The compounds disclosed are useful, inter alia, as modulators of opioid receptors.
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Declaration under Rule 4.17:
— of inventorship (Rule 4.17(iv))
BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention generally relates to N-oxides of 4,5-epoxy-morphinanum analogs (hereinafter referenced as "4,5-epoxy-morphinaniums"), and in particular isolated axial (hereinafter "axial 4,5-epoxy-morphinaniums") and equatorial (hereinafter "equatorial 4,5-epoxy-morphinaniums") stereoisomers of the same, prodrugs, polymorphs, synthetic methods for their preparation, pharmaceutical preparations comprising the same, and methods for their use. This application claims priority to United States Provisional Application Serial No. 60/867,104, filed November 22, 2006, and United States Application Serial No. 11/994,300, filed November 21, 2007, the applications incorporated herein by reference in their entireties.

Description of the Related Art

[0002] Opioid activity of morphinoids has been shown to be particularly sensitive to the nature of their nitrogen substituents. For example, replacement of the N-methyl group in morphine and related opioids by substituents rich in π-electrons, such as allyl, cyclobutylmethyl, and propylmethyl, result in potent antagonists such as nalorphine, naloxone, naltrexone and nalbuphine.

[0003] N-oxides of certain morphinan derivatives are known, e.g., Tiffany, U.S. Pat. No. 2,813,097 which discloses 3-hydroxy-N-methylmorphinan N-oxide and its utility as an analgesic. Tiffany, U.S. Pat. No. 2,813,098 further discloses 3-methoxy-N-methylmorphinan N-oxide and its utility as an antitussive. It is stated that these N-oxides have a higher therapeutic index than the corresponding tertiary amines. Bartels-Keith disclose in U.S. Patent No. 3,299,072 certain thebaine morphinan derivates (having a di-unsaturated cyclohexanone ring in the backbone). The compounds are indicated to have analgesic and/or narcotic antagonist activity. U.S. Patents Nos. 3,144,459 and 3,217,006 disclose N-oxide morphinan structures lacking the 4,5-epoxy.
The N-oxides of morphine and simple morphine derivatives such as codeine, hydromorphone (dihydromorphinone), and hydrocodone (dihydro codeinone), are well known, having been reported by, among others: M. Polonovski et al, Bull. Acad. Med. 103, 174 (1930); N. H. Chang et al, J. Org. Chem. 15, 634 (1950); B. Kelentei et al, Arzneimittel-Forsch. 7, 594 (1957); K. Takagi et al, Yakugaku Zasshi 83, 381 (1963) (Chem. Abs. 59: 9224b); L. Lafon, U.S. Pat. No. 3,131,185; M. R. Fennessy, Brit. J. Pharmacol. 34, 337 (1968); M. R. Fennessy, Eur. J. Pharmacol. 8, 261 (1969); and M. R. Fennessy, J. Pharm. Pharmacol. 21, 668 (1969). Morphine N-oxide is variously reported to be either less active or inactive as an analgesic but an effective antitussive, as well as having somewhat lower toxicity than morphine.

Boswell et al., U.S. Patent No. 4,990,617, disclose the N-oxide derivatives of 3-hydroxymorphinans said to be useful as prodrugs, agonist-antagonists, analgesics and narcotic antagonists. Among the compounds described are the N-oxide of naloxone, naltrexone, nalmefene, nalbuphine, pentazocine, butorphanol, and buprenorphine. The reference suggests improved oral bioavailability for the N-oxide analogs, that appears to result from the biotransformation of the N-oxides to their parent amine forms.

It should be noted that N-oxide morphinan structures are also produced by oxidative metabolism which are excreted among the many metabolic pathways which have been identified in mammals administered various tertiary amines. J. D. Phillipson et al., Eur. J. Drug Metab. Pharmacokinetics 3, 119 (1978), report that morphine and codeine are converted in part to the corresponding N-oxides by a guinea pig liver microsomal preparation, and also that these two drugs are partially metabolized to the N-oxides when administered to rats. T. Ishida et al., Drug Metab. Dispos. 7, 162 (1979), and T. Ishida et al., J. Pharmacobio-Dyn. 5, 521 (1982), report that oxycodone N-oxide is one of a number of identifiable metabolites found in the urine of rabbits administered oxycodone subcutaneously. While other metabolites were found in both free and conjugated forms, oxycodone-N-oxide was found only in the free, unconjugated form. The analgesic activity of oxycodone is believed to be due to the unchanged drug rather than the metabolites. S. Y. Yeh et al., J. Pharm. Sci. 68, 133 (1979), also report isolating morphine N-oxide from the urine of guinea pigs administered morphine sulfate.
The art suggests that isolated stereoisomers of a compound, whether enantiomers or diastereomers, sometimes may have contrasting physical and functional properties, although it is unpredictable whether this is the case in any particular circumstance. Dextromethorphan is a cough suppressant, whereas its enantiomer, levomethorphan, is a potent narcotic. R,R-methylphenidate is a drug to treat attention deficit hyperactivity disorder (ADHD), whereas its enantiomer, S,S-methylphenidate is an antidepressant. S-fluoxetine is active against migraine, whereas its enantiomer, R-fluoxetine is used to treat depression. The S-enantiomer of citalopram is therapeutically active isomer for treatment of depression. The R-enantiomer is inactive. The S-enantiomer of omeprazole is more potent for the treatment of heartburn than the R enantiomer.

The designations "R" and "S" are commonly used in organic chemistry to denote specific configuration of a chiral center. The designations "R" refers to "right" and refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" or "left" refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group.

The priority of groups for the R/S designation is based upon atomic number (heaviest isotope first). A partial list of priorities and a discussion of stereochemistry is contained in the book: The Vocabulary of Organic Chemistry, Orchin, et al. John Wiley and Sons, Inc., page 126 (1980), which is incorporated herein by reference in its entirety. When quaternary nitrogen morphinan structures are produced, such structures may be characterized as (R) or (S) stereoisomers.

The pharmacology of the diastereomeric conformers of N-oxide morphinans has not been elucidated. Given that different stereoisomers of organic compounds have been found in the past to elicit significantly different pharmacological profiles, it is possible that significant differences in pharmacological activity might be seen with select N-oxide morphinans.
SUMMARY OF THE INVENTION

[00011] It is disclosed in equatorial/axial embodiments herein that N-oxides of 4,5-epoxy-morphinanums, and in particular 7,8-saturated-4,5-epoxy-morphinanums, possess significant mu-opioid receptor antagonistic activity at physiological concentrations when the N-oxide is in an axial plane with respect to the nitrogen (i.e., (S) configuration when N is substituted with hydrocarbyl substituents). It is further disclosed that equatorial/axial N-oxide compounds of the present invention having an axial oxygen substituent may be found to display significantly greater antagonist activity than their counterpart equatorial stereoisomers (wherein the oxygen is in an equatorial position). Equatorial-orientation of the oxygen substitutent in such 4,5-epoxy-morphinanium compounds may diminish antagonistic activity.

[00012] In an embodiment there are provided compounds of the formula (I):

or pharmaceutically acceptable salt forms, polymorphs, or prodrugs thereof, wherein:

R1 and R2 are independently H, OH, OR29, halide, silyl;

(C1-C8) alkyl substituted with 0-3 R19;

(C2-C8) alkenyl substituted with 0-3 R19;

(C2-C8) alkynyl substituted with 0-3 R19;

(C3-C10) cycloalkyl substituted with 0-3R20;
(C₃-C₁₀) carbocycle substituted with 0-3R₂;
aryl substituted with 0-3R₂;

or R₁ and R₂ are combined to form a C₁-C₆ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring;

R₃ is H, cyano, OH, OR₂₉, halide, silyl;

(C₁-C₈) alkyl substituted with 0-3R₁₉;
(C₂-C₈) alkenyl substituted with 0-3R₁₉;
(C₂-C₈) alkynyl substituted with 0-3R₁₉;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

R₅ is H, OH, OR₂₉,

(C₁-C₈) alkyl substituted with 0-3R₁₉;
(C₂-C₈) alkenyl substituted with 0-3R₁₉;
(C₂-C₈) alkynyl substituted with 0-3R₁₉;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

R₆ is H, =0, OH, OR₂₉; NR₂₂R₂₃;

(C₁-C₈) alkyl substituted with 0-3R₁₉;
(C₂-C₈) alkenyl substituted with 0-3R₁₉;
(C_2-C_8) alkynyl substituted with 0-3 R_1;
(C_3-C_{10}) cycloalkyl substituted with 0-3R_{20};
(C_3-C_{10}) carbocycle substituted with O-3R_{20};
aryl substituted with 0-3R_{20};
amine, amide, sulfonamide, ester, heterocycle, cyclic carbohydride, aryl;

R_7 is H, OH, OR_{29},

(C_{11}-C_{20}) alkyl substituted with 0-3 R_{19};
(C_{2}-C_{20}) alkenyl substituted with 0-3 R_{19};
(C_{2}-C_{20}) alkynyl substituted with 0-3 R_{19};
(C_{3}-C_{10}) cycloalkyl substituted with O-3R_{20};
(C_{3}-C_{10}) carbocycle substituted with O-3R_{20};
aryl substituted with 0-3R_{20};

or R_8 and R_7 are combined to form an O-fused ring, a C_3-C_6 carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring or a bicyclic combination thereof;

R_8 is H, OH, OR_{29},

(C_{1}-C_{8}) alkyl substituted with 0-3 R_{19};
(C_{2}-C_{8}) alkenyl substituted with 0-3 R_{19};
(C_{2}-C_{8}) alkynyl substituted with 0-3 R_{19};
(C_{3}-C_{10}) cycloalkyl substituted with O-3R_{20};
(C_{3}-C_{10}) carbocycle substituted with O-3R_{20};
aryl substituted with 0-3R_{20};
\( R_{14} \) is H, OH, OR\(_{29}\), NHR\(_{29}\),

\((C_1^r-C_8)\) alkyl substituted with 0-3 \( R_{19} \);

\((C_2^r-C_7)\) alkenyl substituted with 0-3 \( R_{19} \);

\((C_2^r-C_8)\) alkynyl substituted with 0-3 \( R_{19} \);

\((C_3^r-C_{19})\) cycloalkyl substituted with 0-3 \( R_{21} \);

\((C_3^r-C_{19})\) carbocycle substituted with 0-3 \( R_{21} \);

aryl substituted with 0-3 \( R_{25} \); aryloxy, acyloxy,

or \( R_{14} \) is combined with \( R_{14} \) to form an O-fused ring, or a C\(_3\)-C\(_6\) carbocycle fused ring;

\( R_{17} \) is 0 \( R_{25} \),

\((C_4^r-C_{20})\) alkyl substituted with 0-3 \( R_{25} \);

\((C_4^r-C_{20})\) alkenyl substituted with 0-3 \( R_{25} \);

\((C_4^r-C_{20})\) alkynyl substituted with 0-3 \( R_{25} \);

\((C_3^r-C_{19})\) cycloalkyl substituted with 0-3 \( R_{26} \);

\((C_3^r-C_{19})\) carbocycle substituted with 0-3 \( R_{26} \);

aryl substituted with 0-3 \( R_{26} \); or allyl;

\( R_{19} \) is at each occurrence is independently selected from:

H, \( C^r_1-C_6 \) alkyl, CF\(_3\), OR\(_{24}\), Cl, F, Br, I, =O, CN, NO\(_2\), NR\(_{22}\)R\(_{23}\); acyl(\( C^r_1-C_6 \))alkyl;

acylaryl substituted with 0-3 \( R_{23} \);

\( C_3^r-C_{19} \) carbocycle substituted with 0-3 \( R_{21} \);

aralkyl substituted with 0-3 \( R_{21} \); or
5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 \( R_{20} \):

\[ R_{20} \text{ at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO}_2, \]
\[ \text{NR}_{22} R_{23}, \text{acetyl,} \]
\[ C_{1-6} \text{ alkyl, } C_{2-4} \text{ alkoxy, } C_{2-4} \text{ haloalkyl,} \]
\[ C_{4} \text{ haloalkoxy, and } C_{4} \text{ haloalkyl-S-;} \]

\[ R_{23} \text{ at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO}_2, \]
\[ \text{NR}_{22} R_{23}, \text{CF}_3, \text{acetyl,} \]
\[ C_{4} \text{ alkyl, } C_{2-4} \text{ alkoxy, } C_{2-4} \text{ haloalkyl,} \]
\[ C_{4} \text{ haloalkoxy, and } C_{4} \text{ haloalkyl-S-;} \text{ or} \]
\[ \text{NR}_{22} R_{23} \text{ may be a heterocyclic ring selected from the group piperidinyl, homopiperidinyl, and morpholiny;} \]

\[ R_{22} \text{ at each occurrence, is independently selected from H, } C_{1-6} \text{ alkyl,} \]
\[ (C_{1-6} \text{ alkyl})-(=\text{O})-, \text{ and } (C_{1-6} \text{ alkyl})-(\text{S})(=\text{O})_2^- \]

\[ R_{23} \text{ at each occurrence, is independently selected from:} \]
\[ \text{H, (} C_{1-6} \text{ alkyl) alkyl, benzyl, phenethyl,} \]
\[ (C_{1-6} \text{ alkyl})-(=\text{O})-, \text{ and } (C_{1-6} \text{ alkyl})-(\text{S})(=\text{O})_2^- \]

\[ R_{24} \text{ at each occurrence, is independently selected from H, phenyl, benzyl, (} C_{1-6} \text{) alkyl, and } (C_{1-6} \text{) alkoxyalkyl;} \]

\[ R_{25} \text{ at each occurrence, is independently selected from:} \]
\[ \text{H, } C_{1-6} \text{ alkyl, OR}_{24}, \text{Cl, F, Br, =O, CN, NO}_2, \text{NR}_{27} R_{28}; \]
C₃-C₁₀ carbocycle substituted with 0-3 R₁;  
aril substituted with 0-3 R₂; or  
5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂;  

R₂₆, at each occurrence, is independently selected from: H, (C₁-C₆)alkyl, benzyl, phenethyl, (C₁-C₆ alkyl)-C(O)-, halide;  

R₂₇, at each occurrence, is independently selected from:  
  H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy;  

R₂₈, at each occurrence, is independently selected from:  
  H, C₁-C₆ alkyl;  

R₂₉ is at each occurrence is independently selected from:  
  H, C₁-C₆ alkyl, CF₃, acyl(C₁-C₆)alkyl;  

daryl substituted with 0-3 R₃;  

C₃-C₁₀ carbocycle substituted with 0-3 R₂;  
aralkyl substituted with 0-3 R₂;  
5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂; or  
aryl substituted with 0-3 R₂₀; and  

wherein, when RH is OH, and Re is selected from the group consisting of =0 and =C₃H₂, then R₃ is not OH.
There is further disclosed in one embodiment are axial-0 configured N-oxide compounds of Formula (Ia):

![Chemical structure diagram]

[00013] or pharmaceutically acceptable salt forms, polymorphs, or prodrugs thereof, wherein:

R₁ and R₂ are independently H, OH, OR₂₉, halide, silyl;

(C₁-C₈) alkyl substituted with 0-3 R₁₉;

(C₂-C₈) alkenyl substituted with 0-3 R₁₉;

(C₂-C₈) alkynyl substituted with 0-3 R₁₉;

(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;

(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;

aryl substituted with 0-3R₂₀;

or R₁ and R₂ can also be combined to form a C₃-C₆ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring;

R₃ is H, cyano, OH, OR₂₉, halide, silyl;

(C₁-C₈) alkyl substituted with 0-3 R₁₉;
(C\textsubscript{2}-C\textsubscript{8}) alkenyl substituted with 0-3 R\textsubscript{19};

(C\textsubscript{2}-C\textsubscript{8}) alkynyl substituted with 0-3 R\textsubscript{19};

(C\textsubscript{3}-C\textsubscript{10}) cycloalkyl substituted with 0-3R\textsubscript{20};

(C\textsubscript{3}-C\textsubscript{10}) carbocycle substituted with 0-3R\textsubscript{20};

aryl substituted with 0-3R\textsubscript{20};

R\textsubscript{5} is H, OH, OR\textsubscript{29},

(C\textsubscript{1}-C\textsubscript{8}) alkyl substituted with 0-3 R\textsubscript{19};

(C\textsubscript{2}-C\textsubscript{8}) alkenyl substituted with 0-3 R\textsubscript{19};

(C\textsubscript{2}-C\textsubscript{8}) alkynyl substituted with 0-3 R\textsubscript{19};

(C\textsubscript{3}-C\textsubscript{10}) cycloalkyl substituted with 0-3R\textsubscript{20};

(C\textsubscript{3}-C\textsubscript{10}) carbocycle substituted with 0-3R\textsubscript{20};

aryl substituted with 0-3R\textsubscript{20};

R\textsubscript{6} is H, =O, OH, OR\textsubscript{29};

(C\textsubscript{1}-C\textsubscript{8}) alkyl substituted with 0-3 R\textsubscript{19};

(C\textsubscript{2}-C\textsubscript{8}) alkenyl substituted with 0-3 R\textsubscript{19};

(C\textsubscript{2}-C\textsubscript{8}) alkynyl substituted with 0-3 R\textsubscript{19};

(C\textsubscript{3}-C\textsubscript{10}) cycloalkyl substituted with 0-3R\textsubscript{20};

