, IH}), 2.75 (m, IH), 2.10-2.70 (m, 5H), 1.78 (m, 2H), 1.10-1.215 (m, 4H), 0.79-0.85 (m, IH), 0.47-0.44 (m, 2H), 0.093-0.05 (m, 2H). APCI^+ = 533. \]

(v) 17-Cyclopropylmethyl-4,5 \( \alpha \)-epoxy-3-hydroxy-14-[(4’carboxy benzyl) oxyj morphinanum hydrochloride (13)

\[ ^1H \text{ NMR} (300 \text{ MHz, CDCl}_3): \delta 7.75-7.85 (m, 9H), 6.77 (d, J = 8.0 \text{ Hz, IH}), 6.52 (d, J = 8.0 \text{ Hz, IH}), 5.30 (m, 2H), 4.70 (m, 2H), 4.28 (d, J = 10.5 \text{ Hz, IH}), 3.60 (d, J = 4.7 \text{ Hz, IH}), 3.17 (d, J = 17.9 \text{ Hz, IH}), 2.75 (m, IH), 2.10-2.70 (m, 5H), 1.78 (m, 2H), 1.10-1.215 (m, 4H), 0.79-0.85 (m, IH), 0.47-0.44 (m, 2H), 0.093-0.05 (m, 2H). APCI^+ = 533. \]
Example 7

(17-cyclopropylmethyl-4,5-α-epoxy-3-hydroxy-morphinan-6-one-14-yloxy)-propionic acid salt (14)

(i) Compound 2:

To a solution of oxalyl chloride (33 μL, 0.374 mmol) in DCM (10 mL, anhydrous) stirred at -78 °C under N₂ was added DMSO (40 μL, 0.56). After 5 min a solution of 1 (100 mg, 0.187 mmol, synthesized as described in the synthesis of intermediate 3 in Example 4, in DCM (10 mL, anhydrous) was added. After 10 min Et₃N (104 mL, 0.75 mmol) was added. The resulting solution was stirred for 10 min and warmed up to room temperature. After 7 h a solution of Oxone (229 mg, 0.374 mmol) in H₂O (10 mL) was added. After 3 h more Oxone (117 mg, 0.191 mmol) in H₂O (5 mL) was added. The reaction was stopped after 2 h and the DCM layer was separated. The aqueous layer was extracted with DCM (2 X 20 mL). The DCM extracts were combined with the original DCM layer and dried over Na₂SO₄ and filtered. The filtrate was evaporated and the white solid residue was purified by flash chromatography (eluent: 5-15% MeOH in DCM) to give 2 as an off-white solid (51 mg, 50%). Taken on to the next step without further characterization.

(ii) (IT-Cyclopropylmethylα-α-epoxy-B-hydroxy-morphinan-6-one-W-yloxyJ-propionic acid salt (14)

Compound 2 (50 mg, 0.091 mmol) was mixed with HCl (5 mL, 3 N) and heated at reflux for 4 h. After cooled to room temperature the reaction solution was evaporated and the brown solid residue was purified by semi-prep HPLC (eluent: 75% H₂O (with 0.1% TFA)/25% MeOH (with 0.1% TFA)) to give 14 (11.7 mg, TFA salt, 24%) as an off-white foam.

[0258] ¹H NMR (300 MHz, D₂O) δ ppm 6.65 - 6.93 (m, 2H), 5.00 (s, 1H), 4.63 - 4.76 (m, 1H), 3.65 - 3.98 (m, 2H), 3.23 - 3.56 (m, 3H), 2.96 - 3.19 (m, 2H), 2.66 - 2.96 (m,
(numbering in scheme refers to section directly below)

Example 8

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-6-oxo-14-(3'-hydroxypropyloxy) morphinan-N-oxide (15)

(i) 17-Cyclopropylmethyl-3,14-dihydroxy-4,5 α-epoxy-6-spiro-2’-(1,3-dioxalane) morphinan (2)

[0259] A mixture of naltrexone.HCl (1.HCl, 20.4 g, 1 eq.), methanesulfonic acid (7.87 g, 1.5 eq.) and ethylene glycol (200 mL) were heated to 90-100 °C for 3 hours. The reaction mixture was cooled, diluted with water and basified to pH 10 using ammonium hydroxide. The aqueous phase was extracted with chloroform (3X150 mL). The combined organics were dried over MgSO4 and evaporated the solvent to get 2 as a brown oil. The crude material was used as such without further purification for the next step. APCI [M+H] 386.1.

(ii) 3-Benzyl oxy-17-cyclopropylmethyl-4,5 α-epoxy-14-hydroxy-6-spiro-2’-(1,3-dioxalane) morphinan (3)

[0260] A solution of 2 (56.16 mmols in theory, 1 eq.) in DMF (100 mL) was treated with K2CO3 (22.42 g, 3 eq.) and benzyl bromide at room temperature for 20 h. At the end of the reaction, as indicated by mass spec analysis, the reaction mixture was diluted with water and
extracted with dichloromethane. The combined organics were dried over MgSO₄ and concentrated the solvent to get the crude 3 contaminated with benzyl bromide. The crude material was acidified with 2N HCl and washed with diethyl ether. The aqueous layer was basified using 30% NH₄OH and re-extracted with ethyl acetate. The organic extracts were combined and dried over MgSO₄ and evaporated the solvent to get 23 g (86%) of the title compound 3-Benzyl oxy-17-cyclopropylmethyl-4,5 α-epoxy-14-hydroxy-6-methylenedioxy mor phinan 3 as a white solid.

[0261] ¹H NMR (CHLOROFORM-d) δ: 7.29 - 7.50 (m, 5H), 6.77 (d, J = 8.3 Hz, IH), 6.56 (d, J = 8.3 Hz, IH), 5.15 (dd, J = 21.2, 11.8 Hz, 2H), 4.60 (s, IH), 4.13 - 4.23 (m, IH), 3.99 - 4.10 (m, IH), 3.85 - 3.96 (m, IH), 3.73 - 3.85 (m, IH), 2.87 - 3.18 (m, 2H), 2.50 - 2.71 (m, IH), 2.09 - 2.45 (m, 4H), 1.38 - 1.64 (m, 4H), 0.73 - 0.94 (m, IH), 0.43 - 0.66 (m, 2H), 0.03 - 0.24 (m, 2H) APCI [M+H] 516.3

(iii) 14β-AUloxy-3-benzyloxy-17-eyelopropylmethyl-4,5 α-epoxy-6-spiro-2’-(1,3-dioxalane)-mor phinan (4)

[0262] NaH (996 mg, 3 eq, 60% suspension in mineral oil) was added to a solution 3 (4 g, 1 eq.) in DMF under N₂ and cooled down to 0 °C. After 20 minutes allyl bromide (7.5 g, 5 eq.) was added and the resulting mixture was stirred overnight at room temperature. NaH (600 mg, 2 eq.) and allyl bromide (4 g, 3 eq.) was added and stirred 24 hours. Excess NaH was destroyed by the addition of ice. Water was added and the reaction mixture was extracted with dichloromethane. The organics were pooled and dried (MgSO₄) and evaporated. The crude material was dissolved in dichloromethane and acidified with 2N HCl and washed with ether. The aqueous layer was basified using 30% NH₄OH and re-extracted with ethyl acetate. The organic extracts were combined and dried over MgSO₄ and evaporated the solvent. The crude product was purified on a silica gel column using hexane and ethyl acetate as eluent to get 2.68 g (61%) of the title compound 4 as a white solid.

[0263] ¹H NMR (CHLOROFORM-d) δ: 7.29 - 7.54 (m, 5H), 6.77 (d, J = 8.3 Hz, IH), 6.56 (d, J = 8.3 Hz, IH), 5.92 - 6.12 (m, IH), 5.38 (d, J = 1.9 Hz, IH), 5.32 (d, J = 1.9 Hz, IH), 5.23 (s, IH), 5.08 - 5.20 (m, 3H), 4.65 (s, IH), 4.14 - 4.38 (m, 2H), 4.02 - 4.14 (m, IH), 3.70 - 3.98 (m, 3H), 3.46 (d, J = 4.4 Hz, IH), 3.11 (d, J = 17.9 Hz, IH), 2.50 - 2.78 (m, 2H), 2.29 - 2.46 (m, 3H), 2.01 - 2.26 (m, 2H), 1.70 - 1.85 (m, IH), 1.29 - 1.52 (m, 2H), 0.73 - 1.00 (m, IH), 0.36 - 0.60 (m, 2H), 0.13 (d, J = 5.0 Hz, 2H); APCI [M+H] 516.3
(iv) S-Benzylxy-17-cyclopropylmethyl-4,\(\alpha\)-epoxy-6-methylenedioxy-M-\(\alpha\)'-hydroxypropyloxy) morphinan (5)

[0264] Compound 4 (258 mg, 0.50 mmol) was dissolved in THF (6 mL) under \(N_2\) and BH\(_1\) (1.0 mL, 1.0 M in THF, 1.0 mmol) was added. The resulting solution was stirred at room temperature for 1 h. Aqueous NaOH (2.2 mL, 3 M, 6.6 mmol) was added, followed by \(H_2\)O\(_2\) (0.62 mL, 30 wt% in \(H_2\)O). After 1 h \(H_2\)O (20 mL) were added. The resulting mixture was extracted with DCM (2X30 mL). The DCM extracts were combined, dried over Na\(_2\)SO\(_4\) and filtered. The filtrate was evaporated and the opaque gel was purified by column (eluent: 1-2 % MeOH in DCM) to give 5 (62 mg, 23 %) as an opaque gel.