(C\textsubscript{3}-C\textsubscript{10}) carbocycle substituted with 0-3R\textsubscript{20};

aryl substituted with 0-3R\textsubscript{20};

amine, amide, sulfonamide, ester, heterocycle, cyclic carbohydride, aryl;
$R_7$ is H, OH, OR$_{29}$,

- $(C_1-C_8)$ alkyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkenyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkynyl substituted with 0-3 $R_{19}$;
- $(C_3-C_{10})$ cycloalkyl substituted with 0-3$R_{20}$;
- $(C_3-C_{10})$ carbocycle substituted with 0-3$R_{20}$;
- aryl substituted with 0-3$R_{20}$;

or $R_6$ and $R_7$ can also be combined to form an O-fused ring, a $C_3-C_6$ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring, or a combination thereof;

$R_8$ is H, OH, OR$_{29}$

- $(C_1-C_8)$ alkyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkenyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkynyl substituted with 0-3 $R_{19}$;
- $(C_3-C_{10})$ cycloalkyl substituted with 0-3$R_{20}$;
- $(C_3-C_{10})$ carbocycle substituted with 0-3$R_{20}$;
- aryl substituted with 0-3$R_{20}$;

$R_{14}$ is H, OH, OR$_{29}$,

- $(C_1-C_8)$ alkyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkenyl substituted with 0-3 $R_{19}$;

(C₂-C₈) alkynyl substituted with 0-3 R₁₉;

(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;

(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;

aryl substituted with 0-3R₂₀; aryloxy, acyloxy,

or R₁₄ is combined with R₁₈ to form an O-fused ring, or a C₃-C₆ carbocycle fused ring;

R₁₇ is (C₄-C₁₀) alkyl substituted with 0-3 R₂₅;

(C₄-C₁₀) alkenyl substituted with 0-3 R₂₅;

(C₄-C₁₀) alkynyl substituted with 0-3 R₂₅;

(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₆;

(C₃-C₁₀) carbocycle substituted with 0-3R₂₆;

aryl substituted with 0-3R₂₆; or allyl;

R₁₉ is at each occurrence is independently selected from:

H, C₁-C₆ alkyl, CF₃, OR₂₄, Cl, F, Br, I, =O, CN, NO₂, NR₂₂R₂₃;

acyl(C₁-C₆)alkyl, acylaryl substituted with 0-3 R₂₁;

C₃-C₁₀ carbocycle substituted with 0-3 R₂₁;

aralkyl substituted with 0-3 R₂₁; or

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂₁;
R₀ at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO₂,

NR₂₂, R₂₃, acetyl,

C₁⁻C₆ alkyl, C₁⁻C₄ alkoxy, C₁⁻C₄ haloalkyl,

C₁⁻C₄ haloalkoxy, and C₁⁻C₄ haloalkyl-S⁻;

R₂₁, at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO₂,

NR₂₂, R₂₃, CF₃, acetyl,

C₁⁻C₆ alkyl, C₁⁻C₄ alkoxy, C₁⁻C₄ haloalkyl,

C₁⁻C₄ haloalkoxy, and C₁⁻C₄ haloalkyl-S⁻;

R₂₂, at each occurrence, is independently selected from H, C₁⁻C₆ alkyl, (C₁⁻C₆ alkyl)-C(=0)-, and (C₁⁻C₆ alkyl)-S(=O)₂⁻;

R₂₃, at each occurrence, is independently selected from:

H, (C₁⁻C₆) alkyl, benzyl, phenethyl,

(C₁⁻C₆ alkyl)-C(=O)-, and (C₁⁻C₆ alkyl)-S(O)₂⁻;

R₂₄, at each occurrence, is independently selected from H, phenyl, benzyl, (C₆C₆) alkyl, and (C₂⁻C₅) alkoxyalkyl;

R₂₅, at each occurrence, is independently selected from:

H, C₁⁻C₆ alkyl, OR₂₄, =0, CN, NO₂, NR₂₇, R₂₈;

C₃⁻C₁₀ carbocycle substituted with 0-3 R₂₇;

aryl substituted with 0-3 R₂₇; or

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂₇;
R_{26}, at each occurrence, is independently selected from:

H, (C_{1}-C_{6})alkyl, benzyl, phenethyl, (C_{1}-C_{6} alkyl)-C(O)-, halide;

R_{27}, at each occurrence, is independently selected from:

H, OH, C_{1}-C_{6} alkyl, C_{1}-C_{4} alkoxy;

R_{28}, at each occurrence, is independently selected from:

H, C_{1}-C_{6} alkyl;

R_{29} is at each occurrence is independently selected from:

H, C_{1}-C_{6} alkyl, CF_{3}, acyl(d-C_{6})alkyl;

acylaryl substituted with 0-3 $R_{21}$;

C_{3}-C_{10} carbocycle substituted with 0-3 $R_{21}$;

aralkyl substituted with 0-3 $R_{21}$;

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 $R_{21}$; or

aryl substituted with 0-3 R_{20}; and

wherein, when R_{14} is OH, and R_{6} is selected from the group consisting of =0 and =CH_{2}, then R_{3} is not OH.

Further there is disclosed compounds of Formula (1b):
or pharmaceutically acceptable salt forms, polymorphs, or prodrugs thereof, wherein:

R₁ and R₂ are independently H, OH, OR₂₉, halide, silyl;

wherein R₂₀ is at each occurrence is independently selected from:

- H, C₁-C₆ alkyl, CF₃, acyl(C₁-C₆)alkyl;
- acylaryl substituted with 0-3 R₂₁;
- C₃-C₂₀ carbocycle substituted with 0-3 R₂₁;
- aralkyl substituted with 0-3 R₂₁;
- 5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂₁; or
- aryl substituted with 0-3 R₂₀;

R₇ is a substituted or unsubstituted C₂ - C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ alkyne, or, substituted or unsubstituted C₄ - C₂₀ (cycloalkyl)alkyl, C₄-C₁₀ (cycloalkenyl)alkyl, (C₄-C₁₀)cycloheteroalkyl, or (C₄-C₁₀) aryalkyl, alkoxy, C₄-C₂₀ carbocyclohalide;

R₆ is =0, =CH₂, H, alkylhydroxy, C₁-C₆ alkyl, N-dialkyl, C₄ - C₆ alkyne, QR₁₉R₂₀ (wherein Q=C, O, N, CO, CO₂, or CON), NR₂₉COR₂₀, none, a cyclic ring, or forms a cyclic ring with R₁₉ and R₂₀ are independently H, alkyl, aryl;
R₁₄ and R₆ are independently H or alkyl;

R₁₄ is H, OH, halide, substituted or unsubstituted -O-alkyl, -O-alkylaryl, -O-alkenyl, -O-acylalkyl, -O-acylaryl, amidoaryl, or forms a cyclic ring with R₁₇, aryloxy;

R¹ and R₂ are independently H, halide, alkoxy, alkyl, alkyne, alkynyl or aryl;

R₃ is H, cyano, C=ONH₂, OH, C₁₋₃ alkyl, C₄₋₁₀ aryl or C₁₋₃ acyl; and

R₅ is H, OH, alkyl, alkoxy, or aryloxy; and

wherein when R₁₄ is OH and R₆ is selected from the group consisting of =O and =CH₂, then R₃ is not OH.

Further disclosed is axial-0 configured N-oxide compounds of the Formula (Ic),

or a pharmaceutically acceptable salt forms, polymorphs, or prodrugs thereof, wherein:

R₁ and R₂ are independently H, OH, OR₂₀, halide, silyl;

(C₁₋₈) alkyl substituted with 0-3 R₁₉;

(C₂₋₈) alkenyl substituted with 0-3 R₁₉;

(C₂₋₈) alkynyl substituted with 0-3 R₁₉;

(C₃₋₁₀) cycloalkyl substituted with 0-3R₁₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂;
aryl substituted with 0-3R₂₀;
or R₁ and R₂ are combined to form a C₃-C₆ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring;

R₃ is H, cyano, OH, OR₂⁹, halide, silyl, CO₂R₁⁹, SO₂R₁⁹, B(OR₂⁹)₂;

(C₁-C₈) alkyl substituted with 0-3 R₁⁹;
(C₂-C₈) alkenyl substituted with 0-3 R₁⁹;
(C₂-C₈) alkynyl substituted with 0-3 R₁⁹;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

R₅ is H, OH, OR₂⁹,

(C₁-C₈) alkyl substituted with 0-3 R₁⁹;
(C₂-C₈) alkenyl substituted with 0-3 R₁⁹;
(C₂-C₈) alkynyl substituted with 0-3 R₁⁹;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

R₆ is H, =0, OH, OR₂⁹, NR₂₂R₂₃, =R₁⁹ (R₁⁹), =heterocycle substituted with 0-3R₂₀), =(C₃-7 cycle substituted with 0-3R₂₀);

(C₁-C₈) alkyl substituted with 0-3 R₁⁹;
(C₂-C₈) alkenyl substituted with 0-3 R₁⁹;
(C₂-C₈) alkynyl substituted with 0-3 R₁₉;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;
amine, amide, sulfonamide, ester, heterocycle, cyclic carbohydride, aryl;

R₇ is H, OH, OR₂₉,

(C₁-C₂₀) alkyl substituted with 0-3 R₁₉;
(C₂-C₂₀) alkenyl substituted with 0-3 R₁₉;
(C₂-C₂₀) alkynyl substituted with 0-3 R₁₉;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;
or Rᵣ, and R₇ are combined to form an O-fused ring, a C₃-C₆ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring or a bicyclic combination thereof, a 5-, 6-, 5-6-membered aryl with 0-3R₂₀;

R₈ is H, OH, OR₂₉, heterocycle with 0-3R₂₀, alkylaryl with 0-3 R₂₀, arylalkyl with 0-3R₂₀,

wherein X is bond, =0, O, S, N(R₂₉), SO, SO₂, SO₂N(R₂₉), CON(R₂₉), N(R₂₉)CON(R₂₉), N(R₂₉)C(=NR₂₉)N(R₂₉), COO;

(C₁-C₈) alkyl substituted with 0-3 R₁₉;
(C₂-C₈) alkenyl substituted with 0-3 R₁₉;

(C₂-C₈) alkynyl substituted with 0-3 R₁₉;

(C₃-C₁₀) cycloalkyl substituted with O-3R₂₀;

(C₃-C₁₀) carbocycle substituted with O-3R₂₀;

aryl substituted with O-3R₂₀;

R₁₄ is H, OH, OR₂₉, NHR₂₉, heterocycle with 0-3R₂₀, alkylaryl with 0-3R₂₀, arylalkyl with 0-3R₂₀;

wherein X is bond, =0, O, S, N(R₂₉), SO₂, SO₃N(R₂₉), CON(R₂₉), N(R₂₉)CON(R₂₉), N(R₂₉)C(=NR₂₉)N(R₂₉⁻), COO;

(C₁-C₈) alkyl substituted with 0-3 R₁₉;

(C₂-C₈) alkenyl substituted with 0-3 R₁₉;

(C₂-C₈) alkynyl substituted with 0-3 R₁₉;

(C₃-C₁₀) cycloalkyl substituted with O-3R₂₀;

(C₃-C₁₀) carbocycle substituted with O-3R₂₀;

aryl substituted with 0-3R₂₀; aryloxy, acyloxy,

or R₁₄ is combined with R₁₈ to form an O-fused ring, or a C₃-C₆ carbocycle fused ring;

R₁₇ is OR₂₅, heterocycle with O-3R₂₀, alkylaryl with O-3R₂₀, arylalkyl with O-3R₂₀;
and

wherein X is bond, =0, O, S, N(R_{29}), SO, SO_2, SO_2N(R_{29}), CON(R_{29}),
N(R_{29})CON(R_{29}), N(R_{29})C(=NR_{29})N(R_{29}), COO;

(C_4-C_{29}) alkyl substituted with 0-3 R_{25};

(C_4-C_{29}) alkenyl substituted with 0-3 R_{25};

(C_4-C_{29}) alkynyl substituted with 0-3 R_{25};

(C_3-C_{10}) cycloalkyl substituted with 0-3R_{26};

(C_3-C_{10}) carbocycle substituted with 0-3R_{26};

aryl substituted with 0-3R_{26}; or allyl;

R_{10} is at each occurrence is independently selected from:

H, C_1-C_6 alkyl, CF_3, OR_{24}, Cl, F, Br, I, =0, CN, NO_2, NR_{22}R_{23}; acyl(C_1-C_6)alkyl;

acylaryl substituted with 0-3 R_{21};

C_3-C_{10} carbocycle substituted with 0-3 R_{21};

aralkyl substituted with 0-3 R_{21};

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from
nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is
substituted with 0-3 R_{21}; or

aryl substituted with 0-3R_{20};

R_{20} at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO_2,
NR_{22}R_{23}, acetyl, OR_{25}, XR_{25};
C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl,
C_1-C_4 haloalkoxy, and C_1-C_4 haloalkyl-S-;

R_{21}, at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO_2,
NR_{22}R_{23}, CF_3, acetyl, OR_{25}, XR_{25},
C_1-C_6 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl,
C_1-C_4 haloalkoxy, and C_1-C_4 haloalkyl-S-; or

NR_{22}R_{23} may be a heterocyclic ring selected from the group piperidinyl,
homopiperidinyl, and morpholinyl;

R_{22}, at each occurrence, is independently selected from H, C_1-C_6 alkyl,

(C_1-C_6 alkyl)-C(=O)-, and (C_1-C_6 alkyl)-S(=O)2-,
C_6-10 aryl, heteroary1, heterocycle, alky1aryl, arylalkyl;

R_{23}, at each occurrence, is independently selected from:

H, (C_1-C_6) alkyl, heteroaryl, heterocycle, alky1aryl, arylalkyl, C6-10 aryl, heteroaryl, heterocycle, haloalkyl, arylalkyl,

(C_1-C_6 alkyl)-C(=O)-, and (C_1-C_6 alkyl)-S(=O)2-;

or R_{22} and R_{23} are combined to form a 5-, 6-, or 5-6-membered cycle with 0-2R_{20};

R_{24}, at each occurrence, is independently selected from H, phenyl, benzyl, (C_1-C_6) alkyl,
haloalkyl and (C_3-C_6) alkoxyalkyl;

R_{25}, at each occurrence, is independently selected from:

H, C_1-C_6 alkyl, haloalkyl, OR_{25}, Cl, F, Br, =0, CN, NO_2, NR_{27}R_{28};

C_3-C_10 carbocycle substituted with 0-3 R_{27};

aryl substituted with 0-3 R_{27}; or
5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R_{27};

R_{26}, at each occurrence, is independently selected from: H, (C_{1}-C_{6})alkyl, benzyl, phenethyl, (C_{1}-C_{6} alkyl)-C(O)-, halide;

R_{27}, at each occurrence, is independently selected from:

H, OH, C_{1}-C_{6} alkyl, C_{1}-C_{4} alkoxy;

R_{28}, at each occurrence, is independently selected from:

H, C_{1}-C_{6} alkyl;

R_{29} is at each occurrence is independently selected from:

H, C_{1}-C_{6} alkyl, CF_{3}, acyl(C_{1}-C_{6})alkyl;

acylaryl substituted with 0-3 R_{21};

C_{5}-C_{10} carbocycle substituted with 0-3 R_{21};

aralkyl substituted with 0-3 R_{21};

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R_{21}; or

aryl substituted with 0-3R_{20}; and

wherein, when R_{14} is OH, and R_{6} is selected from the group consisting of =0 and =CH_{2}, then R_{3} is not OH.

[00016] Also further disclosed are compounds according to Formula (II), or pharmaceutically acceptable salt forms, polymorphs, or prodrugs thereof, wherein:
wherein:

\[ R_{17} \] is a substituted or unsubstituted \( \text{C}_2\text{-C}_6 \) alkyl, \( \text{C}_4\text{-C}_{10} \) alkoxy, \( \text{C}_4\text{-C}_{10} \) haloalkyl, \( \text{C}_2\text{-C}_6 \) alkenyl, \( \text{C}_3\text{-C}_6 \) alkynyl, or substituted or unsubstituted \( \text{C}_4\text{-C}_{10} \) (cycloalkyl)alkyl, \( \text{C}_4\text{-C}_{10} \) (cycloalkylene)alkyl, \( \text{C}_4\text{-C}_{10} \) (heterocyclo)alkyl or arylalkyl;

\[ R_6 \] is =0, N-dialkyl, \( \text{C}_2\text{-C}_6 \) alkylene, QR\( _{19} \)R\( _{20} \) (wherein Q is C, O, N, CO, CO\( _2 \), CON, or none), and \( R_{19} \) and \( R_{20} \) are independently H, alkyl, aryl, none, or form a carbocycle fused ring), a carbocycle, or \( R_6 \) forms a forms a carbocycle ring with \( R_7 \);

\[ R_7 \text{ and } R_8 \text{ are independently H or alkyl;} \]

\[ R_3 \text{ is H, } \text{C}_1\text{-C}_3 \text{ alkyl, Ct-C}_3 \text{ acyl, C}_4\text{-C}_{10} \text{ aryl;} \]

\[ R_1 \text{ and } R_2 \text{ are independently H, halide, alkoxy, alkyl, alkyene, alkynyl or aryl; and} \]

\[ R_5 \text{ is H, OH, alkyl, alkyene, alkynyl, alkoxy, and aryloxy;} \text{ and} \]

\[ M \text{ is } \text{SO}_2\text{WO, SOWO, COWO, WO, WS, W is } \text{C}_1\text{-C}_3 \text{ substituted with 0-3 } R_{19}. \]

[00017] Additionally disclosed are compounds and their stereoisomers, or pharmaceutically acceptable salt forms, polymorphs, or prodrugs thereof, from the group consisting of:

(S)-17-Cyclopropylmethyl-4,5 \( \alpha \)-epoxy-3,14-dihydroxymorphinan N-oxide;
(S)- 17-Cyclopropylmethyl-4,5-epoxy-morphinan-3,6α,14-triol N-oxide;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propyloxy morphinan-6-one N-oxide;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3’-phenylpropyloxy) morphinan-6-one N-oxide;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3’-phenylpropyloxy) morphinan-6-one N-oxide trifluoroacetic acid salt;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxy-morphinan-6-one N-oxide trifluoroacetic acid salt;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-14-(3’-phenylpropyloxy) morphinan-3,6α-diol N-oxide;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzamido-morphinan-6-one N-oxide;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzamido-morphinan-6-one N-oxide trifluoroacetic acid salt;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzamido-morphinan-6-one N-oxide trifluoroacetic acid salt;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-6α-hydroxymethyl morphinan N-oxide;

(S)- 17-Cyclopropylmethyl-4,5 α-epoxy-14-propyloxy morphinan-3,6 α-diol N-oxide;
(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-carbamoyl-14-hydroxy-morphinan-6-one N-oxide hydrochloride;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-(3'-phenylpropyloxy)morphan-3,6β-diol N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-6α-methyl morphinan-3,14-diol N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-6α-(1H-imidazol-1-yl)methyl morphinan-3,14-diol N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-phenethylamido-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-propyloxy morphinan-3,6β-diol N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-butyloxymorphinan-6-one N-oxide hydrochloride;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzyloxymorphinan-6-one N-oxide hydrochloride;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-ethoxymorphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-acetoxymorphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-allyloxymorphinan-6-one N-oxide;

(S)-Naltrindole-N-Oxide;

(R)-4,5α-epoxy-3-hydroxy-(17,14-N, O-ethylene)morphinanum-6-one N-oxide trifluoroacetic acid salt;

(S)-17-Propargyl-4,5 α-epoxy-3,14-dihydroxy-morphinan-6-one N-oxide trifluoroacetic acid salt;
(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-cyclopropylmethyloxy-morphinan-6-one N-oxide;

(S)-Naltriben N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3'-phenylpropyloxy)-6-methylenemorphinan N-oxide trifluoroacetic acid salt;

(5)-17-(3,3,3-Trifluoropropyl)-4,5 α-epoxy-3,14-dihydroxy-morphinan-6-one N-oxide trifluoroacetic acid salt;

(5)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-acetamido-morphinan-6-one N-oxide trifluoroacetic acid salt;

(5)-SDM25N N-oxide (4bS,8R,8aS,14bR)-5,6,7,8,14,14b-Hexahydro-7-(2-methyl-2-propenyl)-4,8-methanobenzofuro[2,3-a]pyrido[4,3-b]carbazole-1,8a(9H)-dion N-oxide;

(5)-17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(3'-trifluoromethyl)benzyloxy-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propoxy-6-methylenemorphinan N-oxide;

(S)-17-Cyclopropylmethyl-4,5a-epoxy-3,14-dihydroxy-6,7-(4′5′-1H-pyrazole ) morphinan N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5a-epoxy-3,14-dihydroxy-6,7-(2′-oxo-r, 2′-dihydropyridine-3′-carboxylic acid methyl ester ) morphinan N-oxide; and

(S)-17-Cyclopropylmethyl-4,5α-epoxy-3-cyano-14-hydroxy-morphinan-6-one N-oxide.

[00018] Also further disclosed are compounds according to Formula (III),
or pharmaceutically acceptable salt forms, polymorphs, or prodrugs thereof, wherein:

\[ R_6 = O, \text{N-dialkyl, } C_{2-6} \text{ alkylen}, Q R_{19} R_{20} \text{ (wherein } Q = C, O, N, CO, CO_2, C=ON, \text{ or none), and } R_{19} \text{ and } R_{20} \text{ are independently } H, \text{alkyl, aryl, none, or form a carbocycle fused ring, a carbocycle, or } R_6 \text{ forms a carbocycle ring with } R_7; \]

\[ R_3 \text{ and } R_5 \text{ are independently } H, \text{alkyl, aryl; } \]
\[ R_7 \text{ and } R_8 \text{ are independently } H \text{ or alkyl; and } \]
\[ M = O, S, NR_{19}, SO_2, SO, \text{ or CO.} \]

[00019] Also disclosed in one embodiment is a convergent method for synthesizing 17-cyclopropylmethyl-4,5 \( \alpha \)-epoxy-3-methoxy-14-amino morphinan-6-one, an important intermediate *en route* to the synthesis of 14-amino morphinans comprising the steps of:

- adding N-(cyclopropylmethyl)northebaine in ethyl acetate to a suspension of sodium periodate and sodium acetate in water at about 0 °C to form a two phase solution;

- adding benzyl N-hydroxycarbamate portionwise to said two phase solution, and mixing to form a second solution;

- stirring said second solution at about 0°C for about 1 hour;
making said stirred second solution alkaline by the addition of saturated aqueous sodium hydrogen carbonate;

separating the ethyl acetate phase and extracting the aqueous phase with ethyl acetate (about 2 x 20 ml);

combining the ethyl acetate phases and washing with about 5% aqueous sodium thiosulphate, brine, and drying with anhydrous Na₂SO₄;

evaporating any residual solvent to give a crude cycloadduct between N-(cyclopropylmethyl)northebaine and said benzyl N-hydroxycarbamate;

purifying said crude cycloadduct by column chromatography using about 50% ethyl acetate in hexane and evaporating the ethyl acetate and hexane;

isolating the cycloadduct of N-(cyclopropylmethyl)northebaine and benzyl N-hydroxycarbamate;

hydrogenating the cycloadduct of N-(cyclopropylmethyl)northebaine and benzyl N-hydroxycarbamate with Pd/C (10%) in MeOH at about 30 psi hydrogen for about 3 hours;

filtering the Pd/C catalyst and evaporating the methanol solvent to give crude product;

purifying the hydrogenated cycloadduct of N-(cyclopropylmethyl)northebaine and benzyl N-hydroxycarbamate by column chromatography using 5% MeOH in dichloromethane; and

evaporating the 5% MeOH in dichloromethane solvent to isolate 17-cyclopropylmethyl-4,5 α-epoxy-3-methoxy-14-amino morphinan-6-one.

[00020] Also disclosed in one embodiment are a compound, or a pharmaceutically acceptable salt form, polymorph, or prodrug thereof selected from the group consisting of:
Disclosed in embodiments described herein are O-axial N-oxide-4,5-epoxy-morphinanium analogs which have been produced in high purity, permitting the characterization of their relative retention time in chromatography versus that of their corresponding equatorial stereoisomers. The O-axial diastereomers of such analogs have mu-opioid receptor antagonistic activity in contrast to their corresponding equatorial diastereomers which may have significantly different activity.

In an embodiment of the present invention, there is provided substantially or highly pure axial N-oxide-4,5-epoxy-morphinaniums, crystals substantially or highly pure axial N-oxide-4,5-epoxy-morphinaniums and intermediates...
thereof, novel methods for making substantially or highly pure axial N-oxide-4,5-epoxy-
morphinanium compounds, methods for analyzing, quantitating and isolating O-axial N-
oxide-4,5-epoxy-morphinanium compounds in a mixture containing counterpart equatorial 
N-oxide stereoisomer, and its O-equatorial N-oxide-4,5-epoxy-morphinanium stereoisomer. Further disclosed are methods of distinguishing an axial N-oxide 
stereoisomer from its equatorial N-oxide-4,5-epoxy-morphinanium counterpart, 
pharmaceutical products containing the same and related uses of these materials.

[00023] Equatorial N-oxide stereoisomers of the present disclosure may have 
agonist activity and little, if any, antagonist activity. As agonists, the equatorial N-oxide 
stereoisomers may have utility in the prevention, treatment, or management of acute or 
chronic pain, hyperalgesia or diarrhea. A protocol for obtaining equatorial N-oxide 
stereoisomers is also provided. The invention provides synthetic routes for stereoselective 
synthesis of these equatorial N-oxide-4,5-epoxy-morphinaniums, substantially pure 
equatorial N-oxide-4,5-epoxy-morphinaniums, crystals of substantially pure equatorial N-
oxide-4,5-epoxy-morphinaniums, pharmaceutical preparations containing substantially 
one or more pure equatorial N-oxide-4,5-epoxy-morphinaniums, and methods for their 
use.

[00024] According to one embodiment of the invention, a composition is 
provided that comprises an N-oxide-4,5-epoxy-morphinanium, e.g., an N-oxide-7,8-
saturated-4,5-epoxy-morphinanium, in the axial configuration (that is, with respect to the 
nitrogen) is present at greater than 99.5%. In other embodiments, the N-oxide-4,5-epoxy-
morphinanium, e.g., an N-oxide-7,8-saturated-4,5-epoxy-morphinanium in axial 
configuration (with respect to the nitrogen) is present in the composition in greater than 
about 99.6%, or about 99.7%, or about 99.8%, or about 99.9%, or about 99.95%, or 
greater than 99.95%. In one embodiment, there is no detectable counterpart equatorial N-
oxide stereoisomer compound in the analyzed composition using the chromatographic 
procedures described herein. It may be preferred that the composition is free of the 
corresponding equatorial N-oxide stereoisomer as detected on HPLC. In one embodiment, 
there is no HPLC detectable counterpart equatorial N-oxide stereoisomer at a detection 
limit of 0.02% and a quantitation limit of 0.05%. In yet another embodiment the 
composition of the invention contains 99.85% of the N-oxide-4,5-epoxy-morphinanium, 
e.g., an N-oxide-7,8-saturated-4,5-epoxy-morphinanium, in the axial configuration with
respect to nitrogen, and it contains the counterpart stereoisomer\(^4\) equatorial N-oxide stereoisomer compound at a HPLC detectable detection limit of 0.02% and a quantitation limit of 0.05%.

[00025] According to one aspect of the invention, a composition is provided that comprises an N-oxide-4,5-epoxy-morphinanium, e.g., an N-oxide-7,8-saturated-4,5-epoxy-morphinanium, wherein at least 99.6%, 99.7%, 99.8%, 99.85%, 99.9% , and even 99.95% of the N-oxide-4,5-epoxy-morphinanium compound in the composition has the oxygen in the axial configuration with respect to nitrogen, and the composition includes one or more of: a buffering agent, a chelating agent, a permeation enhancer, a preserving agent, a cryoprotecting agent, a lubricating agent, a preservative, an anti-oxidant, or a binding agent.

[00026] The N-oxide-4,5-epoxy-morphinaniums may be salts. Therefore, there will be a counterion, which for the present application includes the zwitterion. More typically, the counterion is a halide, sulfate, phosphate, nitrate, or anionic-charged organic species. Halides include fluoride, chloride, iodide and bromide. In some embodiments, the halide is iodide and in other embodiments the halide is bromide. In some embodiments the anionic-charged species is a sulfonate or a carboxylate. Examples of sulfonates include mesylate, besylate, tosylate, and triflate. Examples of carboxylates include formate, acetate, citrate, and fumarate.

[00027] According to another aspect of the invention, the foregoing compositions with respect to nitrogen may be a crystal, a solution, or a bromide of an N-oxide-4,5-epoxy-morphinanium, e.g., an N-oxide-7,8-saturated-4,5-epoxy-morphinanium. In other embodiments, the foregoing compositions are pharmaceutical preparations, preferably in effective amounts and with a pharmaceutically acceptable carrier.

[00028] According to one aspect of the invention, a crystal of a certain N-oxide-4,5-epoxy-morphinanium, e.g., an N-oxide-7,8-saturated-4,5-epoxy-morphinanium, is provided that is at least about 99.5%, or about 99.6% or about 99.7%, or is about 99.8%, or about 99.9%, or greater than 99.95% of the N-oxide-4,5-epoxy-morphinanium in \(\text{a})\)-axial configuration with respect to the nitrogen.
According to another embodiment of the invention, an equatorial N-oxide stereoisomer compound is provided in isolated form. By isolated, it is meant at least 50% pure. In embodiments, the equatorial N-oxide-4,5-epoxy-morphinanium is provided at 75% purity, at 90% purity, at 95% purity, at 98% purity, and even at 99% purity or 99.5% versus the axial form. In an embodiment, the equatorial N-oxide stereoisomer is in a crystal form.

According to another aspect of the invention, a composition is provided. The composition comprises an N-oxide-4,5-epoxy-morphinanium, e.g., an N-oxide-7,8-saturated-4,5-epoxy-morphinanium, wherein the N-oxide-4,5-epoxy-morphinanium present in the composition is greater than 10% in the axial configuration with respect to nitrogen. More preferably, the N-oxide-4,5-epoxy-morphinanium, e.g., an N-oxide-7,8-saturated-4,5-epoxy-morphinanium, present in the composition is greater than 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 98.5%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, and even 99.9% in the axial configuration with respect to nitrogen. In some embodiments there is no detectable counterpart equatorial N-oxide stereoisomer compound as measured by high performance liquid chromatography (HPLC).

The composition in some embodiments is a solution, in others an oil, in others a cream, and in still others a solid or semi-solid. In one embodiment, the composition is a crystal.

According to another aspect of the invention, a pharmaceutical preparation is provided. The pharmaceutical preparation includes any one of the compositions of a particular axial N-oxide-4,5-epoxy-morphinanium described above in a pharmaceutically acceptable carrier. The pharmaceutical preparation contains a therapeutically effective amount of the axial N-oxide-7,8-saturated-4,5-epoxy-morphinanium. In some embodiments, there is little or no detectable counterpart equatorial N-oxide stereoisomer structure in the composition. If present, axial N-oxide-4,5-epoxy-morphinanium compound is at a level such that therapeutically effective amounts of the axial N-oxide-4,5-epoxy-morphinanium compound are administered to a subject. In some embodiments, the pharmaceutical preparation further includes a pharmaceutical agent, and/or pharmacological agent, other than the axial N-oxide-4,5-
epoxy-morphinanium, e.g., an axial N-oxide-7,8-saturated-4,5-epoxy-morphinanium. In one embodiment, the pharmacological agent is an opioid or opioid agonist. Examples of opioids or opioid agonists are alfentanil, anileridine, asimadoline, 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-glucuronide, naltorphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanil, sufentanil, tilidine, trimebutine, tramadol, or combinations thereof. In some embodiments, the opioid or opioid agonist does not readily cross the blood brain barrier and, therefore, has substantially no central nervous system (CNS) activity when administered systemically (i.e., it is of the class of agents known as "peripherally acting") agents. In one embodiment, the peripheral opioid agonist is a equatorial N-oxide stereoisomer. In other embodiments, the pharmacological agent is not an opioid, opioid agonist, or an opioid antagonist. In another embodiment, the pharmacological agent is an opioid or opioid agonist in combination with a non-opioid analgesic/antipyretic, e.g. such as acetaminophen. For example, the pharmacological agent can be an antiviral agent, antibiotic agent, antifungal agent, antibacterial agent, antiseptic agent, anti-protozoal agent, anti-parasitic agent, anti-inflammatory agent, a vasoconstrictor agent, a local anesthetic agent, an anti-diarrheal agent, an anti-hyperalgesia agent, or combinations thereof.

[00033] In other embodiments the pharmacological agent is an opioid antagonist. Opioid antagonists include peripheral mu opioid antagonists. Examples of peripheral mu opioid antagonists include quaternary derivatives of noroxymorphone (See Goldberg et al, US Patent No. 4,176,186, and Cantrell et al WO 2004/043964), piperidine N-alkylcarboxylates such as described in U.S. patents 5,250,542; 5,434,171; 5,159,081; 5,270,328; and 6,469,030, opium alkaloid derivatives such as described in U.S. patents 4,730,048; 4,806,556; and 6,469,030, quaternary benzomorphan compounds such as described in U.S. patents 3,723,440 and 6,469,030.

[00034] In one embodiment of the invention, the axial N-oxide stereoisomer is combined with an anti-diarrheal agent that is loperamide, loperamide analogs, N-oxides of loperamide and analogs, metabolites and prodrugs thereof, diphenoxylate, cisapride,
antacids, aluminum hydroxide, magnesium aluminum silicate, magnesium carbonate, magnesium hydroxide, calcium carbonate, polycarbophil, simethicone, hyoscyamine, atropine, furazolidone, difenoxin, octreotide, lansoprazole, kaolin, pectin, activated charcoal, sulphaguanidine, succinylsulphathiazole, phthalylsulphathiazole, bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth tartrate, bismuth subsalicylate, bismuth subnitrate and bismuth sulfogallate, opium tincture (paregoric), herbal medicines, plant-derived anti-diarrheal agents or combinations thereof.