[0265] \(^1\)H NMR (CHLOROFORM-d) \(\delta\): 7.30 - 7.51 (m, 5H), 6.78 (d, \(J = 8.3\) Hz, IH), 6.56 (d, \(J = 8.0\) Hz, IH), 5.99 (br. s., IH), 5.16 (dd, \(J = 24.8, 11.8\) Hz, 2H), 4.64 (s, IH), 4.14 - 4.26 (m, IH), 4.01 - 4.13 (m, 2H), 3.87 - 4.01 (m, 3H), 3.55 - 3.86 (m, 7H), 3.43 - 3.50 (m, IH), 3.15 (d, \(J = 18.2\) Hz, IH), 2.64 - 2.75 (m, IH), 2.47 - 2.61 (m, IH), 2.31 - 2.47 (m, 4H), 1.98 - 2.13 (m, 3H), 1.72 - 1.94 (m, 5H), 1.33 - 1.55 (m, 6H), 0.89 - 1.09 (m, IH), 0.49 - 0.63 (m, 2H), 0.11 - 0.24 (m, 2H)

(v) 7-Cyclopropylmethyl-4,5 \(\alpha\)-epoxy-3-hydroxy-14-(3\(\alpha\)-hydroxypropyloxy)morphinan-6-one (6)

[0266] A mixture of 5 (147 mg) and 6\(N\) HCl (5 mL) was heated to 90 \(^\circ\)C for 3.\(h\) hours. At the end of the reaction the reaction mixture was cooled down to room temperature and neutralized with ammonium hydroxide solution. The residue was extracted using chloroform and the chloroform extracts were dried over magnesium sulfate. The solvent was evaporated under reduced pressure to afford the crude product 6 as a white solid (90 mg, 90%) APCI [M+H] 400.2

(iv) 17-Cyclopropylmethyl-4,5 \(\alpha\)-epoxy-3-hydroxy-6-oxo-14-(3 \(\alpha\)-hydroxypropyloxy)morphinan-N-Oxide (15)

[0267] The title compound was prepared from 90 mg of 6 according to the general procedure for N-oxidation using mCPBA. The crude material was purified by column chromatography using chloroform-methanol as eluent to afford 45 mg (63%) of 17-Cyclopropylmethyl-4,5a-epoxy-3-hydroxy-6-oxo-14-(3\'hydroxypropyloxy)morphinan-N-Oxide
[0268] $^1$H NMR (DMSOd$_6$) $\delta$: 6.64 (d, $J = 8.0$ Hz, IH), 6.57 (d, $J = 8.3$ Hz, IH), 4.77 (s, IH), 4.16 - 4.28 (m, IH), 4.08 (d, $J = 4.1$ Hz, IH), 3.62 - 3.73 (m, IH), 3.38 - 3.55 (m, 411), 3.12 (d, $J = 11.0$ Hz, 3H), 2.94 - 3.04 (m, IH), 2.71 - 2.87 (m, 2H), 2.56 - 2.65 (m, IH), 2.24 (d, $J = 14.6$ Hz, 1H), 1.99 (d, $J = 14.9$ Hz, IH), 1.65 - 1.79 (m, IH), 1.54 - 1.65 (m, 3H), 1.34 (d, $J = 14.9$ Hz, 2H), 0.53 - 0.61 (m, 2H), 0.34 - 0.44 (m, 2H); APCI [M+H] 416.2; HPLC (65/35 Water/Methanol with 0.1 % TFA) $R_t = 10.9$ min.

Example 9

17-Cyelopropylmethyl-4,5 $\alpha$-epoxy-3-hydroxy-14-(2',3'-dihydroxy-3'-phenylpropyloxy) morphinan-6-one hydrochloride (16)

( numbering in scheme refers to section directly below)

(i) 17-Cyclopropylmethyl-3-benzyloxy-14-(2',3'-dihydroxy-3'-phenylpropyloxy)-6-(1',3'-dioxolan-2'-yl) -4,5$\alpha$-epoxymorphinan (2)

[0269] Compound 1 (1.1 g, 1.88 mmol, synthesized as described in the synthesis of intermediate 4a in Example 1, was dissolved in acetone (30 mL) and $H_2O$ (3 mL) was added, followed by OsO$_4$ (0.27 mL, 2.5 wt % in tBuOH, 0.01 mmol). After the reaction solution was stirred at room temperature for 10 min NMO (4-methylmorpholine N-oxide, 150 mg, 1.28 mmol) was added. The resulting mixture was stirred for 1 h and acetone was removed. Aqueous Na$_2$CO$_3$ (2M, 40 mL) was added. The resulting mixture was extracted with DCM (3X50 mL). The DCM extracts were combined, dried over Na$_2$SO$_4$ and evaporated. The black gummy
residue was purified by column (eluent: 30-80 % EtOAc in hexanes) to give 2 (0.74g, 63 %) as brown foam.

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\( ^{1} \text{H NMR} \) (300 MHz, CDCl\(_{3}\)) \( \delta \): 7.28 - 7.47 (m, 10H), 6.78 (d, \( J = 8.3 \) Hz, IH), 6.56 (d, \( J = 8.0 \) Hz, IH), 5.04 - 5.25 (m, 2H), 4.59 (s, IH), 4.47 (d, \( J = 5.0 \) Hz, IH), 4.10 - 4.22 (m, IH), 3.97 - 4.08 (m, 2H), 3.70 - 3.94 (m, 2H), 3.35 - 3.57 (m, 4H), 3.15 (d, \( J = 18.4 \) Hz, IH), 2.81 - 2.96 (m, IH), 2.37 - 2.65 (m, 3H), 2.18 (dd, \( J = 12.7, 7.4 \) Hz, IH), 1.87 - 2.03 (m, 2H), 1.61 - 1.74 (m, IH), 1.32 - 1.51 (m, 3H), 0.86 - 1.06 (m, IH), 0.48 - 0.63 (m, 2H), 0.09 - 0.19 (m, 2H). MS \([\text{M+H]}\): 626.1.

(ii) 17-Cyclopropylmethyl-3-hydroxy-14-(2',3'-dihydroxy-3'-phenylpropyloxy)-6-(r,3'\)-dioxo!an-2'\,-yl) ~4.5\(\alpha\)-epoxymorphinan \( (3) \)

\[ \text{02711} \]

Compound 2 (122 mg, 0.179 mmol) was dissolved in MeOH (20 mL). Pd/C (89 mg, 10%, wet, 0.083 mmol) was added. The resulting mixture was stirred at room temperature under a H\(_{2}\) balloon. Mass spectrometry after 0.5 h showed complete conversion of the starting material to the product. The reaction solution was filtered. The filtrate was evaporated and the crude product (99 mg, 100%) was used in the next reaction without further purification.

\[ \text{0272} \]

\( ^{1} \text{H NMR} \) (300 MHz, CDCl\(_{3}\)) \( \delta \): 7.15 - 7.44 (m, 3H), 6.70 (d, \( J = 8.0 \) Hz, IH), 6.52 (d, \( J = 8.0 \) Hz, IH), 4.55 (s, IH), 4.50 (d, \( J = 5.5 \) Hz, IH), 3.52 - 4.18 (m, 9H), 3.31 - 3.45 (m, 2H), 3.11 (d, \( J = 18.4 \) Hz, IH), 2.87 - 3.02 (m, IH), 2.38 - 2.68 (m, 3H), 2.14 - 2.32 (m, IH), 2.03 (d, \( J = 4.1 \) Hz, IH), 1.78 - 1.95 (m, IH), 1.56 - 1.71 (m, IH), 1.21 - 1.49 (m, 3H), 0.85 - 1.07 (m, IH), 0.45 - 0.64 (m, 2H), 0.06 - 0.23 (m, 2H). MS \([\text{M+H]}\]: 536.2.

(iii) 17-Cyclopropylmethyl-4,5 \(\alpha\)-epoxy-3-hydroxy-14-(2',3'-dihydroxy-3'-phenylpropyloxy) morphinan-6-one \textbf{hydrochloride} \( (16) \)

\[ \text{0273} \]

Compound 3 (99 mg, 0.179 mmol) was dissolved in a mixture of THF (5 mL) and HCl (5 mL, 3N) and heated at reflux for 3 h. After the reaction solution was cooled to room temperature aqueous Na\(_{2}\)CO\(_{3}\) (2M, 30 mL) was added. The resulting mixture was extracted with DCM (3X30 mL). The DCM extracts were combined, dried over Na\(_{2}\)SO\(_{4}\) and evaporated. The brown gummy residue was purified by column (eluent: 3% MeOD in DCM) to give 16 (87 mg, 99 %) as an off-white solid. This solid was dissolved in a mixture of MeOH (3 mL) and
aqueous HCl (0.1 N, 3 mL). MeOH was removed and the aqueous residue was lyophilized to give the HCl salt as white foam (80 mg).

\[0274\] ^1H NMR (300 MHz, D$_2$O) δ: 7.28 - 7.47 (m, 5H), 6.68 - 6.82 (m, 2H), 4.93 (s, 1H), 4.69 (d, J = 6.1 Hz, IH), 4.38 (d, J = 6.3 Hz, IH), 4.17 - 4.29 (m, 1H), 3.57 (d, J = 5.8 Hz, 2H), 3.18 - 3.47 (m, 3H), 2.92 - 3.08 (m, 2H), 2.53 - 2.85 (m, 3H), 2.07 - 2.23 (m, 2H), 1.66 (d, J = 12.7 Hz, IH), 1.41 - 1.57 (m, 1H), 0.90 - 1.06 (m, 1H), 0.67 (d, J = 7.7 Hz, 2H), 0.36 (d, J = 5.2 Hz, 2H). HPLC purity: 100%. MS [M+H]: 492.1.