[00035] According to another embodiment, a method is provided for stereoselective synthesis of a 3-O-protected axial N-oxide-4,5-epoxy-morphinanum salt comprising methylating a 3-O-protected-appropriate morphinan compounds with a methylating agent to yield the desired 3-(9-protected-(R)-group. The hydroxyl protecting group of the 3-O-protected group in certain embodiments is isobutryl, 2-methyl butyryl, tert-butyl carbonyl, silyl ethers, 2-tetrahydropyranyl ethers, and alkyl carbonates. The 3-O-protected compound may be a salt with an anion that can be, for example, a halide, sulfate, phosphate, nitrate or an organic anionic-charged species. The halide may be bromide, iodide, chloride, or fluoride. The organic anionic-charged species can be, for example, a sulfonate or carboxylate. Exemplary sulfonates are mesylate, besylate, tosylate, or triflate. Exemplary carboxylates are formate, acetate, citrate, or fumarate. The method can further involve exchanging the anion with a different anion. The alkylating agent can be an alkyl group susceptible to nucleophilic attack, and a leaving group. Exemplary methylating agents may be selected from the group consisting of methyl halide, dimethyl sulfate, methyl nitrate and methyl sulfonate. Methyl halides are methyl iodide, methyl bromide, methyl chloride and methyl fluoride. Methyl sulfonates include methyl mesylate, methyl besylate, methyl tosylate, and methyl triflate. In one embodiment, the alkylation is conducted at a temperature range from about >70°C to about 100°C, or from 80°C to about 90°C, or at about 88°C. The alkylation reaction may be conducted for a significant period of time, for example, about 1 hour to 24 hours, or about 5 hour to 16 hours or for about 10 hours. The method can further involve purification of the 3-O-protected axial N-oxide-4,5-epoxy-morphinanum salt using at least one purification technique, such as chromatography or recrystallization. The chromatography can be reverse-phase chromatography or regular phase chromatography.
In some embodiments, the regular phase chromatography can use alumina or silica gel. The 3-O-protected-intermediate can be purified prior to alkylation.

[00036] According to another aspect of the invention a method for isolation and purification of axial N-oxide-4,5-epoxy-morphinaniums is provided, comprising passing the crude N-oxide-4,5-epoxy-morphinanum through a chromatography column and collecting the axial N-oxide-4,5-epoxy-morphinanum which elutes at the axial N-oxide-4,5-epoxy-morphinanum retention time. This process can be in addition to the method described above, after the deprotecting step and/or the anion exchange resin column step. Equatorial N-oxide-4,5-epoxy-morphinanum may also be isolated by similar methods.

[00037] According to another aspect of the invention a method for analyzing axial N-oxide-4,5-epoxy-morphinanum in a mixture of axial N-oxide-4,5-epoxy-morphinanums and equatorial N-oxide stereoisomers is provided. The method involves conducting high performance liquid chromatography (HPLC) and applying axial N-oxide-4,5-epoxy-morphinanum to the chromatography column as a standard. The method more preferably involves applying both axial N-oxide stereoisomers and equatorial N-oxide-4,5-epoxy-morphinanums as standards to determine relative retention/elution times.

[00038] The foregoing HPLC can be used to determine the relative amount of axial N-oxide-4,5-epoxy-morphinanum, and its equatorial stereoisomer, and the intermediates of the synthesis thereof, by determining the area under the respective curves in the chromatogram produced. According to another aspect of the invention a method for isolation and purification of as axial N-oxide-4,5-epoxy-morphinanum and the 3-O-protected axial N-oxide-4,5-epoxy-morphinanum salt intermediate is provided, comprising recrystallizing the crude axial N-oxide-4,5-epoxy-morphinanum, or intermediates thereof, from a solvent or a mixture of solvents. This process can be in addition to the method described above, after the deprotection step and/or the anion exchange resin column step.

[00039] The pharmaceutical preparations of the invention can take on a variety of forms, including, but not limited to a composition that is enteric coated, a composition that is a immediate release, a controlled release or sustained release
formulation, a composition that is a solution, a composition that is a topical formulation, a composition that is a suppository, a composition that is lyophilized, a composition that is in an inhaler, a composition that is in a nasal spray device, and the like. The composition can be for oral administration, parenteral administration, mucosal administration, nasal administration, topical administration, ocular administration, local administration, etc. If parenteral, the administration can be subcutaneous, intravenous, intradermal, intraperitoneal, intrathecal, etc. The pharmaceutical preparation may be in a packaged unit dosage or multi-unit dosage.

[00040] According to one aspect of the invention a pharmaceutical composition is provided that comprises an axial N-oxide-4,5-epoxy-morphinanium free of its equatorial N-oxide stereoisomer counterpart, as detectable by the chromatography procedures described herein, or comprises the 3-O-protected axial N-oxide-4,5-epoxy-morphinanium intermediate free of its stereoisomer counterpart, and a pharmaceutically acceptable carrier.

[00041] Certain embodiments entail purification of the salt of the axial N-oxide-4,5-epoxy-morphinanium by chromatography, recrystallization, or a combination thereof. In one embodiment, the purification is by multiple recrystallizations.

[00042] According to yet another aspect of the invention, a pharmaceutical preparation containing an axial N-oxide-4,5-epoxy-morphinanium, or the 3-O-protected analog intermediate, in a lyophilized formulation is prepared by combining a cryoprotective agent, such as mannitol, with the same. The lyophilized preparation may also contain any one of, any combination of, or all of a buffering agent, an antioxidant, and an isotonicity agent. In one embodiment the aforementioned pharmaceutical composition can further comprise one pharmaceutical and/or pharmacologic agent that is not an opioid antagonist. In one embodiment of the invention the aforementioned pharmaceutical composition can comprise a pharmaceutical and/or pharmacologic agent that is an opioid. In yet another embodiment, the pharmaceutical composition can further comprise at least one opioid, and at least one pharmaceutical and/or pharmacologic agent that is not an opioid or an opioid antagonist. In one embodiment the pharmaceutical and/or pharmacologic agent that is not an opioid or an opioid antagonist is a non-opioid/antipyretic, an antiviral agent, an anti-infective agent, an anticancer agent, an
antispasmodic agent, an anti-muscarinic agent, a steroidal or non-steroidal anti-inflammatory agent, a pro-motility agent, a 5HT₁ agonist, a 5HT₂ 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-diarrheal medication, a laxative, a stool softener, a fiber or a hematopoietic stimulating agent. In one embodiment the opioid is oxycodone and the non-opioid analgesic/antipyretic is acetaminophen.

[00043] The pharmaceutical compositions of the invention can be provided in kits. The kits may be a package containing a sealed container comprising the pharmaceutical preparations of the present invention and instructions for use. The kits may contain an axial N-oxide-4,5-epoxy-morphinanium that is free of HPLC detectable equatorial counterpart stereoisomer. The kit may further include an opioid or opioid agonist, or it can include at least one pharmaceutical and/or pharmacologic agent that is not an opioid or an opioid antagonist. In one embodiment, the kit is a package containing a sealed container comprising the pharmaceutical preparation that is or the 3-O-protected axial N-oxide-4,5-epoxy-morphinanium salt and instructions for use.

[00044] According to another aspect of the invention, methods are provided for ensuring the manufacture of axial N-oxide-4,5-epoxy-morphinanions of the present disclosure (which are opioid antagonists) that is free of their O-equatorial N-oxide stereoisomer stereoisomers (which are opioid agonists). The methods permit for the first time the assurance that a pharmaceutical preparation of an axial N-oxide-4,5-epoxy-morphinanium which is intended for antagonist activity, is not contaminated with a compound that opposes or dilutes its activity. This is particularly desirable when the axial N-oxide-4,5-epoxy-morphinanium is administered to oppose the side effects of opioid therapy.

[00045] In an embodiment, a method is provided for manufacturing an axial N-oxide-4,5-epoxy-morphinanium stereoisomer. The method entails: (a) obtaining a first composition containing an axial N-oxide-4,5-epoxy-morphinanium, (b) purifying the first composition by chromatography, recrystallization or a combination thereof, (c) conducting HPLC on a sample of purified first composition using the equatorial N-oxide stereoisomer counterpart as a standard, and (d) determining the presence or absence of the equatorial
N-oxide stereoisomer in the sample. In one embodiment, both the axial N-oxide-4,5-epoxy-morphinanium and its counterpart equatorial stereoisomer are used as standards, to determine for example relative retention time of the axial N-oxide-4,5-epoxy-morphinanium and equatorial N-oxide stereoisomer. In one embodiment, the purification involves multiple recrystallization steps or multiple chromatography steps. In another embodiment, the purifying is carried out until equatorial N-oxide stereoisomer is absent from the sample as determined by HPLC. It should be understood, however, that the purified first composition in some aspects of the invention is not necessarily free of detectable equatorial N-oxide stereoisomer. The presence of such equatorial N-oxide stereoisomer, for example, might indicate that further purification steps should be conducted if a purer axial N-oxide-4,5-epoxy-morphinanium is desired.

[00046] The methods can further involve packaging purified first composition that is free of HPLC detectable equatorial N-oxide stereoisomer. The methods further can include providing indicia on or within the package, purified first composition indicating that the packaged, purified first composition is free of the HPLC detectable equatorial N-oxide stereoisomer. The method further can involve packaging a pharmaceutically effective amount for treating anyone of the conditions described herein.

[00047] According to one aspect of the invention, the purification is carried out until 0-equatorial N-oxide stereoisomer is less than 0.4%, 0.3%, 0.2%, 0.15%, 0.1%, 0.05%, even is absent from the purified first composition as determined by HPLC with a detection limit of 0.02 and a quantitation limit of 0.05%. In one embodiment the method provides indicia on or with the packaged purified first composition indicating a level of equatorial N-oxide stereoisomers in the packaged first purified composition.

[00048] According to one aspect of the invention a package is provided that contains a composition comprising an axial N-oxide-4,5-epoxy-morphinanium and indicia on or contained within the package indicating a level of counterpart equatorial N-oxide stereoisomer in the composition. In one embodiment the level of equatorial N-oxide stereoisomer is less than 0.4%, 0.3%, 0.2%, 0.15%, 0.1%, 0.05%, or is absent from the sample. In yet another embodiment, the package further contains, mixed together with the axial N-oxide-4,5-epoxy-morphinanium, one or more of a buffering agent, a chelating
agent, a preserving agent, a cryoprotecting agent, an absorption enhancer, a lubricating agent, a preservative, an anti-oxidant, or a binding agent.

[00049] According to one aspect of the invention a method of preparing a pharmaceutical product in provided, by selecting a composition of axial N-oxide-4,5-epoxy-morphinanium because it contains equatorial N-oxide stereoisomer at a level that is less than 0.4%, 0.3%, 0.2%, 0.15%, 0.1%, 0.05%, or is absent from the composition, and formulating the composition into a unit or multi unit dosage for administration to a patient.

[00050] According to another aspect of the invention, a packaged product is provided. The package contains a composition comprising an axial N-oxide-4,5-epoxy-morphinanium, wherein the composition is free of HPLC detectable equatorial N-oxide stereoisomer counterpart stereoisomer, and indicia on or contained within the package indicating that the composition is free of the HPLC detectable equatorial N-oxide stereoisomer. The composition can take on a variety of forms, including, but not limited to, a standard for use in laboratory experiments, a standard for use in manufacturing protocols, or a pharmaceutical composition. If the composition is a pharmaceutical composition, then one important form of indicia is writing on a label or package insert describing the characteristics of the pharmaceutical preparation. The indicia can indicate directly that the composition is free of an equatorial N-oxide stereoisomer, or it can indicate the same indirectly, by stating for example that the composition is pure or 100% of a particular axial N-oxide-4,5-epoxy-morphinanium. The pharmaceutical composition can be for treating any of the conditions described herein. The pharmaceutical composition can contain an effective amount of the pure axial N-oxide-4,5-epoxy-morphinanium and can take any of the forms described below as if specifically recited in this summary, including, but not limited to, solutions, solids, semi-solids, enteric coated materials and the like.

[00051] According to an embodiment, a method is provided for treating or preventing opioid-induced side effects comprising administering to a patient a physiological concentration of axial N-oxide-4,5-epoxy-morphinanium of the present invention free of detectable equatorial stereoisomer by the chromatography procedures described herein, or the 3-0-protected axial N-oxide-4,5-epoxy-morphinanium salt, in an
amount effective to prevent or treat the opioid-induced side effect. At physiological concentrations, axial N-oxide-4,5-epoxy-morphinaniums of the present disclosure have been found to have opioid antagonist activity, in particular mu-opioid antagonist activity, with low, little, if any, agonist activity.

[00052] In one embodiment of the invention, the patient is chronically administered opioids. In another embodiment the patient is acutely administered opioids. The opioid-induced side effect is preferably selected from a group consisting of constipation, immune suppression, inhibition of gastrointestinal motility, inhibition of gastric emptying, nausea, emesis, incomplete evacuation, bloating, abdominal distension, increased gastroesophageal reflux, hypotension, bradycardia, gastrointestinal dysfunction, pruritus, dysphoria, and urinary retention. In one embodiment the opioid-induced side effect is constipation. In another embodiment the opioid-induced side effect is inhibition of gastrointestinal motility or inhibition of gastric emptying. In yet another embodiment the opioid-induced side effect is nausea or emesis. In yet another embodiment the opioid-induced side effect is pruritus. In yet another embodiment the opioid-induced side effect is dysphoria. In yet another embodiment the opioid-induced side effect is urinary retention.

[00053] According to one embodiment, a method is provided for treating a patient receiving an opioid for pain resulting from surgery comprising administering to the patient an axial N-oxide-4,5-epoxy-morphinanium (or the 3-O-protected axial N-oxide-4,5-epoxy-morphinanium salt intermediate) composition free or substantially free of its detectable equatorial N-oxide stereoisomer by the chromatography procedures described herein in an amount effective to promote gastrointestinal motility, gastric emptying or relief of constipation.

[00054] According to another aspect of the invention, a method is provided for inducing taxation in a patient in need of taxation, comprising administering to the patient an axial N-oxide-4,5-epoxy-morphinanium, or the 3-O-protected intermediate, free of detectable equatorial counterpart stereoisomer by the chromatography procedures described herein in an effective amount.
[00055] According to yet another aspect of the invention, a method is provided for preventing and/or treating impaction in a patient in need of such prevention/treatment, comprising administering to the patient an axial N-oxide-4,5-epoxy-morphinanum, e.g., an axial N-oxide-7,8-saturated-4,5-epoxy-morphinanum (or the 3-O-protected-O-axial N-oxide-4,5-epoxy-morphinanum intermediate) composition of the present disclosure free of detectable counterpart equatorial N-oxide stereoisomer by the chromatography procedures described herein or in an effective amount.

[00056] According to yet another aspect of the invention, a method is provided for preventing and/or treating post-operative bowel dysfunction following surgery, in particular abdominal surgery in a patient in need of such prevention/treatment, comprising administering to the patient an O-axial N-oxide-4,5-epoxy-morphinanum composition (or the 3-O-protected axial N-oxide-4,5-epoxy-morphinanum intermediate) of the present disclosure free of it equatorial N-oxide stereoisomeric counterpart as detectable by the chromatography procedures described herein in an effective amount.

[00057] According to one aspect of the invention, a method is provided for treating or preventing endogenous opioid-induced dysfunction comprising administering to the patient an axial N-oxide-4,5-epoxy-morphinanum of the disclosure, or the 3-O-protected axial N-oxide-4,5-epoxy-morphinanum intermediate thereof, free of its equatorial N-oxide stereoisomer, as judged by detection by the chromatography procedures described herein, in an amount effective to treat the endogenous opioid-induced dysfunction. The dysfunction can be selected from the group consisting of gastrointestinal dysfunction, obesity, hypertension, and addiction. The gastrointestinal dysfunction can be selected from a group consisting of inhibition of gastrointestinal motility, constipation and ileus. In some embodiments of the invention the ileus is selected from the group comprising of: post-operative ileus, post-partum ileus, paralytic ileus.

[00058] According to one aspect of the invention, a method is provided for preventing or treating idiopathic constipation comprising administering to the patient an axial N-oxide-4,5-epoxy-morphinanums composition free of detectable equatorial N-oxide stereoisomers by the chromatography procedures described herein or the 3-O-
protected axial N-oxide-4,5-epoxy-morphinanums intermediate in an amount effective to prevent or treat the idiopathic constipation.

[00059] According to yet another aspect of the invention, a method is provided for treating irritable bowel syndrome comprising administering to the patient an axial N-oxide-4,5-epoxy-morphinanium composition (or the 3-O-protected equatorial N-oxide-4,5-epoxy-morphinanium salt intermediate thereof) free of detectable equatorial N-oxide stereoisomer by the chromatography procedures described herein in an amount effective to ameliorate at least one symptom of the irritable bowel syndrome. In some embodiments of the invention the axial N-oxide-4,5-epoxy-morphinanium composition, or the 3-O-protected axial N-oxide-4,5-epoxy-morphinanium composition, further comprises at least one irritable bowel syndrome therapeutic agent. The irritable bowel syndrome therapeutic agent can be selected from the groups consisting of antispasmodics, antimuscarinics, anti-inflammatory agents, pro-motility agents, 5HT1 agonists, 5HT3 antagonists, 5HT4 antagonists, 5HT3 agonists, bile salt sequestering agents, bulk-forming agents, alpha2-adrenergic agonists, mineral oils, antidepressants, herbal medicines, anti-diarrheal medication and combinations thereof.

[00060] According to one aspect of the invention methods are provided for parenteral administration of the compounds and compositions of the invention including but not limited to intravenous, intramuscular and subcutaneous administration. In one embodiment of the invention the compounds of the invention are in pharmaceutical preparations suitable for use in pre-filled syringes, pre-filled pen injectors, cartridges for use in pen injectors, reusable syringes or other medical injectors, liquid dry injectors, needleless pen systems, syrettes, autoinjectors, or other patient-controlled injection devices. These and other aspects of the invention are described in greater detail herein.

[00061] According to one aspect of the invention, a method is provided for treating obesity comprising administering to the patient an axial N-oxide-4,5-epoxy-morphinanium composition (or the 3-O-protected equatorial N-oxide-4,5-epoxy-morphinanium salt intermediate thereof) free of detectable equatorial N-oxide stereoisomer by the chromatography procedures described herein in an amount effective to ameliorate obesity. In some embodiments of the invention the axial N-oxide-4,5-epoxy-morphinanium composition, or the 3-O-protected axial N-oxide-4,5-epoxy-morphinanium
composition, further comprises at least one weight-management drug, such as anti-obesity drugs. An anti-obesity drug includes, without limitation, orlistat, sibutramine, metformin, byetta, symlin, rimonabant, pyruvate, and phenylpropanolamine.

[00062] Compounds of the present invention may also find use in attenuating endothelial cell proliferation (e.g., vascular endothelial cells), treating or preventing unwanted angiogenesis (particularly in cancer compromised individuals, and in diabetes, sickle cell anemia, vascular wound, unwanted ocular neovascularization, proliferative retinopathy), inhibition of VEGF activity in endothelial cells, inhibiting Rho A and activation in endothelial cells, treating or preventing an increase in lethal factor production from opportunistic infections agents (e.g. *Pseudomonas* aeroginosa), treatment of acute or chronic pain, treatment of inflammatory conditions such as arthritis, treatment of infectious diseases, and treatment of obesity, when administered alone and/or in combination with other drugs (including, without limitation, methylnaltrexone and other opioid compounds). The compounds may also find use in improving wound healing. Such compounds, further, may be used to reduce opioid side-effects as set forth above, including (without limitation) dysphoria, pruritis, urinary retention, nausea, emesis, opioid-induced immune suppression.

**BRIEF DESCRIPTION OF THE FIGURE**

[00063] Figure 1 shows the competition curve obtained with an exemplary compound, C0021 (0-5720), obtained at the human mu receptor as a function of concentration.

**DETAILED DESCRIPTION OF THE INVENTION**

[00064] The invention provides for axially configured N-oxide-4,5-epoxy-morphinanium analog compounds, synthetic routes for stereoselective synthesis of axial N-oxide-4,5-epoxy-morphinanium compounds, substantially pure axial N-oxide-4,5-epoxy-morphinanium compounds, crystals of substantially pure axial N-oxide-4,5-epoxy-morphinanium compounds, methods of analysis of axial N-oxide-4,5-epoxy-morphinanium compounds, pharmaceutical preparations containing substantially pure axial N-oxide-4,5-epoxy-morphinanium compounds, and methods for their use. It also
provides for the equatorial stereoisomeric counterparts. Also included are oxazolidine compounds.

[00065] Exemplary embodiments of axial configured N-oxide-4,5-epoxy-morphinanium analogs are set forth in the Summary section above.

[00066] 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 example of an "acylamino" radical is acetylamine (CH$_3$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).

[00067] 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.

[00068] 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 alkyene" herein refers to those alkylene 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, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, 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 alkycarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

"Alkenylene", in general, refers to an alkylene group containing at least one carbon—carbon double bond. Exemplary alkenylene groups include, for example, ethenylene (-CH=CH-) and propenylene (-CH=CHCH₂-). Preferred alkenylene groups have from 2 to about 4 carbons.

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 dialkoxyalkyl 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 trifluoromethoxy.

"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 alkycycloalkyl 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, 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, diarylamine, and alkylarylaminio), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkythio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sulfonato, 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 phenethyl 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.

[00072] 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 cyclopentylmethyl iodide.

[00073] The term "alkylsilyl" denotes a silyl radical substituted with an alkyl group. The term "alkylsilyloxy" denotes a silyloxy radical (-O-Si-) substituted with an alkyl group. An example of an "alkylsilyloxy" radical is $-$O$-$Si-t-BuMe$_2$.

[00074] The term "alkylsulfenyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-$S(=O)$-$ atom. The term "arylsulfenyl" embraces aryl radicals attached to a divalent $-$S(=O)$-$ atom (e.g., $-$S=OAr).

[00075] The term "alkythio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. The term "arylsulfenyl" embraces aryl radicals attached to a divalent sulfur atom (-SAr) An example of "alkythio" is methylthio, (CH$_3$ $-$ (S)$-$).

[00076] 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 cycloalkenyl or cycloalkenyl substituted alkynyl groups.

[00077] 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.

[00078] 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 —C(=NH) —NH₂ radical. The term "cyanoamidino" denotes an -C(=N--CN)--NH₂ radical.

[00079] The term "aryl", alone or in combination, means a carbo cyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

[00080] "Aryl-substituted alkyl", in general, refers to an 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.

[00081] The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.
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, fluorenlyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Preferred "carbocycle" are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

"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 C₃-C₈ cycloalkyl group. Typical cycloalkyl-substituted alkyl groups include cyclohexylmethyl, cyclohexylethyl, cyclopentylethyl, cyclopentylpropyl, cyclopropylmethyl and the like.

"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 C₅-C₈ cycloalkenyl group, i.e., a cycloalkenyl group having from about 5 to about 8 carbons.

"Dipolar aprotic" solvents are protophilic solvents that cannot donate labile hydrogen atoms and that exhibit a permanent dipole moment. Examples include acetone, ethyl acetate, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF) and N-methylpyrrolidone.

"Dipolar protic" solvents are those that can donate labile hydrogen atoms and that exhibit a permanent dipole moment. Examples include water, alcohols such as 2-propanol, ethanol, methanol, carboxylic acids such as formic acid, acetic acid, and propionic acid.

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 0% by weight of the compound crosses the blood-brain barrier.
[00088] 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.

[00089] As used herein, the term "heterocycle" or "heterocyclic ring" is 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 morpholinyl.

[00090] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

[00091] The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (—CH₂—) radical.

[00092] 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.

[00093] As used herein, "N-oxide" refers to compounds wherein the basic nitrogen atom of either a heteroaromatic ring or tertiary amine is oxidized to give a quaternary nitrogen bearing a positive formal charge and an attached oxygen atom bearing a negative formal charge.
"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, acetone, hexane, ether, chloroform, acetic acid, acetonitrile, chloroform, cyclohexane, methanol, and toluene. Anhydrous organic solvents are included.

It should also be understood that when referring to compounds of the invention, it is meant to encompass hydrates, solvates, and polymorphs of the same. 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 know 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.
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 0% of the pharmacological activity of the compounds employed in the present methods is exhibited in the CNS.

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. Included as useful for the conditions discussed herein are the prodrugs, pharmaceutical acceptable salts, stereoisomers, hydrates, solvates, acid hydrates and N-oxides of the compounds of formula I, I(a), I(b), I(c), II and III. For example, prodrugs are known to enhance a number of desirable pharmaceutical qualities (e.g., solubility, bioavailability, manufacturing, etc.). Prodrugs of the compounds of formula I, I(a), I(b), I(c), II and III 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.

As used herein, "pharmacologically 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, "pharmacologically 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. 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, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, 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. 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.

[000102] 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.

[000103] 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.

[000104] The terms "sulfamyl" or "sulfonamidyl", whether alone or used with terms such as "N-alkylsulfamyl", "N-arylsulfamyl", "N,N-dialkylsulfamyl" and "N-alkyl-N-arylsulfamyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide (-SO₂ NH₂). The terms "N-alkylsulfamyl" and "N,N-dialkylsulfamyl"
denote sulfamyl radicals substituted, respectively, with one alkyl radical, a cycloalkyl ring, or two alkyl radicals. The terms "N-arylsulfamyl" and "N-alkyl-N-arylsulfamyl" denote sulfamyl radicals substituted, respectively, with one aryl radical, and one alkyl and one aryl radical.

[000105] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals --SO₂ --. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical.

[000106] "Tertiary amines" has its common, ordinary meaning. In general, the tertiary amines useful in the invention have the general formula:

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<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
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<td>N</td>
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wherein R₁, R₂, and R₃ are identical or a combination of different straight or branched chain alkyl groups, alkenyl groups, alkyne groups, alkenylene groups, cycloalkyl groups, cycloalkyl-substituted alkyl groups, cycloalkenyl groups, alkoxy groups, alkoxy-alkyl groups, acyl groups, aryl groups, aryl-substituted alkyl groups, and heterocyclic groups. Exemplary tertiary amines useful according to the invention are those where R₁-3 is an alkyl group of the formula (CₙH₂ₙ₊₁), n=1-4), or aralkyl group of the formula (C₆H₅(CH₂)ₙ-)[n=l-2]. Exemplary tertiary amines useful according to the invention also are cycloalkyl tertiary amines (e.g., N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine), pyridine and Proton Sponge® (N,N,N',N' -tetramethyl-1,8-naphthalene).

[000107] An O-axial N-oxide stereoisomer exhibits properties different from those of its corresponding O-equatorial N-oxide-4,5-epoxy-morphinanum and different properties from a mixture of both. Those properties may include mobility on chromatography columns, biological and functional activity, and crystal structure. It is believed that the in vivo clearance rate, the side-effect profile, and the like may also differ from one O-axial N-oxide-4,5-epoxy-morphinanum and mixtures of the O-axial N-oxide-4,5-epoxy-morphinanum and its counterpart O-equatorial N-oxide stereoisomer. Pure O-
equatorial N-oxide stereoisomers may behave as agonists of peripheral opioid receptors as, for example, inhibiting gastrointestinal transit or may have little or no opioid activity. As a consequence, O-equatorial N-oxide stereoisomer activity may interfere with or counter or lessen O-axial N-oxide stereoisomer activity in mixtures containing both O-axial N-oxide stereoisomers and O-equatorial N-oxide stereoisomers. It therefore is highly desirable to have axial N-oxide stereoisomers in isolated and substantially pure form.

[000108] In one aspect of the invention, methods for the synthesis of O-axial N-oxide-4,5-epoxy-morphinanum are provided. An O-axial N-oxide-4,5-epoxy-morphinanum may be produced at a purity of greater than or equal to 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 98.5%, 99%, and 99.5% area under the curve (AUC) based on chromatographic techniques. In an embodiment, the purity of an O-axial N-oxide-4,5-epoxy-morphinanum is 98% or greater. The amount of a corresponding O-equatorial N-oxide stereoisomer in the purified O-axial N-oxide-4,5-epoxy-morphinanum may be less than or equal to about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 3%, 2%, 1%, 0.5%, 0.3%, 0.2%, 0.1% (AUC) or undetectable by chromatographic techniques described herein. It will be appreciated by the skilled artisan that the detection of the methods will depend upon the detection and quantitation limits of the employed technique. Quantitation Limit is the lowest amount of O-axial N-oxide-4,5-epoxy-morphinanum that can be consistently measured and reported, regardless of variations in laboratories, analysts, instruments or reagent lots. Detection Limit is the lowest amount of O-equatorial N-oxide stereoisomer in a sample which can be detected but not necessarily quantitated as an exact value. In one embodiment of the invention the detection limit is 0.1% and the quantitation limit is 0.2%. In yet another embodiment the detection limit is 0.02% and the quantitation limit is 0.05%.

[000109] Purification and isolation may be done using methods known to those skilled in the art, such as by using separation techniques like chromatography, recrystallization, or combinations of various separation techniques as are known the art. In one embodiment, flash chromatography using a C18 column may be used. For example, a CombiFlash™ Sq 16x from ISCO using a Reverse Phase (C18) RediSep column may be used. Analytic HPLC may be performed, for example, on a Phenomenex Prodigy 5 urn OD53 IOOA column and purification performed on a semi-prep
Phenomenex Prodigy 5 µm OD53 10OA column. Different solvents, such as aqueous methanol solvent modified with 0.2 % HBr, may be employed with methanol content varying from, for example, about 2.5 % to about 50%. The O-axial N-oxide-4,5-epoxy-morphinanum may be purified using recrystallization. The process may be repeated until desired purity of product is obtained. In one embodiment, the axial-O N-oxide-4,5-epoxy-morphinanum is recrystallized at least two times, three times, or four or more times to achieve the desired level of purity. For example, an O-axial N-oxide-4,5-epoxy-morphinanum may be obtained at purities of greater than or equal to 50 %, 80 %, 85 %, 90 %, 95 %, 97 %, 98 %, 98.5 %, 99.8% (AUC) based on chromatographic techniques. Any impurities may include the starting material, with no detectable axial N-oxide stereoisomer. Recrystallization may be achieved using a single solvent, or a combination of solvents. In one embodiment, recrystallization is achieved by dissolving O-axial N-oxide-4,5-epoxy-morphinanum in a polar solvent, and then adding a less polar cosolvent. In another recrystallization embodiment, O-axial N-oxide-4,5-epoxy-morphinanum is purified by recrystallization from a solvent. The recrystallization is repeated to achieve desired purity. In one embodiment, the recrystallization solvent may be an organic solvent or a mixture of organic solvents or a mixture of organic solvent(s) plus water. The solvent may be an alcohol, such as a low molecular weight alcohol, e.g., methanol.

[000110] The O-axial and O-equatorial N-oxide-4,5-epoxy-morphinanumns of the present invention, and their derivatives, may be produced in the salt form. Derivatives such as zwitterions are included. The O-axial and O-equatorial N-oxide-4,5-epoxy-morphinanum may include a positively charged quaternary ammonium group and may be paired with a counterion such as a monovalent or multivalent anion. These anions may include, for example, halides, sulfates, phosphates, nitrates and charged organic species such as sulfonates and carboxylates. Preferred anions include halides such as bromide, chloride, iodide, fluoride, and combinations thereof. In some embodiments, bromide is most preferred. Specific anions may be chosen based on factors such as, for example, reactivity, solubility, stability, activity, cost, availability and toxicity.

[000111] Counterions of an O-axial or O-equatorial N-oxide-4,5-epoxy-morphinanumina salt can be exchanged for alternative counterions. When an alternative counterion is desired, an aqueous solution of the N-oxide-4,5-epoxy-morphinanum salt can be passed over an anion exchange resin column to exchange some or all of the
counterion of the salt for a preferred alternative counterion. Examples of anion exchange resins include AG 1-X8 in a 100 to 200 mesh grade, available from Bio-Rad. In another embodiment, the N-oxide-4,5-epoxy-morphinanium cation can be retained on a cation exchange resin and can then be exchanged by removing the N-oxide-4,5-epoxy-morphinanium from the resin with a salt solution that includes a preferred anion, such as bromide or chloride, forming the desired N-oxide salt in solution.

[000112] The O-axial N-oxide-4,5-epoxy-morphinaniums of the present invention have numerous utilities. One aspect of the invention is an O-axial N-oxide-4,5-epoxy-morphinanium as a chromatographic standard in identifying and distinguishing its counterpart O-equatorial N-oxide stereoisomer from other components in a sample in a chromatographic separation. Another aspect of the invention is the use of an O-axial N-oxide-4,5-epoxy-morphinanium as a chromatographic standard in identifying and distinguishing an O-axial N-oxide-4,5-epoxy-morphinanium in a mixture containing an O-axial N-oxide-4,5-epoxy-morphinanium and O-equatorial N-oxide stereoisomer counterpart. An isolated O-axial N-oxide-4,5-epoxy-morphinanium is also useful in the development of protocols for purifying and distinguishing an O-axial N-oxide-4,5-epoxy-morphinanium from an O-equatorial N-oxide stereoisomer in reaction mixtures.

[000113] The O-axial N-oxide-4,5-epoxy-morphinanium may be provided in kit form with instruction for its use as a standard. The kit may further comprise an authentic O-equatorial N-oxide stereoisomer as a standard. The O-axial N-oxide-4,5-epoxy-morphinanium for use as a standard preferably has a purity of 99.8% or greater with no detectable stereoisomeric O-equatorial N-oxide stereoisomer.

[000114] One embodiment of the invention is a method of resolving and identifying an O-axial N-oxide-4,5-epoxy-morphinanium and a counterpart O-equatorial N-oxide stereoisomer in a solution of N-oxide-4,5-epoxy-morphinanium. The O-axial N-oxide-4,5-epoxy-morphinanium also is useful in HPLC assay methods of quantifying an amount of an O-axial N-oxide-4,5-epoxy-morphinanium in a composition or mixture in which the method comprises applying a sample of the composition or mixture to a chromatography column, resolving the components of the composition or mixture, and calculating the amount of an O-axial N-oxide-4,5-epoxy-morphinanium in the sample by comparing the percentage of a resolved component in the sample with the percentage of a
standard concentration of an O-axial N-oxide-4,5-epoxy-morphinanium. The method is particularly useful in reverse phase HPLC chromatography. The O-axial N-oxide-4,5-epoxy-morphinanium of the present invention by virtue of its counterpart activity on opioid receptors, is useful as a standard of antagonist activity in in vitro and in vivo opioid receptor assays such as those described herein.

[000115] An O-axial N-oxide-4,5-epoxy-morphinanium can be used to regulate a condition mediated by one or more opioid receptors, prophylactically or therapeutically. Of particular interest are O-axial-N-oxide-4,5-epoxy-morphinans that antagonize peripheral opioid receptors, in particular peripheral mu opioid receptors. The subjects being administered an O-axial N-oxide-4,5-epoxy-morphinanium may receive treatment acutely, chronically or on an as needed basis.