**Example 10**

IT-Cyclopropylmethyl-M-carboxymethoxy^Sa-epoxy-S-hydroxy-morphinan

**trifluoroacetic acid salt (17)**

(i) 3-Benzyloxy-14-cinnamyloxy-17-cyclopropylmethyl-4,5cc-epoxy-morphinan  (2)

\[0275\] Compound 1 (2.0 g, 4.80 mmol, synthesized as described in the synthesis of intermediate 3, Example 6) was dissolved in anhydrous DMF (30 mL) and stirred under N$_2$. NaH (1.15 g, 60% in mineral oil, 28.8 mmol) was added. After 30 min cinnamyl bromide (2.83 g, 14.4 mmol) was added. The resulting mixture was stirred at room temperature for 3.5 h and EtOAc (200 mL) was added. This solution was washed with water (3X 100 mL) and brine (100 mL), dried over Na$_2$SO$_4$ and filtered. The filtrate was evaporated and the brown oily residue was purified by column (eluent: 10 - 50% EtOAc in hexanes) to give 2 (1.0 g, 36%) as a yellow oil.
(0276) ¹H NMR (300 MHz, CDCl₃) δ: 7.17 - 7.49 (m, 10H), 6.75 (d, J = 8.3 Hz, IH), 6.62 - 6.71 (m, IH), 6.56 (d, J = 8.0 Hz, IH), 6.33 - 6.48 (m, IH), 5.17 (d, J = 3.6 Hz, 2H), 4.79 (t, J = 7.7 Hz, IH), 4.30 - 4.43 (m, IH), 3.95 - 4.08 (m, IH), 3.46 (d, J = 5.0 Hz, IH), 3.13 (d, J = 18.2 Hz, IH), 2.64 - 2.76 (m, IH), 2.48 - 2.62 (m, IH), 2.31 - 2.48 (m, 3H), 2.08 - 2.25 (m, 2H), 1.66 - 1.85 (m, 2H), 1.20 - 1.43 (m, 3H), 1.03 - 1.20 (m, IH), 0.82 - 0.99 (m, IH), 0.42 - 0.58 (m, 2H), 0.07 - 0.20 (m, 2H). MS [M+H]: 534.2.

(ii) 3-Benzoylxy-14-carboxymethoxy-l 7-cyclopropylmethyl-4,5 α-epoxy-morphinan (3)

[0277] Compound 2 (556 mg, 1.04 mmol) was dissolved in acetone (20 mL) and H₂O (2 mL) was added, followed by OsO₄ (0.13 mL, 2.5 wt % in tBuOH, 0.01 mmol). After the reaction solution was stirred at room temperature for 10 min NMO (4-methylmorpholine N-oxide, 146 mg, 1.25 mmol) was added. The resulting mixture was stirred for 1 h and acetone was removed. DCM (20 mL) was added, followed by NaIO₄ (0.44 g in 10 mL H₂O, 2.09 mmol). This biphasic solution was stirred for 30 min and Oxone (1.28 g in 20 mL H₂O, 2.09 mmol) was added. After 2 h the DCM layer was separated. The aqueous layer was extracted with DCM (30 mL). The DCM extract was combined with the above DCM layer, dried over Na₂SO₄ and filtered. The filtrate was evaporated and the black gummy residue was purified by column (eluent: 0 - 10 % MeOH in DCM) to give 3 (199 mg, 40 %) as a yellow solid.

[0278] ¹H NMR (300 MHz, CDCl₃) δ: 7.22 - 7.53 (m, 5H), 6.81 (d, J = 8.3 Hz, IH), 6.62 (d, J = 8.3 Hz, IH), 5.07 - 5.25 (m, 2H), 4.62 - 4.84 (m, IH), 4.09 (br. s., 2H), 3.40 - 3.77 (m, 2H), 3.05 - 3.20 (m, IH), 2.68 - 3.05 (m, 3H), 2.08 - 2.64 (m, 3H), 1.83 (d, J = 12.7 Hz, IH), 1.48 - 1.69 (m, 2H), 1.01 - 1.47 (m, 5H), 0.51 - 0.90 (m, 2H), 0.28 (br. s., 2H). MS [M+H]: 476.2.

(iii) π -Cyclopropylmethyl-M-carboxymethoxy^^ α-epoxy-S-hydroxy-morphinan trifluoroacetic acid salt (17)

[0279] Compound 3 (62 mg, 0.131 mmol) was dissolved in MeOH (30 mL). Pd/C (70 mg, 10%, wet, 0.065 mmol) was added. The resulting mixture was stirred at room temperature under a H₂ balloon. Mass spectrometry after 0.5 h showed complete conversion of the starting material to the product. The reaction solution was filtered. The filtrate was evaporated and the crude product was purified by semi-prep HPLC (eluent: 70% H₂O (with 0.1% TFA)/30% MeOH (with 0.1% TFA)) to give 17 (30 mg, TFA salt, 46%) as a white foam.
**Example 11**

**IT-Cyclopropylmethyl**^S α-epoxy-S-hydroxy-M^-β, 3'-dihydroxypropyloxy)-morphinan-6-one trifluoroacetic acid salt (18)

(i) 3-Benzxyloxy-17-cyclopropylmethyl-4,5 α-epoxy-14-hydroxy-6,6-dimethoxymorphinan (2)

[0281] (a) To a solution of naltrexone hydrochloride (1* HCl, 2.2 g, 1 eq.) in methanol (30 mL) was added trimethylorthoformate (2.04g, 3.3 eq.) and HCl in ether (2M, 3.2 mL, 1.1 eq.) and the mixture was stirred at room temperature for 3h. The reaction mixture was diluted with water (150 mL) and basified using NH₄OH and extracted with dichloromethane (2 X 200 mL). The combined organics were dried over MgSO₄ and concentrated to get the crude 17-cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-6,6-dimethoxymorphinan as a white foam.

[0282] H NMR (301 MHz, CHLOROFORM-d) ppm 6.68 (d, J=8.3 Hz, 1 H), 6.51 (d, /=8.0 Hz, 1 H), 5.18 (br. s., 1 H), 4.58 (s, 1 H), 3.36 (s, 3 H), 3.10 (s, 4 H), 2.99 (d, 7=18.2 Hz, 1 H), 2.51 - 2.71 (m, 2 H), 2.35 (dd, J=6.6, 1.4 Hz, 2 H), 2.24 - 2.33 (m, 1 H), 2.06 -
2.21 (m, 1 H), 1.83 - 1.97 (m, 1 H), 1.34 - 1.60 (m, 4 H), 0.75 - 0.92 (m, 1 H), 0.41 - 0.59 (m, 1 H), 0.08 - 0.21 (m, 2 H); APCI [M+H] 388.1.

(b) To a solution of 17-cyclopropylmethyl-4, 5 α-epoxy-3, 14-dihydroxy-6, 6-
dimethoxymorphin (2.1 g, 1 eq.) in DMF under N₂ was added K₂CO₃ (1.72 g, 2.2 eq.) followed by benzyl bromide (1.1 g, 1.2 eq.). The mixture was stirred for 20 h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organics were dried over MgSO₄ and the solvent concentrated to get the crude product which was purified on a silica column using hexane and ethyl acetate as eluent to get 2.41 g of the title compound 2 (with small amount of DMF as impurity) as a highly viscous liquid.

(ii) 14-Allyloxy-3-benzyloxy-1 7-cyclopropylmethyl-4, 5 α-epoxy-6, 6-dimethoxymorphin (3)

NaH (628 mg, 3 eq, 60% suspension in mineral oil) was added to a solution 2 (2.41 g,l eq.) in DMF under N₂. After 20 minutes allyl bromide (1.9 g, 1.3 eq.) was added and the resulting mixture was stirred overnight at room temperature. Excess NaH was destroyed by the addition of ice. Water was added and the reaction mixture was extracted with dichloromethane. The organics were pooled and dried (MgSO₄) and evaporated. The crude product was purified on a silica gel column using hexane and ethyl acetate as eluent to get 1.3 g of 3 as a viscous liquid.

[0286] ¹H NMR (301 MHz, CHLOROFORM-d) ppm 7.28 - 7.49 (m, 5 H), 6.70 (d, J=8.0 Hz, 1 H), 6.48 (d, J=8.3 Hz, 1 H), 5.95 - 6.08 (m, 1 H), 5.28 - 5.42 (m, 1 H), 5.24 (d, J=Il. 2 Hz, 2 H), 5.13 (dd, J=10.5, 1.7 Hz, 1 H), 4.66 (s, 1 H), 4.15 - 4.25 (m, 1 H), 3.80 (dd, J=I 1.8, 5.2 Hz, 1 H), 3.43 (d, J=4.1 Hz, 1 H), 3.38 (s, 3 H), 3.07 (d, J=17.9 Hz, 1 H), 2.97 (s, 3 H), 2.50 - 2.71 (m, 2 H), 2.24 - 2.44 (m, 2 H), 2.05 - 2.13 (m, 1 H), 1.81 - 2.04 (m, 1 H), 1.65 - 1.73 (m, 1 H), 1.57 - 1.62 (m, 1 H), 1.28 - 1.42 (m, 1 H), 1.07 - 1.22 (m, 1 H), 0.73 - 0.91 (m, 1 H), 0.42 - 0.60 (m, 2 H), 0.1 1 (m, 2 H); APCI [M+H] 518.2.
(iii) 3-Benzyloxy-17-eyelopropylmethyl-14-(2', 3'-dihydroxypropyloxy)-6-dimethoxy-4,5  α-epoxymorphinan  (4)

[0287] Compound 3 (1.06 g, 2.05 mmol) was dissolved in acetone (30 mL) and H₂O (3 mL)) was added. The resulting solution was stirred at 0 °C and OSO₄ (0.26 mL, 2.5 wt% in /-BuOH, 0.0205 mmol) was added. After 10 min NMO (0.48 g, 4.11 mmol) was added. The reaction solution was stirred at 0°C for 2 h and at room temperature for 2.5 h. Aqueous Na₂CO₃ (1M, 80 mL) was added. The resulting mixture was extracted with DCM (2X70 mL). The DCM extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated and the white foamy residue was purified by column (eluent: 5 % MeOH in DCM) to give 4 (0.86 g, 76 %) as a pale gum.