[000111] The subjects to which the O-axial N-oxide-4,5-epoxy-morphinanium 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.

[000116] 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 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. In the case of constipation, an effective amount, for example, is that amount which relieves a symptom of constipation, which induces a bowel movement, which increases the frequency of bowel movements, or which decreases oral-cecal transit time.

[000117] 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). In other words, a patient is not constipated (i.e., has "regular bowel movements" as used herein) if the patient has at least one bowel movement every three days and at least three bowel movements per week. Accordingly, at least one bowel
movement every two days would be considered regular bowel movements. Likewise, at least one bowel movement per day is a regular bowel movement. Effective amounts therefore can be those amounts necessary to treat, establish or maintain regular bowel movements.

[000118] In certain instances, the amount is sufficient to induce a bowel movement within 24 hours of administration of the O-axial N-oxide-4,5-epoxy-morphinanum, or the O-axial N-oxide-4,5-epoxy-morphinanum intermediate, or 3-O-protected O-axial N-oxide-4,5-epoxy-morphinanum 12 hours, 10 hours, 8 hours, 6 hours, 4 hours, 2 hours, 1 hour and even immediately upon administration, depending upon the mode of administration. Intravenous administration may in the appropriate dose produce an immediate effect of laxation in chronic opioid users. Subcutaneous administration may result in a bowel movement within hours of administration. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment and, especially, concurrent treatment with opioids where opioids are administered chronically; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation.

[000119] 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 al, Gastroenterology VoI 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 (eg., digital evacuation, support of the pelvic floor), f) fewer than 3 defecations per week.
The pharmaceutical preparations of the invention are administered in a therapeutically effective amount to treat or relieve at least one symptom of constipation, for example, the effective amount provides 3 or more defecations per week. 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.

Patients amenable to the therapy for opioid agonist induced constipation of the present invention include but are not limited to terminally ill patients, patients with advanced medical illness, cancer patients, AIDS patients, post-operative patients, patients with acute pain, patients with chronic pain, patients with neuropathies, patients with rheumatoid arthritis, patients with osteoarthritis, patients with chronic back pain, patients with spinal cord injury, patients with chronic abdominal pain, patients with chronic pancreatic pain, patients with pelvic/perineal pain, patients with fibromyalgia, patients with chronic fatigue syndrome, patients infected with HCV, patients with irritable bowel syndrome, patients with migraine or tension headaches, patients with sickle cell anemia, patients on hemodialysis, and the like.

Patients amenable to the therapy of the present invention also include but are not limited to patients suffering from other dysfunctions caused by opioid agonists, and as well as dysfunctions caused by endogenous opioids, especially in post-operative settings. In certain embodiments, the O-axial N-oxide-4,5-epoxy-morphinanum, or intermediate thereof may be employed in an amount sufficient to accelerate discharge from hospital post-surgery, including abdominal surgeries such as rectal resection, colectomy, hernia repair, stomach, esophageal, duodenal, appendectomy, hysterectomy, or non-abdominal surgeries such as orthopedic, trauma injuries, thoracic or transplantation surgery. This treatment may be effective to shorten the length of the time in the hospital, or to shorten the time to a hospital discharge order written post-operatively, for example, by shortening the time to bowel sounds after surgery, or first flatus, to first taxation or to solid diet intake following surgery compared to an average group of patients who have not received the O-axial-N-oxide-4,5-epoxy-morphnan. An O-axial N-oxide-4,5-epoxy-
morphinanum of the present disclosure, or intermediate thereof, or prodrug thereof, may continue to be provided after the patient has ceased to receive opioid pain medications post-operatively.

[000123] 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.

[000124] The subjects can be treated with a combination of the O-axial N-oxide-4,5-epoxy-morphinanum, e.g., an O-axial N-oxide-7,8-saturated-4,5-epoxy-morphinanum, or the 3-O-protected O-axial N-oxide-4,5-epoxy-morphinanum, or prodrug thereof, and a laxative and/or a stool softener (and optionally, an opioid). In these circumstances, the O-axial N-oxide-4,5-epoxy-morphinanum or the intermediate thereof and the other therapeutic agent(s) may be administered close enough in time such that the subject experiences the effects of the various agents as desired, which typically is at the same time. In some embodiments the O-axial N-oxide-4,5-epoxy-morphinanum analogs, or the intermediate thereof, will be delivered first in time, in some embodiments second in time, and still in some embodiments at the same time. As discussed in greater detail herein, the invention contemplates pharmaceutical preparations where the O-axial N-oxide-4,5-epoxy-morphinanums, or intermediate thereof, or prodrug thereof, is administered in a formulation including the O-axial N-oxide-4,5-epoxy-morphinanum or the intermediate thereof (or prodrug thereof) and one or both of a laxative and a stool softener (and, optionally, an opioid). These formulations may be parenteral or oral, such as the ones described in U.S. Serial No. 10/821,809. Included are solid, semisolid, liquid, controlled release, lyophilized and other such formulations.
In an embodiment, the administered amount of O-axial N-oxide-4,5-epoxy-morphinanium is sufficient to induce laxation. This has particular application where the subject is a chronic opioid user. Chronic opioid use as used herein includes daily opioid treatment for a week or more or intermittent opioid use for at least two weeks. It has been reported that patients receiving opioids chronically become tolerant to opioids and need increasing doses. Thus, a patient receiving oral doses of opioids chronically could be receiving between 40 and 100 mg per day or greater of a morphine-equivalent dose of opioid. Certain O-axial N-oxide-4,5-epoxy-morphinaniums may require a different dose, in patients that have become more tolerant to opioids and taken an increasing dose.

Patients using opioids chronically include late stage cancer patients, elderly patients with osteoarthritic changes, methadone maintenance patients, neuropathic pain and chronic back pain patients. Treatment of these patients 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.

The opioid can be any pharmaceutically acceptable opioid. Common opioids are those selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallophan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol. The opioid also may be mixed together with the equatorial N-oxide-4,5-epoxy-morphinanium or intermediate thereof having agonist activity and provided in any of the forms described above in connection with equatorial N-oxide-4,5-epoxy-morphinanium or intermediate thereof.

Dosage may be adjusted appropriately to achieve desired drug levels, local or systemic, depending on the mode of administration. For example, it is expected that the dosage for oral administration of the opioid antagonists in an enterically-coated formulation would be lower than in an immediate release oral formulation. 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.

[000129] 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, intradermal, 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.

[000130] 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.

[000131] 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, salicylic, p-toluensulfonic, tartaric, citric, methanesulfonic, formic, succinic, naphthalene-2-sulfonic, pamoic, 3-hydroxy-2-naphthalencarboxylic, and benzene sulfonic.

[000132] It should be understood that when referring to O-axial N-oxide-4,5-epoxy-morphinaninium and an O-equatorial N-oxide stereoisomer, and therapeutic agent(s) of the invention, it is meant to encompass salts of the same. Such salts 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.

[000133] 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.

[000134] Aqueous formulations may include a chelating agent, a buffering agent, an anti-oxidant and, optionally, an isotonicity agent, preferably pH adjusted, for example, to between 3.0 and 3.5. Examples of such formulations that are stable to autoclaving and long term storage are described in co-pending U.S. Application Serial No. 10/821,811, entitled "Pharmaceutical Formulation."
Chelating agents include, for example, ethylenediaminetetraacetic acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, sodium deoxycholate and derivatives thereof, and L-glutamic acid, N, N-diacetic acid and derivatives thereof. EDTA derivatives include dipotassium edetate, disodium edetate, calcium disodium edetate, sodium edetate, trisodium edetate, and potassium edetate.

Buffering agents include those selected from the group consisting of 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 include those selected from the group consisting of 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 sulfite. The preferred antioxidant is monothioglycerol.

Isotonicity agents include those selected from the group consisting of sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol.

Preservatives that can be used with the present compositions include 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. It 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 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 pill 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.

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).

[000144] 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.

[000145] 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.

[000146] 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.

[000147] 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.

[000148] 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.

[000149] 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).

[000150] 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.

[000151] 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).

[000152] 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.
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.

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.

Systems making use of the enterobacteria can be classified into those utilizing degradation of azaaromatic 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. Bau 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.

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/carer/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.

[000157] Suitable enteric coating materials include, but are not limited to: cellulosic 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, vinlylacetate 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.

[000158] A particular methacryliic 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 ACRYL-EZE™ (methacrylic acid co-polymer type C; Colorcon, West Point, PA).

[000159] 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.

[000160] 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 (Citroflec 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.

[000161] 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.

[000162] 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 trilmate, 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.

[000163] 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.

[000164] 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 methacrylic acid and esters thereof, containing at least 40% methacrylic 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 methoxy 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.

[000168] 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.

[000169] 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.

[000170] 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 hydroxy! 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.).

[000171] 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 \textregistered WITEP S O L, waxes such as lanolin and reduced lanolin; hydrocarbons such as \textregistered Vaseline, squalene, squalane and liquid paraffin; long \textregistered 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.

1000172J 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.

[000173] 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.

[000174] 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.

[000175] 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.

[000176] 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.
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.

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

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.

Various 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.
With respect to topical and/or local administration of the present compositions, desirable efficacy may involve, for example, penetration of therapeutic agent(s) of the invention into the skin and/or tissue to substantially reach a hyperalgesic site to provide desirable anti-hyperalgesic pain relief. The efficacy of the present compositions may be about the same as that achieved, for example, with central opiate analgesics. But, as discussed in detail herein, the efficacy achieved with therapeutic agent(s) of the invention is preferably obtained without the undesirable effects that are typically associated with central opiates including, for example, respiratory depression, sedation, and addiction, as it is believed that therapeutic agent(s) of the invention does not cross the blood brain barrier.

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.

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 isotonically buffered saline or are combined with a biocompatible support or bioadhesive intended for internal administration.

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
dimethylpolysiloxanes, 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 acetylated monoglycerides. (e) Ethoxylated glycerides, such as ethoxylated glyceryl monostearate. (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 isostearate, 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-octyl 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. (l) 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, polyethylene 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.sub.15 -C.sub.18 vicinal glycol and polyoxypropylene derivatives of trimethylolpropane. (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 glycercyl monostearate, 1,3-butyylene glycol monostearate, 1,3-butylen 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.

[000185] 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. 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.

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, such as loperamide, is dissolved, suspended or otherwise uniformly dispersed in the mixture.

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.

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. 5,116,868, 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.

To improve oral bioavailability of the compounds of the present invention, excipients may be used that increase intestinal membrane permeability (Aungst, BJ. J Pharmaceutical Science Vol. 89, Issue 4, pp. 429-442, 2000). 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, glycodeoxycholate, glycosursodeoxycholate, ethylenediaminetetraacetic acid, hydroxypropyl-beta-cyclodextrin, hydroxypropyl-gamma-cyclodextrin, gamma-cyclodextrin, tetradecyl-beta-D-maltose, octylglucoside, citric acid, glycyrrhetinic acid, and Tween-80® (Shah, R.B. et al J Pharm. Sci Apr 93(4): 1070-82, 2004).
[000195] The following are abbreviations familiar to one skilled in the art: DCM-dichloromethane; NMR-nuclear magnetic resonance; $^1$H NMR - proton NMR; $\delta$-chemical shift in parts per million from standard; J-splitting constant, measured in cycles per second (Hertz); MS-mass spectrometry; APCI-atmospheric chemical (+) ionization; (M+1)-parent mass + 1 atomic mass unit; HPLC-high performance liquid chromatography; UV-ultraviolet; THF-tetrahydrofuran; DMF-dimethylformamide; EtOAc-ethyl acetate; mCBA-m-chlorobenzoic acid; mCPBA-meta-chloroperoxybenzoic acid; K-selectride-1.0 M potassium tri-^ec-butylborohydride in tetrahydrofuran; Et$_2$O-diethyl ether; Bn-benzyl; BnBr-benzyl bromide; PMBBr-p-methoxy benzylbromide; Oxone®-potassium peroxymonsulfate; DMSO-dimethylsulfoxide; TFA-trifluoroacetic acid; TsCl-p-toluenesulfonyl chloride; LAH-lithium aluminum hydride; RT-room temperature; DAMGO- D-Ala$^2$N-Me-Phe$^4$,Gly$^5$-ol-enkephalin

**Example 1**

(S)-17-Cyclopropylmethyl-4,5 $\alpha$-epoxy-3,14-hydroxy-raorphinan-6-one N-oxide (COOOl) (Naltrexone N-oxide)

![Chemical Structure](image)  

Naltrexone  \( \rightarrow \) COOOl

**Synthetic Procedure.**

[000196] Naltrexone (160 mg, 0.47 mmol) was dissolved in dichloromethane (5 mL). 3-Chloroperbenzoic acid (104 mg, 77%, 0.47 mmol) was added. The resulting mixture was stirred at room temperature. TLC after 4 hours indicated complete disappearance of naltrexone. Dichloromethane (10 mL) was added. The solution was washed with saturated NaHCO$_3$, dried over Na$_2$SO$_4$ and filtered. The filtrate was evaporated. The solid crude product was purified by column (eluent: 3-8% MeOH in CHCl$_3$) to give COOOl (80 mg, 48%) as a white solid.
Example 2

(S)-17-Cyclopropylmethyl-4,5α-epoxy-morphinan-3,6α,14-triol N-oxide (C0003)
Compound COOO1 (126 mg, 0.353 mmol, prepared as described previously) was dissolved in a mixture of THF (10 mL) and MeOH (10 mL) and stirred at 0 °C. NaBH₄ (26 mg, 0.684 mmol) was added. The resulting solution was stirred for 1 h. Solvents were evaporated and the residue was purified by column (eluent: 5% Et₃N and 10 % MeOH in DCM) to give 100 mg of product, which was further purified by semi-prep HPLC to give C0003 44 mg, TFA salt, 26 %) as a white foam.

[000201] ¹H NMR (300 MHz, D₂O) δ ppm 6.78 (d, 1 H), 6.64 (d, J=8.3 Hz, 1 H), 4.81 (d, J=5.0 Hz, 1 H), 4.40 (d, J=5.2 Hz, 1 H), 4.15 - 4.26 (m, 1 H), 3.85 (dd, J=13.8, 6.9 Hz, 1 H), 3.60 - 3.73 (m, 1 H), 3.22 - 3.50 (m, 4 H), 2.63 - 2.83 (m, 1 H), 1.50 - 1.91 (m, 4 H), 1.15 - 1.37 (m, 2 H), 0.73 (d, J=8.3 Hz, 2 H), 0.34 - 0.58 (m, 2 H). HPLC purity: 100%. MS [M+H]: 360.2.

Example 4

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3’-phenyl) propyloxymorphinan-6-one N-oxide (C0004)
(i) 17-Cyclopropylmethyl-4,5α-epoxy-3-benzyloxy-14-cinnamyloxymorphinan-6-one dimethyl ketal (2)

[000202] Compound 1 (2.88 g, 6.04 mmol) was dissolved in anhydrous DMF (40 mL) and stirred under N₂. 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 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 (1.38 g, 39 %) as a yellow solid and 2a (0.76 g, 22%) as a yellow gum.
[000203] 2: $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.19 - 7.49 (m, 10 H), 6.72 (d, $J$=8.0 Hz, 1 H), 6.66 (d, $J$=16.0 Hz, 1 H), 6.50 (d, $J$=8.3 Hz, 1 H), 6.34 - 6.46 (m, 1 H), 5.16 - 5.36 (m, 2 H), 4.70 (s, 1 H), 4.33 - 4.43 (m, 1 H), 3.95 - 4.04 (m, 1 H), 3.49 (d, $J$=4.4 Hz, 1 H), 3.40 (s, 3 H), 3.11 (d, $J$=I7.6 Hz, 1 H), 2.99 (s, 3 H), 2.55 - 2.76 (m, 2 H), 2.27 - 2.45 (m, 3 H), 1.90 - 2.16 (m, 2 H), 1.63 - 1.75 (m, 2 H), 1.12 - 1.42 (m, 2 H), 0.82 - 0.96 (m, 1 H), 0.45 - 0.56 (m, 2 H), 0.08 - 0.20 (m, 2 H). MS [M+H]: 594.3.

[000204] 2α: $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.16 - 7.46 (m, 10 H), 6.70 (d, $J$=8.0 Hz, 1 H), 6.64 (d, $J$=16.0 Hz, 1 H), 6.52 (d, $J$=8.3 Hz, 1 H), 6.32 - 6.44 (m, 1 H), 5.13 - 5.25 (m, 2 H), 4.96 (d, $J$=I.1 Hz, 1 H), 4.58 (dd, $J$=6.6, 1.9 Hz, 1 H), 4.37 - 4.46 (m, 1 H), 4.32 - 4.37 (m, 1 H), 4.03 - 4.12 (m, 1 H), 3.60 (d, $J$=6.1 Hz, 1 H), 3.54 (s, 3 H), 3.14 (d, $J$=18.4 Hz, 1 H), 2.54 - 2.75 (m, 2 H), 2.39 - 2.50 (m, 2 H), 2.26 - 2.38 (m, 1 H), 2.12 - 2.25 (m, 1 H), 1.80 - 1.90 (m, 1 H), 1.49 - 1.57 (m, 1 H), 0.84 - 0.96 (m, 1 H), 0.49 - 0.57 (m, 2 H), 0.12 - 0.19 (m, 2 H). MS [M+H]: 562.3.

(i) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propyloxymorphinan-6-one dimethyl ketal (3)

[000205] Compound 2 (1.02 g, 1.72 mmol) was dissolved in EtOH (250 mL). Pd/C (0.49 g, 10%, wet, 0.455 mmol) was added. The resulting mixture was stirred at room temperature under a H$_2$ balloon. Mass spectrometry after 2.5 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 column (6% MeOH in DCM) to give 3 (674 mg, 78 %) as a yellow foam.

[000206] $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.13 - 7.39 (m, 5 H), 6.66 (d, $J$=8.0 Hz, 1 H), 6.49 (d, $J$=8.5 Hz, 1 H), 4.65 (s, 1 H), 4.62 - 4.76 (m, 1 H), 3.57 - 3.71 (m, 1 H), 3.39 (s, 3 H), 3.35 - 3.45 (m, 1 H), 3.20 - 3.32 (m, 1 H), 2.98 (s, 3 H), 2.93 - 3.12 (m, 2 H), 2.75 - 2.88 (m, 2 H), 2.55 - 2.74 (m, 2 H), 2.23 - 2.42 (m, 3 H), 1.82 - 2.17 (m, 4 H), 1.55 - 1.75 (m, 1 H), 1.26 - 1.40 (m, 1 H), 1.06 - 1.22 (m, 1 H), 0.67 - 0.83 (m, 1 H), 0.44 (d, $J$=7.7 Hz, 2 H), 0.01 - 0.17 (m, 2 H). MS [M+H]: 506.3.

(iii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propyloxymorphinan-6-one dimethyl ketal N-oxide (4)
To a solution of compound 3 (474 mg, 0.94 mmol) in DCM (20 mL) was added mCPBA (220 mg, 77%, 0.99 mmol). The resulting mixture was stirred at room temperature for 90 min. DCM was removed to give 4 (710 mg, 100%) as a yellow foam. 1H NMR showed this is a mixture of pure product and mCBA. This was used in the next reaction without purification.

1H NMR (300 MHz, CDCl₃) δ ppm 7.12 - 7.47 (m, 5 H), 6.76 (d, J=8.3 Hz, 1 H), 6.55 (d, J=8.3 Hz, 1 H), 5.31 (s, 1 H), 5.18 (br. s., 1 H), 4.66 (s, 1 H), 4.48 - 4.59 (m, 1 H), 4.06 - 4.17 (m, 1 H), 3.78 - 3.91 (m, 1 H), 3.36 (s, 3 H), 3.09 - 3.32 (m, 3 H), 2.99 (d, J=4.7 Hz, 1 H), 2.92 (s, 3 H), 2.64 - 2.85 (m, 3 H), 1.96 - 2.12 (m, 2 H), 1.46 - 1.86 (m, 5 H), 1.09 - 1.23 (m, 1 H), 0.68 - 0.84 (m, 2 H), 0.42 (d, J=5.0 Hz, 2 H). MS [M+H]: 522.3

(iv) (S)-17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14(3′ phenyl)propyloxy morphinan-6-one N-oxide (C0004)

Compound 4 (610 mg, 0.78 mmol, from the above reaction) was dissolved in a mixture of aqueous HCl (50 mL, 1 N) and Et₂O (40 mL) and stirred at room temperature. After 20 minutes MeOH (10 mL) was added to dissolve remaining solid. Stirring was continued for another hour. Et₂O layer was removed. The aqueous layer was washed with more Et₂O (50 mL) and then basified with NaHCO₃ (6 g). This basified solution was extracted with DCM (3X 30 mL). The DCM extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated and the brown solid residue was purified by column (eluent: 5-12% MeOH in DCM). The purified product was dissolved in a mixture of water (20 mL) and MeOH (20 mL). MeOH was removed by rotary evaporation. The cloudy aqueous solution was lyophilized to give C0004 (335 mg, 90%) as a white foam.

1H NMR (300 MHz, CDCl₃) δ ppm 7.09 - 7.25 (m, 5 H), 6.83 (d, J=8.0 Hz, 1 H), 6.54 (d, J=8.0 Hz, 1 H), 4.58 (s, 1 H), 4.14 - 4.34 (m, 2 H), 3.59 - 3.85 (m, 2 H), 3.15 - 3.48 (m, 3 H), 2.45 - 3.08 (m, 6 H), 1.95 - 2.23 (m, 5 H), 1.38 - 1.77 (m, 3 H), 0.55 - 0.81 (m, 2 H), 0.30 (d, J=2.5 Hz, 2 H). HPLC purity: 100%. MS [M+H]: 476.3.
Example 5

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-(3'-phenylpropyloxy) naorphinan-3,6 α-diol N-oxide (C0005).

[000211] Compound C0004 (106 mg, 0.22 mmol) was dissolved in anhydrous THF (20 mL) and stirred at 0 °C under N₂. K-selectride (1.1 mL, 1 N in THF, 1.1 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 4 h and at room temperature for 16 h. THF was removed and the residue was purified by column (eluent: 10 - 15 % MeOH in DCM). The purified product was dissolved in a mixture of MeOH (10 mL) and water (10 mL). MeOH was removed by rotary evaporation and the aqueous residue was lyophilized to give C0005 (54 mg, 51 %) as a white foam.

10002121 m.p.: 155-159 °C. 1H NMR (300 MHz, D₂O) δ ppm 7.16 - 7.39 (m, 5 H), 6.72 (d, J=8.0 Hz, 1 H), 6.58 (d, J=8.0 Hz, 1 H), 4.62 (d, J=5.2 Hz, 1 H), 4.21 (d, J=5.2 Hz, 1 H), 4.06 - 4.15 (m, 1 H), 3.62 - 3.83 (m, 2 H), 3.44 - 3.57 (m, 2 H), 3.35 (d, J=20.6 Hz, 1 H), 2.95 - 3.22 (m, 3 H), 2.56 - 2.80 (m, 3 H), 1.82 - 2.03 (m, 3 H), 1.49 - 1.63 (m, 2 H), 1.05 - 1.38 (m, 3 H), 0.59 - 0.74 (m, 2 H), 0.34 (d, J=4.7 Hz, 2 H). HPLC purity: 100%. MS [M+H]: 478.2.

Example 6

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-propyloxymorphinan-3,6 α-diol N-oxide hydrochloric acid salt (C0006)
(j) 17-Cyclopropylmethyl-4,5-α-epoxy-3-benzyloxy-14-allyloxymorphinan-6-one (2)

[000213] Compound 1 (297 mg, 0.574 mmol) was dissolved in THF (6 mL). Aqueous HCl (6 mL, 1 N) was added. The resulting solution was stirred at room temperature for 20 h. This was basified with aqueous Na₂CO₃ (25 mL, 2 M) and extracted with DCM (3X 30 mL). The DCM extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated to give 2 (250 mg, 92%) as a yellow foam. This crude product was used in the next reaction without purification.

[000214] ¹H NMR (300 MHz, D₂O) δ ppm 7.42 - 7.50 (m, 2 H), 7.29 - 7.40 (m, 3 H), 6.71 (d, J=8.3 Hz, 1 H), 6.55 (d, J=8.3 Hz, 1 H), 5.99 - 6.14 (m, 1 H), 5.26 (d, J=9.6 Hz, 2 H), 5.14 - 5.44 (m, 3 H), 4.71 (s, 1 H), 4.30 - 4.41 (m, 1 H), 3.93 (dd, J=1.18, 5.5 Hz, 1 H), 3.57 (d, J=5.0 Hz, 1 H), 3.14 (d, J=18.2 Hz, 1 H), 2.80 - 2.94 (m, 1 H), 2.66 - 2.79 (m, 2 H), 2.38 (d, J=6.6 Hz, 2 H), 2.28 - 2.41 (m, 1 H), 2.00 - 2.25 (m, 3 H), 1.41 - 1.57 (m, 3 H), 0.80 - 0.94 (m, 1 H), 0.48 - 0.60 (m, 2 H), 0.08 - 0.20 (m, 2 H). MS [M+H]: 472.3.

(ii) 17-Cyclopropylmethyl-4,5-α-epoxy-3-benzyloxy-14-allyloxy-6α-hydroxy morphinan

[000215] Compound 2 (250 mg, 0.531 mmol, from the above reaction) was dissolved in anhydrous THF (20 mL) and stirred at 0 °C under N₂. K-selectride (2.65 mL, 1 N in THF, 2.65 mmol) was added dropwise. The resulting solution was stirred for 4 h.
THF was removed and the residue was purified by column (eluent: 50 - 100 % EtOAc in hexanes) to give 3 (400 mg with solvents, 100 %) as a white foam.

**[000216]** $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.30 - 7.47 (m, 5 H), 6.77 (d, $J$=8.3 Hz, 1 H), 6.54 (d, $J$=8.3 Hz, 1 H), 5.88 - 6.05 (m, 1 H), 5.07 - 5.36 (m, 4 H), 4.69 (d, $J$=5.0 Hz, 1 H), 4.08 - 4.35 (m, 2 H), 3.80 - 3.94 (m, 1 H), 3.67 - 3.80 (m, 1 H), 3.45 (d, $J$=5.8 Hz, 1 H), 3.10 (d, $J$=18.4 Hz, 1 H), 2.49 - 2.69 (m, 1 H), 2.08 - 2.44 (m, 2 H), 2.02 (d, $J$=9.6 Hz, 1 H), 1.68 - 1.87 (m, 1 H), 1.27 - 1.64 (m, 3 H), 1.07 - 1.26 (m, 2 H), 0.70 - 1.07 (m, 2 H), 0.45 - 0.57 (m, 3 H), 0.12 (d, $J$=5.0 Hz, 2 H). MS [M+H]: 474.3.

(iii) 17-Cyclopropylmethyl-4,5 α-epoxy-3,6α-dihydroxy-14-propyloxy-morphinan (3)

**[000217]** Compound 3 (400 mg, 0.574 mmol, from the above reaction) was dissolved in MeOH (40 mL). Pd/C (140 mg, 10%, wet, 0.131 mmol) was added. The resulting mixture was stirred at room temperature under a H$_2$ balloon. Mass spectrometry after 95 min showed complete conversion of the starting material to the product. The reaction solution was filtered and the filtrate was evaporated. The yellow oily residue was purified by column (eluent: 5 - 10 % MeOH in DCM) to give 4 (160 mg, 72 %) as a white foam.

**[000218]** $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 6.70 (d, $J$=8.0 Hz, 1 H), 6.52 (d, $J$=8.3 Hz, 1 H), 5.73 (br. s., 1 H), 4.70 (d, $J$=4.1 Hz, 1 H), 4.28 - 4.44 (m, 1 H), 3.59 - 3.70 (m, 1 H), 3.43 (d, $J$=6.1 Hz, 1 H), 3.18 - 3.30 (m, 1 H), 3.09 (d, $J$=18.4 Hz, 1 H), 2.46 - 2.71 (m, 3 H), 2.10 - 2.43 (m, 4 H), 1.75 - 1.90 (m, 1 H), 1.52 - 1.70 (m, 4 H), 1.43 (dd, $J$=12.1, 2.5 Hz, 1 H), 0.96 (t, 3 H), 0.77 - 1.16 (m, 3 H), 0.51 (dd, $J$=8.0, 1.7 Hz, 1 H), 0.12 (d, $J$=4.7 Hz, 2 H). MS [M+H]: 386.3.

(iv) (S)-17-Cyclopropylmethyl-4,5α-epoxy-14-propyloxy-morphinan-3,6α-diol N-oxide trifluoroacetic acid salt (C0006)

**[000219]** To a solution of compound 4 (156 mg, 0.405 mmol) in DCM (10 mL) was added mCPBA (91 mg, 77 %, 0.405 mmol). The resulting mixture was stirred at room temperature for 30 min. DCM was evaporated and the residue was purified by column (eluent: 5 - 10 % MeOH in DCM). The purified product (120 mg yellowish foam) was dissolved in aqueous HCl (40 mL, 0.5 N) and washed with Et$_2$O (2X50 mL). After the
residual Et₂O was removed by rotary evaporation the aqueous solution was lyophilized to give C0006 (98.2 mg, HCl salt, 55%) as a tan solid.

[000220] ¹H NMR (300 MHz, D₂O) δ ppm 6.81 (d, 1 H), 6.66 (d, J=8.3 Hz, 1 H), 4.84 (d, J=5.2 Hz, 1 H), 4.72 (s, 1 H), 4.10 - 4.21 (m, 1 H), 3.92 (dd, J=13.8, 6.9 Hz, 1 H), 3.57 - 3.82 (m, 3 H), 3.17 - 3.54 (m, 4 H), 2.75 - 2.93 (m, 1 H), 2.05 - 2.19 (m, 1 H), 1.90 - 2.14 (m, 1 H), 1.87 (dd, J=15.1, 2.8 Hz, 1 H), 1.55 - 1.77 (m, 3 H), 1.21 - 1.45 (m, 3 H), 0.92 (t, J=7.4 Hz, 3 H), 0.69 - 0.82 (m, 2 H), 0.38 - 0.59 (m, 2 H). HPLC purity: 100%. MS [M+H]: 402.3.

Example 7

(5)-17-Cyclopropylmethyl-4,5 α-epoxy-3-carbamoyl-14-hydroxy-morphinan-6-one N-oxide hydrochloride (C0007)

(i) (5)-17-Cyclopropylmethyl-4,5 α-epoxy-3-carbamoyl-14-hydroxy-morphinan-6-one dimethyl ketal N-oxide (2)

[000221] To a solution of compound 1 (380 mg, 0.41 mmol) in DCM (20 mL) was added mCPBA (220 mg, 77 %, 0.99 mmol), followed by MeOH (5 mL). The resulting mixture was stirred at room temperature for 3 h. The reaction solution was concentrated and the residue was purified by column (eluent: 3-10% MeOH in DCM) to give 2 (140 mg, 90%) as a white foam, which was a mixture of pure product and mCBA according to ¹H NMR. This product was used in the next reaction without further purification.

[000222] ¹H NMR (300 MHz, METHANOL-d4) δ ppm 7.70 (d, J=8.3 Hz, 1 H), 6.85 (d, J=8.3 Hz, 1 H), 4.96 (br. s., 1 H), 3.79 - 3.89 (m, 1 H), 3.49 - 3.69 (m, 2 H), 3.39 (s, 3 H), 3.08 - 3.24 (m, 2 H), 2.96 (d, J=9.4 Hz, 1 H), 2.90 (s, 3 H), 1.93 - 2.11 (m, 2 H),
1.72 - 1.88 (m, 2 H), 1.62 - 1.72 (m, 1 H), 1.43 - 1.61 (m, 2 H), 1.24 - 1.41 (m, 1 H), 0.67 -
0.84 (m, 2 H), 0.42 - 0.59 (m, 2 H). MS [M+H]: 432.2.

(ii) (S)-17-Cyclopropylmethyl-4,5α-epoxy-3-carbamoyl-14-hydroxy-morphinan-6-one
N-oxide hydrochloride (C0007)

[000223] Compound 2 (140 mg, 0.41 mmol) was dissolved in a mixture of
aqueous HCl (10 mL, 1 N) and Et₂O (20 mL). Et₂O layer was removed. The aqueous layer
was washed with more Et₂O (20 mL) and stirred at room temperature for 4 h. This was
then evaporated and lyophilized. The solid residue was purified by semi-prep HPLC to
give C0007 (67.2 mg, 43 %) as a white foam. ¹H NMR (300 MHz, D₂O) δ ppm 7.99 (d,
J=8.3 Hz, 1 H), 7.32 (d, 1 H), 5.62 (s, 1 H), 4.89 (d, J=5.8 Hz, 1 H), 4.07 - 4.36 (m, 2 H),
3.72 - 4.06 (m, 3 H), 3.46 - 3.65 (m, 1 H), 3.19 - 3.43 (m, 2 H), 2.48 - 2.71 (m, 2 H), 2.18 -
2.37 (m, 1 H), 1.96 - 2.16 (m, 1 H), 1.56 - 1.80 (m, 1 H), 1.11 (d, J=7.7 Hz, 2 H), 0.72 -
0.96 (m, 2 H). HPLC purity. 100%. MS [M+H]: 385.2.

Example 8

(S)-17-Cyclopropylmethyl-4,5α-epoxy-14-cyclopropymethyloxy-morphinan-6-one
N-oxide (C0008)
A mixture of Naltrexone hydrochloride 1 (3.0 g, 7.94 mmol), benzyl bromide (1.43 g, 8.34 mmol) and \( \text{K}_2\text{CO}_3 \) (3.0 g, 21.7 mmol) in anhydrous DMF (30 mL) was stirred at RT under \( \text{N}_2 \) overnight. The reaction mixture was poured onto water (500 mL), extracted with \( \text{CH}_2\text{Cl}_2 \), washed with water, brine and dried (\( \text{Na}_2\text{SO}_4 \)). The solvent was evaporated under reduced pressure to obtain a residue, which was dissolved in 2N HCl (200 mL) and extracted with ether (to remove excess BnBr). The organic phase was discarded and the aqueous phase was made basic with \( \text{c. NH}_4\text{OH} \), the precipitated white solid was extracted with \( \text{CH}_2\text{Cl}_2 \), washed with brine, dried (\( \text{Na}_2\text{SO}_4 \)) and the solvent was removed under reduced pressure to obtain 2 (3.30 g, 96%) as a white foam.
[000225] 1H NMR (300 MHz, chloroform-d): δ 7.20-7.50 (m, 5H), 6.71 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.13 (dd, J = 13.5, 11.8 Hz, 2H), 4.70 (s, IH), 4.83 (s, 1H), 3.00-3.18 (m, 3H), 2.28-2.74 (m, 6H), 2.13 (dt, J = 8.5, 3.6 Hz, 1H), 1.50-1.70 (m, 2H), 0.85 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H). APCI+ = 432.