[0288] ¹H NMR (300 MHz, CDCl₃) δ ppm 7.29 - 7.50 (m, 5H), 6.73 (d, J = 8.3 Hz, I1H), 6.50 (d, J = 8.0 Hz, IH), 5.16 - 5.35 (m, 2H), 4.67 (s, IH), 3.90 - 4.01 (m, IH), 3.72 - 3.83 (m, IH), 3.42 - 3.59 (m, 4H), 3.40 (s, 3H), 3.12 (d, J = 18.4 Hz, IH), 2.99 (s, 3H), 2.88 - 2.96 (m, IH), 2.52 - 2.65 (m, 2H), 2.41 (dd, J = 19.0, 5.0 Hz, IH), 1.92 - 2.16 (m, 2H), 1.71 - 1.82 (m, 2H), 1.59 - 1.66 (m, IH), 1.39 - 1.49 (m, IH), 1.18 - 1.31 (m, IH), 0.87 - 1.01 (m, IH), 0.54 (t, J = 7.7 Hz, 2H), 0.12 (d, J = 5.8 Hz, 2H). MS [M+H]: 552.3.

(iv) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(2', 3'-dihydroxypropyloxy)-morphinan-6-one trifluoroacetic acid salt (18)

[0289] Compound 4 (94 mg, 0.17 mmol) was mixed with HCl (5 mL, 3 N) and heated at reflux for 1.5 h. After cooled to room temperature the reaction solution was concentrated to 0.8 mL and purified by semi-prep HPLC (eluent: 75% H₂O (with 0.1% TFA)/25% MeOH (with 0.1% TFA)) to give 18 (86 mg, TFA salt, 95 %) as a white foam.

[0290] ¹H NMR (300 MHz, D₂O) δ ppm 6.63 - 6.89 (m, 2H), 5.03 (s, IH), 4.45 (d, J = 6.3 Hz, IH), 3.99 - 4.16 (m, IH), 3.55 - 3.84 (m, 4H), 3.20 - 3.50 (m, 3H), 2.92 - 3.13 (m, 2H), 2.53 - 2.91 (m, 3H), 2.11 - 2.40 (m, 2H), 1.43 - 1.79 (m, 2H), 0.91 - 1.15 (m, IH), 0.61 - 0.79 (m, 2H), 0.27 - 0.48 (m, 2H). HPLC purity: 100%. MS [M+H]: 416.3.
Example 12

17-Cyclopropylmethyl-Sα-epoxy-S-hydroxy-H-earboxymethoxy-morphinan-ό-one N-oxide trifluoroacetic acid salt (19)

![Chemical Structures](https://example.com/structures.png)

(numbering in scheme refers to section directly below)

(i) 17-Cyclopropylmethyl-3-benzyloxy-14-(2',3'-dihydroxypropyloxy)-6-(1',3'-dioxolan-2'-yl) -4,5α-epoxymorphinan (2)

[0291] Compound 1 (4.56 g, 8.85 mmol, synthesized as described in the synthesis of intermediate 2 of Example 4) was dissolved in acetone (150 mL) and H₂O (15 mL) was added, followed by OsO₄ (0.30 mL, 2.5 wt % in tBuOH, 0.045 mmol). The resulting mixture was stirred at room temperature for 10 min and NMO (4-methylmorpholine N-oxide, 1.24 g, 10.62 mmol) was added. After 24 h acetone was removed. The aqueous residue was diluted with Na₂CO₃ (1M, 50 mL) and extracted with DCM (3x70 mL). The DCM extracts were combined, dried over Na₂SO₄ and evaporated. The brown gummy residue was purified by column (eluent: 50-100 % EtOAc in hexanes) to give 2 (3.6, 63 %) as white foam. MS [M+HJ: 550.3. This sample was taken used in the next step without further characterization.

(ii) 17-Cyclopropylmethyl-3-benzyloxy-14-carboxymethoxy-6-(1',3'-dioxolan-2'-yl) -4,5α-epoxymorphinan (3)

[0292] Compound 2 (358 mg, 0.652 mmol) was dissolved in DCM (10 mL). mCPBA (168 mg, 77%, 0.75 mmol) was added. The resulting mixture was stirred at room
temperature for 50 min. Aqueous NaI (277 mg in 10 mL of H₂O, 1.30 mmol) was added. After 10 min aqueous Oxone (801 mg in 10 mL of H₂O, 1.30 mmol) was added. After another 30 min the reaction solution was acidified with aqueous HCl (3 N) and extracted with DCM (2X15 mL). The DCM extracts were combined, dried over Na₂SO₄ and evaporated to give 3 as yellow foam (486 mg, 100%). [M+H]: 550.2. Taken on to the next step without further characterization.

(iii) π-CyclopropylmethylM^α-epoxy-S-hydroxy-H-carboxymethoxy-morphinan-6-one N-oxide trifluoroacetie acid salt (19)

[0293] Compound 3 (262 mg, 0.351 mmol, crude product from the above reaction) was mixed with aqueous HCl (50 mL, 3N) and heated at reflux for 3 h. After cooled to room temperature the reaction solution was washed with Et₂O (2X50 mL) and concentrated to 10 mL. This solution was filtered. The filtrate was concentrated to ~ 1.0 mL and purified by semi-prep HPLC to give 19 (TFA salt, 20 mg, 11%) as white foam.

[0294] ¹H NMR (300 MHz, D₂O) δ: 6.77 - 6.85 (m, IH), 6.68 - 6.76 (m, IH), 5.13 (s, IH), 4.82 (d, J = 4.7, IH), 4.37 - 4.50 (m, IH), 4.20 - 4.33 (m, IH), 3.92 - 4.07 (m, IH), 3.73 - 3.87 (m, IH), 3.04 - 3.61 (m, 5H), 2.65 - 2.85 (m, IH), 2.19 - 2.43 (m, 2H), 1.83 - 1.97 (m, IH), 1.56 - 1.77 (m, IH), 1.17 - 1.40 (m, IH), 0.65 - 0.86 (m, 2H), 0.34 - 0.60 (m, 2H). HPLC purity: 100%. M.S [M+H]: 416.1.

Example 13

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(3'-phenylurea)-morphinan-6-one trifluoroacetie acid salt (20)
(i) Cycloadduct 3

[0295] To a suspension of sodium periodate (0.91 g, 0.0042 mole) and sodium acetate (0.584 g, 0.0071 mole) in water (15 ml) was added N-(cyclopropylmethyl)northebame (1) (1.0 g, 0.0028 mole) in ethyl acetate (30 ml) at 0 °C. To this resulting two phase solution was added, portion-wise, hydroxamic acid (2) (0.715 g, 0.0043 mole). The mixture was stirred at the same temperature for additional 1 h then made alkaline by addition of saturated aqueous sodium hydrogen carbonate (20 ml). The ethyl acetate phase was separated and the aqueous phase was extracted with ethyl acetate (2 X 20 ml). The combined organic phases were washed with 5% aqueous sodium thiosulphate (10 ml), brine (20 ml) and dried (Na₂SO₄). Evaporation of the solvent gave the crude cycloadduct, which was purified by column chromatography using 50% ethyl acetate in hexane and provided the cycloadduct 3. Isolated yield = 1.4 g (quantitative).

[0296] ¹H NMR (300 MHz, CDCl₃): δ 7.22-7.43 (m, 5H), 6.67 (d, J = 8.26 Hz, IH), 6.53 (d, J = 8.26 Hz, IH), 6.01-6.06 (m, 2H), 5.04-5.18 (m, 2H), 4.55 (s, IH), 3.79 (s, 3H), 3.47 (s, 3H), 3.24 (d, J = 18.71 Hz, IH), 2.79 (td, J = 12.38, 4.13 Hz, 2H), 2.37-2.54 (m, 3H), 2.01-2.12 (m, IH), 1.9 (d, J = 10.18 Hz, IH), 1.64-1.72 (m, IH), 0.92-0.94 (m, IH), 0.42-0.47 (m, 2H), 0.07-0.09 (m, 2H). (APCI⁺): 517 (M+1).
(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-methoxy-14-amino morphinan-6-one (4)

[0297] A mixture of cycloadduct 3 (0.1 g, 0.19 mmol) and Pd/C (10%) in MeOH (5 ml) was hydrogenated at 30 psi for 3 h. The catalyst was filtered and the solvent was evaporated to give crude product. Purification of this crude product by column chromatography using 5% MeOH in DCM gave 18 mg (25%) of the pure desired product.

[0298] H NMR (300 MHz, CDCl₃); δ 6.68 (d, J = 8.26 Hz, IH), 6.60 (d, J = 8.26 Hz, IH), 4.71 (s, IH), 3.86 (s, 3H), 2.97-3.08 (m, 3H), 2.68-2.79 (m, 2H), 2.25-2.54 (m, 5H), 2.10 (dd, J = 3.58, 12.1 Hz, IH), 2.04 (s, IH), 1.66-1.79 (m, 2H), 1.54 (dd, J = 2.19, 12.9 Hz, IH), 0.82-0.88 (m, IH), 0.49-0.56 (m, 2H), 0.11-0.15 (m, 2H). (APCI+): 355 (M+).

(iii) Compound 5

[0299] To a solution of compound 4 (210 mg, 0.60 mmol) in anhydrous dichloromethane was added phenyl isocyanate (0.08 mL, 0.75 mmol) followed by triethylamine (0.095 mL, 0.72 mmol). The mixture was stirred at room temperature overnight. The mixture was combined with a previous reaction product (40 mg, 0.12 mmol). The combined reaction mixtures were concentrated and purified by silica gel column (eluent: 3-8% MeOH in CH₂Cl₂ containing 0.5% NH₄OH) to afford 290 mg of 5 (88%) as a pale yellow solid.

[0300] H NMR (300 MHz, CDCl₃); δ 7.41-7.27 (m, 4H), 7.1-7.03 (m, IH) 6.78 (brs, IH), 6.72 (d, J = 8.25 Hz, IH), 6.63 (d, J = 8.25 Hz, IH), 6.48 (brs, IH), 4.96 (s, IH), 3.88 (s, 3H), 3.48-3.41 (m, IH), 3.10-2.99 (m, 2H), 2.75-2.53 (m, 2H), 2.44-2.26 (m, 3H), 2.21-2.06 (m, 3H), 1.79-1.68 (m, IH), 1.61-1.50 (m, IH), 0.75-0.63 (m, IH), 0.52-0.35 (m, 2H), 0.14-0.06 (m, 2H). MS [M+H]: 474.2.

(iv) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hy droxy-1 4-(3'-phenylurea)-morphinan-6-one trifluoroacetic acid salt (20)

[0301] To a −78 °C solution of compound 5 (190 mg, 0.40 mmol) in anhydrous dichloromethane (6 mL) was added boron tribromide (IM in dichloromethane) (1.6 mL, 1.6 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to warm to −25 °C and stirred for 4 h. The reaction mixture was then cooled down again to −78 °C and quenched by the addition of MeOH. The reaction mixture was concentrated, dissolved again in dichloromethane, and basified by addition of aqueous ammonia. The reaction mixture was combined with another previous crude reaction mixture (75 mg, 0.158 mmol). The combined reaction mixtures were
evaporated and purified by silica gel column (eluent: 6% MeOH in CH₂Cl₂ containing 1.0% NH₄OII) to afford 220 mg of 20 as a slightly impure material. This material was further purified by semi-prep HPLC (eluent: 0.1% TFA in MeOH/H₂O) and afforded 36 mg of 20 (TFA salt) as a white solid.

[0302] ¹H NMR (300 MHz, CD₄OD) δ 7.52-7.40 (m, 2H), 7.31-7.25 (m, 2H), 7.05-7.00 (m, 1H), 6.76 (s, 2H), 5.54 (d, J = 5.78 Hz, 1H), 4.98 (s, 1H), 3.42-3.30 (m, 3H), 3.25-3.06 (m, 3H), 2.88-2.64 (m, 3H), 2.38-2.28 (m, 1H), 1.86-1.75 (m, 1H), 1.68-1.57 (m, 1H), 1.18-1.04 (m, 1H), 0.92-0.73 (m, 2H), 0.54-0.43 (m, 2H). MS [M+H]: 460.1 HPLC purity: 100% (UV detection at 254 nm).

**Example 14**

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-[2'-{2H-tetrazol-5-yl-ethoxyl-morphinan-6-one trifluoroacetic acid salt (21)

[0303] The following reaction sequence was used for the preparation of 21.

(numbering in scheme refers to section directly below)
(i) Compound 2

To a mixture of acid 1 (360 mg, 0.66 mmol, synthesized as in intermediate 2 in Example 7) in DCM (10 ml) at room temperature was added ammonium chloride (140 mg, 2.6 mmol), DiPEA (0.573 ml, 3.3 mmol) and HATU (0.38 g, 0.99 mmol) portion-wise. The resulting mixture was stirred overnight at room temperature. After the aqueous work-up the crude product was purified by column chromatography using 5% MeOH in DCM to get 0.3 g (83%) of 2 as white foam.

\[ \text{[0305]} \]
\[ ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta \text{ 10.25 (bs, IH), 7.25-7.45 (m, 5H), 6.85 (d, J = 8.22 Hz, IH), 6.67 (d, J = 8.22 Hz, IH), 6.29 (bs, IH), 5.82 (bs, IH), 5.15 (dd, } J_1 = 12.09 \text{ Hz, } J_2 = 4.41 \text{ Hz, 2H), 4.61 (s, IH), 4.40 (d, J = 3.84 Hz, IH), 4.11-4.17 (m, IH), 3.97 (q, J = 6.3 Hz, IH), 3.75-3.9 (m, 3H), 3.48-3.54 (m, IH), 3.02-3.32 (m, 4H), 2.70-2.75 (m, 2H), 2.55 (d, J = 8.22 Hz, 2H), 1.97-2.06 (m, IH), 1.74-1.85 (m, IH), 1.40-1.56 (m, 3H), 1.24-1.34 (m, IH), 0.76-0.84 (m, 2H), 0.38-0.48 (m, 2H). (APCI \text{\raisebox{0.5ex}{\textdagger}}: 547 (M+1).} \]

(ii) Compound 3:

To an ice cooled solution OfPOCl\text{\textsubscript{3}} (0.16 ml, 0.35 mmol) in CH\text{\textsubscript{3}}CN (4 ml) was added dropwise DMF (0.4 ml, 5.25 mmol) followed by compound 2 (0.19 g, 0.35 mmol) in CH\text{\textsubscript{3}}CN (4 ml). At the same temperature pyridine (0.7 ml, 8.75 mmol) was added and stirred for 30 minutes and quenched by adding MeOH. All the volatile impurities were evaporated and the residue was basified at 0 °C using saturated aq. NaHCO\text{\textsubscript{3}}. The product was extracted with ethyl acetate and used for the next step without further purification.

\[ \text{[0307]} \]
\[ ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta \text{ 7.25-7.43 (m, 5H), 6.75 (d, J = 8.25 Hz, IH), 6.54 (d, J = 8.25 Hz, IH), 5.14 (q, J = 12.63 Hz, 2H), 4.61 (s, IH), 4.12-4.2 (m, IH), 4.03 (q, IH), 3.82-3.96 (m, 2H), 3.72-3.79 (m, IH), 3.47-3.54 (m, IH), 3.34-3.40 (m, IH), 3.10 (d, J = 17.85 Hz, IH), 2.62 2.72 (m, 3H), 2.46-2.58 (m, IH), 2.0-2.42 (m, 5H), 1.64-1.73 (m, IH), 1.30-1.47 (m, 3H), 0.76-0.87 (m, IH), 0.45-0.56 (m, 2H), 0.08-0.15 (m, 2H). (APCI \text{\raisebox{0.5ex}{\textdagger}}: 529 (M+1).} \]

(iii) Compound 4:

A mixture of compound 3 (0.126 g, 0.24 mmol), NaN\text{\textsubscript{3}} (0.078 g, 1.2 mmol) and NH\text{\textsubscript{4}}Cl (0.064 g, 1.2 mmol) in DMF (10 ml) was heated to 90 °C for 17 h. The solvent was evaporated to dryness and stirred with water (4 ml) for 1 h. The solid was filtered
and washed with minimum amount of water and dried to get 107 mg (74%) of 4. The product was used as such for the next step without further purification.

**[0309]** $^1$H NMR (300 MHz, CD$_3$OD): $\delta$ 7.39-7.44 (m, 2H), 7.25-7.36 (m, 3H), 6.90 (d, J = 8.25 Hz, IH), 6.73 (d, J = 8.25 Hz, IH), 5.1 (q, 2H), 4.63 (d, J = 5.49 Hz, IH), 4.56 (s, IH), 4.08-4.15 (m, IH), 3.84-4.05 (m, 5H), 3.73-3.78 (m, IH), 3.38-3.44 (m, 2H), 3.02-3.30 (m, 4H), 2.62-2.72 (m, IH), 2.39-2.49 (m, IH), 2.06-2.12 (m, IH), 1.88-2.0 (m, IH), 1.50-1.62 (m, 2H), 1.40 (dd, J = 12.9 Hz, J$_2$ = 3.84 Hz, IH), 1.1-1.22 (m, IH), 0.69-0.78 (m, IH), 0.52-0.62 (m, IH), 0.42-0.5 (m, IH), 0.2-0.28 (m, IH). (APCI$^+$): 572 (M$^+$).

(iv) 17-Cyclopropylmethyl-4,5 $\alpha$-epoxy-3-hydroxy-14-[2'-{2H-tetrazol-5-yl}-ethoxy]-morphinan-6-one trifluoroacetic acid salt (21)

**[0310]** A mixture of compound 4 (0.09 g) and 6N HCl (10 ml) was heated to 90 $^\circ$C for 2.5 h. All the volatile impurities were removed and the residue was purified by semi-prep HPLC using MeOH/Water = 30/70 with 0.1% TFA as eluent to get 55 mg (64%) of the product 21.

**[0311]** $^1$H NMR (300 MHz, D$_2$O): $\delta$ 6.78-6.84 (m, 2H), 4.94 (s, IH), 4.77 (d, IH), 4.07-4.19 (m, 2H), 3.33-3.53 (m, 5H), 3.08-3.26 (m, 2H), 2.54-2.86 (m, 3H), 2.41-2.50 (m, IH), 2.24-2.33 (m, IH), 1.57-1.70 (m, 2H), 1.12-1.22 (m, IH), 0.72-0.8 (m, IH), 0.61-0.7 (m, IH), 0.42-0.5 (m, IH), 0.27-0.33 (m, IH). (APCI$^+$): 438 (M$^+$).

**Example 15**

17-Cyclopropylmethyl-4,5 $\alpha$-epoxy-3-hydroxy-14-(N-acetyl-3'-amino-3'-oxo-propoxy)-morphinan-6-one trifluoroacetic acid salt (22)

**[0312]** The following reaction sequence was used for the preparation of 22:
(numbering in scheme refers to section directly below)

(i) Compound 2:

A pressure vessel under an argon atmosphere was charged with AgOCN (1.2 g, 8 mmol) and acetyl chloride (0.2 ml, 3.6 mmol) in toluene (10 ml). The vessel was sealed and heated to 100-110 °C with vigorous stirring for 1 h. The heating was stopped and the heterogeneous reaction mixture was allowed to settle. While it was hot the supernatant liquid was syringed out and added to acid 1 (0.1 g, 0.18 mmol, prepared as intermediate 2 in Example 7) in DCM (30 ml). The resulting mixture was stirred at room temperature for 30 min. All the volatile impurities were evaporated and the residue was dissolved in DCM and washed with 4% aq. NaOH (2 X 5 ml), water (5 ml), brine (5 ml) and dried (MgSO-O. Evaporation of solvent gave crude product (110 mg) and used as such for the next step.

^1H NMR (300 MHz, CDCl₃): δ 10.83 (bs, 1H), 7.25-7.42 (m, 5H), 6.77 (d, J = 8.22 Hz, IH), 6.57 (d, J = 8.22 Hz, IH), 5.14 (q, J = 11.79 Hz, 2H), 4.57 (s, IH), 4.14-4.22 (m, IH), 4.05 (q, J = 6.33 Hz, IH), 3.70-3.92 (m, 4H), 3.43-3.48 (m, IH), 3.19 (d, J = 18.39 Hz, IH), 2.66-2.92 (m, 4H), 2.49 (s, 3H), 2.24-2.44 (m, 3H), 1.92-2.10 (m, 2H), 1.79-1.84 (m, IH), 1.24-1.48 (m, 3H), 0.77-0.94 (m, IH), 0.38-0.58 (m, 2H), 0.06-0.2 (m, 2H). (APCI⁺): 589 (M+1).
(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(N-acetyl-3’-amino-3’-oxo-propoxy)-morphinan-6-one trifluoroacetic acid salt (22)

The mixture of compound 2 (0.11 g) and TFA (10 ml) was refluxed for 7 h. All the volatile impurities were removed and the residue was purified by semi-prep HPLC using MeOH/Water = 25/75 with 0.1% TFA as eluent to get 51 mg (54%) of the product 22.

Example 16

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-[3’-methanesulfonyl amino-3’-oxo-propoxy]-morphinan-6-one trifluoroacetic acid salt (23)

The following reaction sequence was used for the preparation of 23.

(i) Compound 2:

A mixture acid 1 (220 mg, 0.402 mmol, prepared as intermediate 2 in Example 7) and CDI (88 mg, 0.543 mmol) in 8 ml of THF and 4 ml of DCM was heated to 70 °C for 1 h. After cooling to room temperature, DMAP (60 mg, 0.492 mmol) and MeSO₂NH₂ (110 mg, 1.16 mmol) was added and the reaction stirred for 1.5 days. All the volatiles were evaporated and the residue diluted with DCM, washed with water, brine and dried (MgSO₄). Evaporation of the solvent gave a crude residue that was purified by column chromatography.
using 10% MeOH in DCM to provide the pure product (180 mg, 70%) as a white crystalline solid.

\[0319\] 1 H NMR (300 MHz, CDCl₃): δ 7.25-7.40 (m, 5H), 6.85 (d, J = 8.25 Hz, IH), 6.64 (d, J = 8.25 Hz, IH), 5.16 (dd, J₁ = 11.79 Hz, J₂ = 19.23 Hz, 2H), 4.65 (s, IH), 4.29 (d, J = 4.68 Hz, IH), 4.18 (q, J = 6.87 Hz, IH), 4.01 (q, J = 6.3 Hz, IH), 3.89 (q, J = 6.6 Hz, IH), 3.67-3.81 (m, 3H), 3.54-3.62 (m, IH), 3.4-3.48 (m, IH), 3.23 (d, J = 19.23 Hz, IH), 3.13 (s, 3H), 2.71-2.97 (m, 4H), 2.62 (d, J = 17.31, IH), 2.34-2.45 (m, IH), 1.85-1.97 (m, 2H), 1.43-1.54 (m, 4H), 1.1 1-1.21 (m, IH), 0.67-0.87 (m, 3H), 0.44-0.54 (m, IH). (APCI⁺): 625 (M⁺)

(ii) 1T-Cyclpropylmethyl^-S α-epoxy-S-hydroxy-l 4-[3'-methanesulfonlamino-S'-oxo-propoxy]-morphinan-6-one trifluoroacetic acid salt (23)

\[0320\] A mixture of compound 2 (180 mg) and TFA (10 ml) was refluxed for 6.5 h. All the volatile impurities were removed and the residue was purified twice by column chromatography using 5-10% MeOH in DCM to give 27 mg of the desired product 23 as its TFA salt.

\[0321\] 1 H NMR (300 MHz, CD₃OD): δ 6.73 (s, 2H), 4.87 (s, IH), 4.69 (d, IH), 3.86-3.94 (m, IH), 3.35-3.68 (m, 5H), 3.00-3.09 (m, 4H), 2.59-2.90 (m, 5H), 2.33-2.41 (m, IH), 2.19-2.25 (m, IH), 1.46-1.64 (m, 2H), 1.28-1.37 (m, IH), 0.70-0.85 (m, 3H), 0.44-0.52 (m, IH). (APCI⁺): 491 (M⁺)

**Example 17**

**Biological Screening of Compounds of The Invention**

\[0322\] Exemplary compounds 8-23 were tested for their affinities towards human mu-, kappa-, and delta-opioid receptors. The compounds displayed varying degrees of selectivity for kappa- vs. mu-, delta- vs. mu-, and kappa- vs. delta-receptors. The mu-receptor binding affinities (Ki) ranged from about 0.1 nanomolar to about 80 nm.

\[0323\] Compounds of the invention were initially screening in mu-, delta-, and kappa-opioid radioligand binding assays. The Ki and specificity for mu-, delta-, and kappa-opioid receptors was determined. Functional assays for mu-, delta-, and kappa-opioid receptors were conducted as described above. Oral PK and brain permeability studies were conducted in rats on exemplary compounds of the invention that demonstrated potent and selective Mu-antagonism. A summary of results is provided in Table I for 2 compounds of the invention.
TABLE I

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Binding Ki (nM)</th>
<th>Mu Antagonist IC50 (nM)</th>
<th>Brain Penetration</th>
<th>Rat PO F%</th>
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</thead>
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<tr>
<td></td>
<td>mu</td>
<td>Kappa</td>
<td>delta</td>
<td></td>
</tr>
<tr>
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<td>230</td>
<td>10000</td>
<td>50</td>
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<tr>
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<td>110</td>
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</tr>
<tr>
<td>B</td>
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<td>3</td>
<td>37</td>
<td>1.9</td>
</tr>
</tbody>
</table>

* Not tested

[0324] The results demonstrate that Compound A is a potent, mu-selective and peripherally restricted opioid receptor antagonist. Compound A has approximately 12-fold better oral bioavailability than the peripherally restricted Mu-opioid receptor antagonist, methylnaltrexone (MNTX). The results indicate that Compound A has utility in preventing or treating opioid-induced side effects, with little or no effect on centrally mediated analgesia.

[0325] The results show that Compound B is highly specific for mu-opioid receptors, has high potency as a mu-opioid receptor antagonist, and demonstrated approximately 45% brain permeability following IV administration. The results indicate that Compound B has utility in preventing or treating opioid-induced side effects which occur both centrally and peripherally.

Example 18

In Vivo Efficacy of a Compound of The Invention

Rat Charcoal Meal Test

[0326] Test compounds were administered orally to evaluate their ability to reverse the constipation condition induced by the opioid, morphine. Rats were administered with test compounds or control compounds at various concentrations. Morphine was injected 30 minutes later, followed 20 minutes later by a charcoal solution provided by gavage. The gastrointestinal tract was dissected and the distance traveled by charcoal was measured. GI motility was calculated as % inhibition compared to vehicle control. The results are summarized in Figure 1. The compound of the invention reversed morphine-induced inhibition of GI transit following
administration in rats. This establishes that the compound of the invention has utility orally in preventing or reversing opioid-induced side-effects, in particular, the side effect of constipation.


STATEMENT REGARDING EMBODIMENTS

(0328) While the invention has been described with respect to embodiments, those skilled in the art will readily appreciate that various changes and/or modifications can be made to the invention without departing from the spirit or scope of the invention as defined by the appended claims. All documents cited herein are incorporated by reference herein where appropriate for teachings of additional or alternative details, features and/or technical background.
1. We claim:

compounds of formula I and pharmaceutically acceptable salt forms, base forms, stereoisomers, N-oxides, polymorphs, and prodrugs thereof, wherein:

\( R_{i_7} \) is selected from:

- unsubstituted or substituted: (cycloalkyl)alkyl, (cycloalkenyl)alkyl, (cycloheteryl)alkyl, (cycloaryl)alkyl; (cycloalkyl)alkyl or (cycloalkenyl)alkyl, (cycloheteryl)alkyl, (cycloaryl)alkyl, linear or branched alkyl, alkenyl, or alkynyl;

\( R_{i_6} \) is selected from none, H, OH, OR, NH, NHR, NR, amino acids;

\( R_7, R_g, R_{i_1}, \) and \( R_{i_2} \) are independently H, OH, unsubstituted or substituted alkyl;

\( R_{i_1} \) and \( R_{i_2} \) may form a substituted cyclic or heterocyclic ring, said ring to which \( Z \) may be attached at any position, consistent with valency requirements;

\( R_{i_0} \) is H, unsubstituted or substituted alkyl, halogen;

\( R_6 \) is H, \( =0, =CH_2 \), or any unsubstituted cyclic ring, heterocycle, or forms a substituted cyclic or substituted heterocyclic ring with \( R_7 \).
Rs is H, OH, unsubstituted or substituted alkyl, unsubstituted or unsubstituted alkoxy;
R3 is H, alkyl, aryl, alkyaryl, alkoxy, acyloxyalkyl, acyloxyaryl, aminoaalkyl, aminoaryl, amido, aminoalkyl, carboxamide, carboxyl, carboxylester, or forms a substituted cyclic or heterocyclic ring with R2, any of the preceding groups being substituted or unsubstituted as valency allows.

Ri and R2 are independently H, halide, alkoxy, alkyl, aralkyl, or alkyaryl, the preceding groups being substituted or unsubstituted as valency allows;

Y is O, S, CH2, NH or NH-(C=Z2)-NH-R,, wherein when Y = NH, R6 is H, CH2, or any unsubstituted cyclic or forms a substituted cyclic or substituted heterocyclic ring with R7;

Z is CH2, CH2OH, CHOHR1, C=O, S(=O)q, -(O)s-P(=O)(OH)r-, wherein q = 1-2, r = 0-2, S = O-I;
p = 0-6;
Z2 is O, S; and
X is an anion.

2. Compounds having the formula I(a):

and pharmaceutically acceptable salt forms, base forms, stereoisomers, N-oxides, polymorphs, and prodrugs thereof, wherein:
$R_i$ is H, $C_1$-$C_4$ alkyl, or $C_{i-i}$ acyl, the preceding groups being substituted or unsubstituted;

$Z$ is $CH_2$, $CH_2OH$, $CHOH-R_i$, $C=O$, $S(=O)q$, -(O)s-P(=O)(OH)r, wherein $q = 1-2$, $r = 0-2$, $s = 0-1$;

$R_{i_6}$ is selected from none, H, OH, OR?, NH$_2$, NHR, NR$_2$Rg, amino acids;

$p = 0-6$; and

$X$ is an anion.

3. Compounds having the formula I(b):

![Chemical structure diagram](image)

and pharmaceutically acceptable salt forms, N-oxides, stereoisomers, polymorphs, and prodrugs thereof, wherein:

$R_{i_7}$ is selected from:

$C_{4}$-$C_{10}$ cycloalkyl)alkyl or (cycloalkenyl)alkyl, (cycloheteryl)alkyl, (cycloaryl)alkyl; $C_{4}$-$C_{10}$ cycloalkyl)alkyl or (cycloalkenyl)alkyl, (cycloheteryl)alkyl, (cycloaryl)alkyl linear or branched $C_1$-$C_3$ alkyl, halogenated $C_2$-$C_6$ alkenyl, or $C_3$ alkynyl, the preceding groups being optionally substituted or unsubstituted;

$R_{i_8}$ is H, unsubstituted or substituted alkyl, halogen;

$R_7$ and $R_{g}$ are H or substituted or unsubstituted alkyl;
$R_i$ is H, =0, =CH$_2$, or any cyclic ring, or forms an imsubstituted or substituted cyclic or heterocyclic ring with $R_7$;

$R_i$ is H, OH, alkyl, alkoxy, or arlyoxy, the preceding groups being substituted or unsubstituted as valency allows;

$R_3$ is H, C$_1$-C$_4$ alkyl, or C$_1$-C$_3$ acyl, the preceding groups being substituted or unsubstituted;

$R_1$ and $R_2$ are independently H, halide, alkoxy, alkyl, or aryl, the preceding groups being substituted or unsubstituted as valency allows;

$p = 0-6$; and

$X$ is an anion.

4. A pharmaceutical composition comprising a compound of either of claims 1-3 and a pharmaceutically acceptable carrier.

5. The pharmaceutical composition of claim 4, wherein the pharmaceutical composition comprises a parenteral formulation, an oral formulation, an immediate release formulation, an enteric coating, a sustained release formulation or a lyophilized preparation.

6. The pharmaceutical composition of claim 5, wherein the pharmaceutical formulation is a packaged unit dosage.

7. The pharmaceutical composition of claim 6, wherein the packaged unit dosage is a solution.

8. The pharmaceutical composition of claim 5, further comprising an opioid.

9. The composition of claim 8, wherein the opioid is selected from the group consisting of alfentanil, anileridine, asimodiline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenyloxylic acid, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucuronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, tramadol, and combinations thereof.
10. The pharmaceutical composition of claim 5, further comprising at least one pharmaceutical agent that is not an opioid or an opioid antagonist.

11. The pharmaceutical composition of claim 10, wherein at least one pharmaceutical agent is a non-opioid analgesic/anti-pyretic, an antiviral agent, an anti-infective agent, an anticancer agent, an antispasmodic agent, an anti-muscarinic agent, an anti-inflammatory agent, a pro-motility agent, a 5HT₆ agonist, a 5HT₃ antagonist, a 5HT₄ antagonist, a 5HT₄ agonist, a bile salt sequestering agent, a bulk-forming agent, an alpha₂-adrenergic agonist, a mineral oil, an antidepressant, a herbal medicine, an anti-emetic agent, an anti-diarrheal agent, a laxative, a stool softener, a fiber or a hematopoietic stimulating agent.

12. The composition of claim 11, wherein the anti-inflammatory agent is selected from the group consisting of non-steroidal anti-inflammatory drugs (NSAIDS), tumor necrosis factor inhibitors, basiliximab, daclizumab, infliximab, mycophenolate mofetil, azothioprine, tacrolimus, steroids, sulfasalazine, olsalazine, mesalamine, and combinations thereof.

13. The pharmaceutical composition of claim 4 wherein the composition is an oral formulation.

14. The pharmaceutical composition of claim 13 wherein the composition is an immediate or sustained release formulation.

15. The pharmaceutical composition of claim 4 wherein the composition is a lyophilized formulation or is a parenteral formulation.

16. A method for modulating mu-opioid receptors comprising administering to a patient in need of mu-opioid receptor modulation the composition of claim 4 in a modulation effective amount.

17. The method of claim 16, wherein said administration occurs before, concurrently with, or after a step of administering as least one opioid.

18. The method of claim 17, wherein the opioid is selected from the group consisting of alfentanil, anileridine, asimodiline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine,
nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanil, sufentanil, tilidine, trimebutine, tramadol, and combinations thereof.

19. The method of claim 16 wherein the mu-opioid receptor modulation is consistent with an opioid agonist.

20. The method of claim 19 wherein the effective amount is sufficient to provide antitussive, sedative, anesthetic or antidiarrheal activity.

21. The method of claim 16 wherein the mu-opioid receptor modulation is consistent with an opioid antagonist.

22. The method of claim 21 wherein the mu-opioid receptor modulation is effective to treat at least one opioid-induced side effect.

23. The method of claim 22 wherein the opioid-induced side effect is constipation, dysphoria, respiratory depression, dizziness, nausea, dependence, pruritis, urinary retention, inhibition of intestinal motility, gastrointestinal dysfunction, bowel hypomotility, impaction, gastric hypomotility, GI sphincter constrictions, increased sphincter tone, inhibition of gastrointestinal motility, inhibition of gastric emptying, delayed gastric emptying, incomplete evacuation, emesis, cutaneous flushing, bloating, and abdominal distension.

24. A method for modulating kappa opioid receptors and/or delta opioid receptors comprising administering to a patient in need of such modulation the composition of claim 4 in a modulation effective amount.

25. The method of claim 24 wherein the kappa opioid receptor modulation is consistent with a kappa agonist.

26. The method of claim 24 wherein the kappa opioid receptor modulation is consistent with a kappa antagonist.

27. The method of claim 24, wherein the delta modulation is consistent with a delta agonist.

28. The method of claim 24, wherein the delta modulation is consistent with a delta antagonist.

29. The method of claim 20 wherein the composition is subcutaneously administered.
30. The method of claim 20, wherein the composition is intravenously administered.

31. The method of claim 20 wherein the composition is administered orally.

32. The method of claim 20 wherein the composition is administered topically.

33. The method of claim 20 wherein the composition is administered rectally.

34. The method of claim 20 wherein the composition is administered buccally.

35. A pharmaceutical composition comprising the compound of claim 2 and a pharmaceutically acceptable carrier.

36. A pharmaceutical composition comprising a compound of claim 3 and a pharmaceutically acceptable carrier.

37. A method of synthesizing the compounds of claim 3 comprising the steps of:

- mixing in ethereal solvent a 17-alkyl-3-aryloxy-4,5α-epoxy-14-(3'-substituted allyloxy)-6-one with osmium tetroxide for about 5-20 minutes at about 15°C-30°C, then adding aqueous oxidant and stirring for about 8-24 hours, followed by extracting with haloalkane solvent and isolating the 17-alkyl-3-aryloxy-4,5α-epoxy-14-(2',3'-dihydroxy-3'-substituted)propyloxy-morphinan-6-one derivative therefrom;

- mixing in haloalkane solvent the 17-alkyl-3-aryloxy-4,5α-epoxy-14-(2',3'-dihydroxy-3'-substituted)propyloxy-morphinan-6-one derivative with oxidant in water, for about 30 to 120 minutes, separating the haloalkane solvent layer and further extracting with haloalkane solvent;

- oxidizing the combined haloalkane solvent extracts with Oxone® in water for about one to three hours, separating the haloalkane solvent layer, and isolating the 17-alkyl-3 aryloxy-4,5α-epoxy-14-carboxymethoxy morphinan-6-one derivative therefrom; and

- hydrogenating the 17-alkyl-3-aryloxy-4,5α-epoxy-14-carboxymethoxy morphinan-6-one on Pd/C in alcoholic solvent under a hydrogen atmosphere for about 0.5 to 3 hours at 15°C-30°C, isolating, and then semi-preparatively chromatographing the reaction product using an acidified mobile phase, collecting and isolating the purified 17-alkyl-4,5α-epoxy-3-hydroxy-14-carboxymethoxy-morphinan-6-one salt from the chromatographic eluent.
38. The following compound, its pharmaceutically acceptable salts, stereoisomers, N-oxides, bases, polymorphs and prodrugs thereof:

![Chemical structure image]

wherein $X^-$ is an anion.

39. The following compound, its pharmaceutically acceptable salts, bases, stereoisomers, N-oxides, polymorphs and prodrugs thereof:

![Chemical structure image]

wherein $X^-$ is an anion.

40. The following compound, its pharmaceutically acceptable salts, bases, stereoisomers, N-oxides, polymorphs and prodrugs thereof:
41. The following compound, its pharmaceutically acceptable salts, stereoisomers, N-oxides, bases, polymorphs and prodrugs thereof:

wherein $X^-$ is an anion.

42. The following compound, its pharmaceutically acceptable salts, stereoisomers, N-oxides, bases, polymorphs and prodrugs thereof:

wherein $X^-$ is an anion.
wherein $X^-$ is an anion.

43. The following compound, its pharmaceutically acceptable salts, stereoisomers, N-oxides, bases, polymorphs and prodrugs thereof:

![Chemical Structure 1]

wherein $X^-$ is an anion.

44. The following compound, its pharmaceutically acceptable salts, stereoisomers, N-oxides, bases, polymorphs and prodrugs thereof:

![Chemical Structure 2]

wherein $X^-$ is an anion.

45. The following compound, its pharmaceutically acceptable salts, bases, stereoisomers, polymorphs and prodrugs thereof:

![Chemical Structure 3]
46. The following compound, its pharmaceutically acceptable salts, bases, stereoisomers, N-oxides, polymorphs and prodrugs thereof:

![Chemical Structure](image)

wherein X- is an anion.

47. The following compound, its pharmaceutically acceptable salts, N-oxides, bases, polymorphs and prodrugs thereof:

![Chemical Structure](image)

wherein X- is an anion.

48. The following compound, its pharmaceutically acceptable salts, stereoisomers, bases, N-oxides, polymorphs and prodrugs thereof:

![Chemical Structure](image)

wherein X- is an anion.
49. The following compound, its pharmaceutically acceptable salts, bases, stereoisomers, polymorphs and prodrugs thereof:

![Chemical Structure 1]

50. The following compound, its pharmaceutically acceptable salts, bases, stereoisomers, N-oxides, polymorphs and prodrugs thereof:

![Chemical Structure 2]

wherein $X^-$ is an anion.

51. The following compound, its pharmaceutically acceptable salts, bases, stereoisomers, N-oxides, polymorphs and prodrugs thereof:

![Chemical Structure 3]

wherein $X^-$ is an anion.

52. The following compound, its pharmaceutically acceptable salts, bases, stereoisomers, N-oxides, polymorphs and prodrugs thereof:
wherein X⁻ is an anion.

53. A compound of claim 1 and its pharmaceutical compositions, wherein Z is O or S.

54. One or more compounds, pharmaceutically acceptable salts, stereoisomers, N-oxides, polymorphs and prodrugs thereof, selected from the group comprising:

4-((17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-morphinan-14-yloxy-methyl)benzoic acid;

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(3-hydroxypropoxy)-morphinan-6-one;

4-(17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-oxo-morphinan-14-ylamino)-3-oxopropyl)benzoic acid;

4-((17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-morphinan-14-yloxy)-propionic acid;

14-Butoxy-17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-oxo-holino-morphinan;

4-((17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-morphinan-14-yloxy)methyl) benzoic acid;

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-[(4′carboxybenzyl) oxy] morphinan;

(17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-morphinan-6-one-14-yloxy)-propionic acid;
17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-oxo-14-(3'-hydroxypropyloxy) morphinan-N-oxide;

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(2',3'-dihydroxy-3'-phenylpropyloxy) morphinan-6-one;

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(2',3'-dihydroxypropyloxy)-morphinan-6-one;

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(2'-{2H-tetrazol-5-yl}-ethoxy)-morphinan-6-one;

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(N-acetyl-3'-amino-3'-oxo-propoxy)-morphinan-6-one; and

17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(3'-methanesulfonyl amino-3'-oxo-propoxy)-morphinan-6-one.

55. A composition of matter comprising a pharmaceutically acceptable salt, hydrate, stereoisomer, base, polymorph, or prodrug of 17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(2',3'-dihydroxypropyloxy)-morphinan-6-one.

56. A composition of matter comprising a pharmaceutically acceptable salt, hydrate, stereoisomer, base, polymorph, or prodrug of 4-(17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-oxo-morphinan-14yloxy)-butanoic acid.

57. A method of synthesizing the compound of claim 48 comprising the steps of:

(a) mixing naltrexone hydrochloride with an excess of trimethylorthoformate in acidified ether for a period of about 1-6 hours at room temperature and then isolating the 17-cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxy-6,6-dimethoxymorphinan from the basified mixture;
(b) mixing 17-cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxy-6,6-dimethoxy morphinan with an equivalent amount of benzyl bromide in basic DMF solvent for about 10-30 hours at room temperature and then isolating 3-benzyloxy-17-cyclopropylmethyl-4,5α-epoxy-14-hydroxy-6,6-dimethoxymorphinan from the mixture;

(c) mixing 3-benzyloxy-17-cyclopropylmethyl-4,5α-epoxy-14-hydroxy-6,6-dimethoxymorphinan in DMF solution with excess sodium hydride, adding excess allyl bromide, and stirring for about 10-30 hours at room temperature, then destroying the excess sodium hydride and isolating M-allyloxy-3-benzyloxy-17-cyclopropylmethyl-4,5α-epoxy-6,6-dimethoxymorphinan from the mixture;

(d) mixing 14-allyloxy-3-benzyloxy-17-cyclopropylmethyl-4,5α-epoxy-6,6-dimethoxymorphinan with a catalytic equivalent of osmium tetroxide in ketone solution at about 0°C for about 5-20 minutes, adding excess N-morpholine-N-oxide, and stirring for about 1-3 hours at about 0°C, followed by stirring for about 1-5 hours at room temperature, adding sodium carbonate, and then isolating 3-benzyloxy-17-cyclopropylmethyl-14-(2',3'-dihydroxypropyloxy)-6-dimethoxy-4,5α-epoxymorphinan from the mixture;

(e) heating 3-benzyloxy-17-cyclopropylmethyl-14-(2',3'-dihydroxypropyloxy)-6-dimethoxy-4,5α-epoxymorphinan in aqueous mineral acid at reflux temperature for about 0.5-3 hours and isolating 17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(2',3'-dihydroxypropyloxy)-morphinan-6-one trifluoroacetic acid salt after chromatographing the reaction mixture by liquid chromatography using an eluent containing TFA.

58. A method of synthesizing the TFA salt of the compound of claim 44 comprising the steps of:

(a) mixing naltrexone hydrochloride with an excess of methanesulfonic acid in ethylene glycol for a period of about 1-6 hours at about 80-120 °C and then isolating the 17-cyclopropylmethyl-3,14-dihydroxy-4,5α-epoxy-6-spiro-2'-(1,3-dioxolane) morphinan from the basified mixture;

(b) mixing 17-cyclopropylmethyl-3,14-dihydroxy-4,5α-epoxy-6-spiro-2'-(1,3-dioxolane) morphinan with an excess amount of benzyl bromide in basic DMF solvent for about 10-30 hours at room temperature and then isolating 3-benzyloxy-17-cyclopropylmethyl-3,14-dihydroxy-4,5α-epoxy-6-spiro-2'-(1,3-dioxolane) morphinan from the mixture;
(c) mixing 3-benzyloxy-17-cyclopropylmethyl-3,14-dihydroxy-4,5 α-epoxy-6-spiro-2'-
(1,3-dioxolane) morphinan in DMF solution with excess sodium hydride, adding excess allyl bromide, and stirring for about 10-30 hours at room temperature, then destroying the excess sodium hydride and isolating M-allyloxy-S-benzyloxy-LT-cyclopropylmethyl-
4,5α-epoxy-6-spiro-2'-(1,3-dioxolane) morphinan from the mixture;

(d) mixing 14-allyloxy-3-benzyloxy-17-cyclopropylmethyl-4,5 α-epoxy-6-spiro-2'-(1,3-
dioxolane) morphinan with an equivalent amount of BH3 in THF solution at room temperature for about 1-3 hours, adding sodium hydroxide solution, followed by aqueous hydrogen peroxide, stirring for about 1-3 hours at room temperature, and then isolating 3-
benzyloxy-17-cyclopropylmethyl-6-(1',3'-dioxolan-2'yl)-4,5 α-epoxy-14-(3'-
hydroxypropyloxy) morphinan from the mixture;

(e) adding 3-benzyloxy-17-cyclopropylmethyl-6-(1',3'-dioxolan-2'yl)-4,5 α-epoxy-14-
(3'-hydroxypropyloxy)morphinan to a solution containing excess oxalyl chloride and
DMSO at about -78 °C for about 5-20 minutes, adding excess triethylamine, warming at
room temperature for about 5-10 hours, adding excess potassium peroxymonosulfate and
reacting for about 2-6 hours, and then isolating (3-benzyloxy-17-cyclopropylmethyl-6-
(r,3'-dioxolan-2'yl)-4,5 α-epoxy-morphinanl4-yloxy) propionic acid;

(f) heating (3-benzyloxy-17-cyclopropylmethyl-6-(1',3'-dioxolan-2'yl)-4,5 α-epoxy-
morphinanl4-yloxy) propionic acid in aqueous mineral acid at reflux temperature for
about 2-6 hours, and isolate (17-cyclopropylmethyl-4,5α-epoxy-S-hydroxy-morphinan-ό-
one-14-yloxy) propionic acid salt.
Figure 1

% Inhibition of morphine-induced decrease in GI motility

MNTX (3, 30, 300)  CPD A (0.3, 3, 30)

Treatment (Doses mg/kg, PO)