(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-hydroxy-6,6-dimethoxy morphinan (3)

[000226] To a solution of the ketone 2 (2.63 g, 5.56 mmol) in anhydrous methanol (10 mL) was added trimethyl orthoformate (10 mL) and cone. sulfuric acid (2 mL). This mixture was heated to reflux for 4h under N₂. Volatiles were removed under reduced pressure to obtain a residue to which was added cone. NH₄OH and this mixture was then extracted with chloroform. The organic phase was washed with water, brine and dried (Na₂SO₄). Evaporation of the solvent provided a yellow oil, which was purified by flash chromatography using 1-10% MeOH / CHCl₃ to isolate 3 (0.43 g) and a mixture of 3 and 3a (10:1) (2.0 g). Total yield = 94%.

[000227] 1H NMR (300 MHz, chloroform-d): δ 7.20-7.50 (m, 5H), 6.71 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.27 (dd, J = 13.5, 11.8 Hz, 2H), 4.60 (s, IH), 3.43 (s, 3H), 2.96-3.15 (m, 5H), 2.54-2.65 (m, 2H), 2.29-2.36 (m, 3H), 2.13 (dt, J = 8.5, 3.6 Hz, 1H), 1.91-2.05 (m, IH), 1.30-1.70 (m, 5H), 0.85 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H). APCI+ = 478.

(iii) 17-Cyclopropylmethyl-4,5 αα-epoxy-3-benzyloxy-14-cyclopropylmethyloxy-6,6-dimethoxymorphinan (4)

[000228] To a solution of compound 3 (0.5 g, 1.05 mmol) in anhydrous DMSO (8 mL) under N₂ was added NaH (60%, 210 mg, 5.25 mmol) and it was stirred at RT for 1h. Cyclopropylmethyl bromide (710 mg, 5.25 mmol) was then added and the reaction mixture was stirred at RT for 48h. 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 (NaTSO₄). 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 (83 mg, 15%) as a colorless oil.
[000229] 1H NMR (300 MHz, CDCl₃): δ 7.50-7.20 (m, 5H), 6.70 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.95-6.05 (m, 1H), 5.30 (d, J = 12.1 Hz, 1H), 5.17 (d, J = 12.1 Hz, 1H), 4.70 (s, 1H), 3.50 (dd, J = 6.0, 3.3 Hz, 1H), 3.40 (s, 3H), 3.31 (d, J = 4.7 Hz, 1H), 3.00-3.20 (m, 2H), 2.94 (s, 3H), 2.54-2.64 (m, 2H), 2.35-2.41 (m, 2H), 1.93-2.09 (m, 2H), 1.24-1.32(m, 2H), 1.10-1.14 (m, 2H), 0.89 (m, 1H), 0.69 (m, 1H), 0.49 (m, 2H), 0.3 1.0-0.28 (m, 2H), 0.21 (m, 1H), 0.093 (m, 2H). APCI = 532.

(iv) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-cyclopropylmethyloxy-6-oxomorphinan (5)

[000230] A solution of compound 4 (83 mg, 0.16 mmol) in TFA (2 mL) was heated to reflux for 1h. The mixture was cooled to RT, poured onto sat. NaHCO₃ solution, extracted with EtOAc, washed with brine, dried (Na₂SO₄) and evaporated to isolate crude 5, which was purified by flash chromatography using 1-2% MeOH / CHCl₃ as eluent to obtain pure 5 (18 mg, 30%) as a white solid.

[000231] 1H NMR (300 MHz, MeOH-d3): δ 6.61 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 4.72 (s, 1H), 3.60-3.72 (m, 2H), 3.20-3.30 (m, 2H), 2.67-2.91 (m, 3H), 2.30-2.44 (m, 3H), 2.10-2.104(m, 3H), 1.30-1.44 (m, 3H), 1.18 (m, 1H), 0.16-0.55 (m, 8H). APCI⁺ = 396.

(v) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-cyclopropylmethyloxy-6-oxomorphinan N-oxide (C0008)

[000232] To a solution of compound 5 (18 mg, 0.046 mmol) in CHCl₃ (1 mL) at 0 °C was added mCPBA (77%, 10.2 mg, 0.046 mmol) and the mixture was stirred for 1h. K₂CO₃ (~ 100 mg) was added to the solution and it was stirred for 10 min. The solid was filtered, washed with CHCl₃ and the filtrate was evaporated to isolate the crude product. This material was purified by flash chromatography using 1-8% MeOH / CHCl₃ + 0.1-0.2% NH₄OH as eluent to obtain the pure product C0008 (12.1 mg, 65%) as a white solid.

[000233] 1H NMR (300 MHz, MeOH-d3): δ 6.71 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 4.91 (s, 1H), 4.45 (m, 1H), 3.85-3.95 (m, 2H), 3.70-3.77 (m, 1H), 3.30-3.55 (m, 1H), 3.25-3.0 (m, 5H), 2.70-2.80 (m, 1H), 2.30-2.38 (m, 1H), 2.21-2.13 (m, 1H),
1.73-1.77 (m, 1H), 1.44-1.61 (m, 2H), 1.21 (m, 1H), 0.81 (m, 2H), 0.53-0.63 (m, 2H), 0.43-0.51 (m, 2H), 0.30-0.33 (m, 2H). APCI+ = 412. HPLC = 100%.

Example 9

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-propyloxymorphinan-3,6 β-diol N-oxide trifluoroacetic acid salt (C0009)

(i) 17-Cyclopropylmethyl-4,5 α-epoxy-3,6β,14-trihydroxymorphinan (2)

[000234] Naltrexone hydrochloride (9.57 g, 25.3 mmol) was dissolved in aqueous NaOH (75 mL, 1.0 N) and stirred at room temperature under N2. Formamidinesulfinic acid (10.9 g, 101.3 mmol) in NaOH (75 mL, 1.0 N) was added over 25 min. The resulting solution was heated at 85 °C for 2 h. After the reaction solution was cooled with an ice bath aqueous NH4Cl (13.6 g in 150 mL of water) was added dropwise. This was extracted with 10% MeOH in CHCl3 (5X 200 mL). The remaining solid in the
aqueous layer was collected by filtration and dissolved in 10% MeOH in CHCl₃ (200 mL). The filtrate was basified with aqueous NH₃ and extracted with 10% MeOH in CHCl₃ (200 mL). All organic solutions were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated to give 2 (8.66 g, 90%) as a tan solid.

[000235] ¹H NMR (300 MHz, CDCl₃) δ ppm 6.71 (d, J=8.0 Hz, 1 H), 6.57 (d, J=8.3 Hz, 1 H), 4.57 (d, J=6.1 Hz, 1 H), 3.53 - 3.66 (m, 1 H), 3.11 (d, J=5.8 Hz, 1 H), 3.03 (d, J=18.2 Hz, 1 H), 2.53 - 2.70 (m, 2 H), 2.37 (d, J=6.6 Hz, 2 H), 1.92 - 2.32 (m, 3 H), 1.65 (dd, J=10.2, 1.7 Hz, 2 H), 1.30 - 1.54 (m, 2 H), 0.76 - 0.91 (m, 1 H), 0.47 - 0.60 (m, 2 H), 0.06 - 0.19 (m, 2 H). MS [M+H]: 344.2.

(ii) 17-Cyclopropylmethyl-4,5-α-epoxy-3-benzyloxy-6 β,14-dihydroxymorphinan (3)

[000236] Compound 2 (7.76 g, 22.6 mmol) and K₂CO₃ (6.85 g, 49.7 mmol) were combined in anhydrous DMF (40 mL) and stirred under N₂. Benzyl bromide (0.21 mL, 1.80 mmol) was added. The resulting mixture was stirred at room temperature overnight. Water (200 mL) was added and the mixture was extracted with 10% MeOH in CHCl₃ (3X 200 mL). The CHCl₃ extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated and the yellow gummy solid residue was purified by column (eluent: 0-10% MeOH in DCM) to give 3 (8.51 g, 87%) as a tan solid.

[000237] ¹H NMR (300 MHz, CDCl₃) δ ppm 7.29 - 7.47 (m, 5 H), 6.77 (d, J=8.3 Hz, 1 H), 6.56 (d, J=8.3 Hz, 1 H), 5.11 - 5.27 (m, 2 H), 4.47 (d, J=5.8 Hz, 1 H), 3.43 - 3.57 (m, 1 H), 3.09 (d, J=5.5 Hz, 1 H), 3.02 (d, J=18.4 Hz, 1 H), 2.80 (d, J=5.8 Hz, 1 H), 2.51 - 2.69 (m, 2 H), 2.36 (d, J=6.3 Hz, 3 H), 2.05 - 2.31 (m, 2 H), 1.84 - 2.01 (m, 1 H), 1.45 - 1.67 (m, 3 H), 1.26 - 1.42 (m, 1 H), 0.76 - 0.91 (m, 1 H), 0.53 (dd, J=8.3, 1.4 Hz, 2 H), 0.07 - 0.18 (m, 2 H). MS [M+H]: 434.3.

(iii) 17-Cyclopropylmethyl-4,5-α-epoxy-3-benzyloxy-6 β-(4-methoxybenzyloxy)-14-hydroxymorphinan (4)

[000238] Compound 3 (4.9 g, 11.3 mmol) was dissolved in anhydrous DMF (30 mL) and stirred under N₂. NaH (0.68 g, 60% in mineral oil, 17.0 mmol) was added. After 20 min 4-methoxybenzyl bromide (PMBr) (1.98 mL, 13.6 mmol) was added. The resulting mixture was stirred at room temperature overnight. Water (100 mL) was added
and the mixture was extracted with EtOAc (3X 100 mL). The EtOAc extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated and the yellow gummy solid residue was purified by column (eluent: 0-10 % MeOH in DCM) to give 4 (5.7 g, 91 %) as a tan solid.

[000239] ¹H NMR (300 MHz, CDCl₃) δ ppm 7.43 - 7.51 (m, 2 H), 7.29 - 7.41 (m, 6 H), 6.71 - 6.85 (m, 3 H), 6.55 (d, J=8.3 Hz, 1 H), 5.21 (s, 2 H), 4.60 - 4.77 (m, 3 H), 3.75 (s, 3 H), 3.28 - 3.40 (m, 1 H), 3.08 (d, J=5.5 Hz, 1 H), 3.01 (d, J=18.4 Hz, 1 H), 2.49 - 2.69 (m, 2 H), 2.36 (d, J=6.6 Hz, 2 H), 2.19 - 2.32 (m, 1 H), 1.89 - 2.17 (m, 2 H), 1.69 - 1.82 (m, 1 H), 1.44 - 1.65 (m, 2 H), 1.25 - 1.41 (m, 1 H), 0.76 - 0.92 (m, 1 H), 0.48 - 0.59 (m, 2 H), 0.07 - 0.18 (m, 2 H). MS [M+H]: 554.3.

(iv) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzylxyloxy-6 β-(4-methoxybenzylxyloxy)-14-propyloxy morphinan (5)

[000240] Compound 4 (4.5 g, 8.14 mmol) was dissolved in anhydrous DMF (30 mL) and stirred under N₂. NaH (2.6 g, 60% in mineral oil, 65.12 mmol) was added. After 20 min dipropyl sulfate (10.77 mL, 65.12 mmol) was added. The resulting mixture was stirred at room temperature overnight. Water (100 mL) was added and the mixture was extracted with EtOAc (3X 100 mL). The EtOAc extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated and the yellow gummy solid residue was purified by column (eluent: 0-10 % MeOH in DCM) to give 5 (3.4 g, 70 %) as a tan solid.

[000241] ¹H NMR (300 MHz, CDCl₃) δ ppm 7.43 - 7.52 (m, 3 H), 7.29 - 7.42 (m, 6 H), 6.77 - 6.86 (m, 2 H), 6.74 (d, J=8.3 Hz, 1 H), 6.53 (d, J=8.3 Hz, 1 H), 5.15 - 5.27 (m, 2 H), 4.59 - 4.78 (m, 3 H), 3.75 (s, 3 H), 3.47 - 3.58 (m, 1 H), 3.41 (d, J=4.7 Hz, 1 H), 3.26 - 3.38 (m, 1 H), 3.15 - 3.25 (m, 1 H), 3.08 (d, J=18.2 Hz, 1 H), 2.49 - 2.72 (m, 2 H), 2.25 - 2.42 (m, 3 H), 1.71 - 2.08 (m, 2 H), 1.52 - 1.71 (m, 2 H), 1.30 - 1.38 (m, 1 H), 1.03 - 1.17 (m, 1 H), 0.98 (d, J=7.2 Hz, 3 H), 0.77 - 0.92 (m, 1 H), 0.45 - 0.54 (m, 2 H), 0.07 - 0.17 (m, 2 H). MS [M+H]: 596.3.

(v) 17-Cyclopropylmethyl-4,5 α-epoxy-3, 6β-dihydroxy)-14-propyloxy morphinan (6)

[000242] Compound 5 (1.0 g, 1.67 mmol) and TFA (4 mL) were combined in a sealed tube and heated at 80 °C for 2 h. TFA was removed and the solid residue was
dissolved in DCM (50 mL). This was washed with aqueous NH₃, dried over Na₂SO₄ and filtered. The filtrate was evaporated and the yellow gummy solid residue was purified by column (eluent: 0-10 % MeOH in DCM) to give 6 (0.44 g, 68 %) as a tan solid.

\[
\text{[000243]} \quad ^1H \text{ NMR (300 MHz, CDCl}_3 \) \delta \text{ ppm 6.69 (d, } J=8.3 \text{ Hz, 1 H), 6.54 (d, } J=8.3 \text{ Hz, 1 H), 4.56 (d, } J=4.7 \text{ Hz, 1 H), 3.57 - 3.68 (m, 2 H), 3.40 - 3.47 (m, 1 H), 3.22 - 3.38 (m, 2 H), 3.10 (d, } J=18.2 \text{ Hz, 1 H), 2.62 - 2.74 (m, 1 H), 2.47 - 2.62 (m, 1 H), 2.27 - 2.44 (m, 3 H), 2.03 - 2.16 (m, 1 H), 1.76 - 1.92 (m, 2 H), 1.53 - 1.73 (m, 3 H), 1.31 - 1.45 (m, 2 H), 1.07 - 1.19 (m, 1 H), 0.99 (t, } J=7.4 \text{ Hz, 3 H), 0.79 - 0.92 (m, 1 H), 0.50 (d, } J=7.7 \text{ Hz, 2 H), 0.12 (d, } J=4.1 \text{ Hz, 2 H). MS [M+H]: 402.2.}
\]

(vi) (S)-17-Cyclopropylmethyl-4,5α-epoxy-14-propyloxymorphinan-S^β-diol N-oxide trifluoroacetic acid salt (C0009)

\[
\text{[000244]} \quad \text{To a solution of compound 6 (440 mg, 1.14 mmol) in DCM (20 mL) was added mCPBA (306 mg, 77 %, 1.37 mmol). The resulting mixture was stirred at room temperature for 3 h. DCM was removed and the residue was purified by column (eluent: 3-10% MeOH in DCM) to give C0009 (320 mg, 70%) as a white foam.}
\]

\[
\text{[000245]} \quad ^1H \text{ NMR (300 MHz, METHANOL-}d_4 \) \delta \text{ ppm 6.64 (d, } J=8.3 \text{ Hz, 1 H), 6.55 (d, } J=8.3 \text{ Hz, 1 H), 4.34 (d, } J=6.3 \text{ Hz, 1 H), 3.86 (d, } J=3.3 \text{ Hz, 1 H), 3.65 - 3.82 (m, 1 H), 3.48 - 3.63 (m, 2 H), 3.24 - 3.44 (m, 2 H), 2.63 - 3.23 (m, 5 H), 1.97 (d, } J=14.3 \text{ Hz, 1 H), 1.31 - 1.76 (m, 6 H), 1.09 - 1.24 (m, 1 H), 0.94 (t, } J=7.4 \text{ Hz, 3 H), 0.53 - 0.73 (m, 2 H), 0.22 - 0.37 (m, 2 H). HPLC purity: 100%. MS [M+H]: 402.2.}
\]

\[
\text{[000246]} \quad \text{In a smaller scale synthesis crude C0009 was purified by semi-prep HPLC to give pure C0009 as a TFA salt.}
\]

\[
\text{[000247]} \quad ^1H \text{ NMR (300 MHz, } D_2O \) \delta \text{ ppm 6.81 (d, } J=8.3 \text{ Hz, 1 H), 6.71 (d, } J=8.3 \text{ Hz, 1 H), 4.73 (br. s., 1 H), 4.58 (d, } J=6.6 \text{ Hz, 1 H), 3.93 (dd, } J=14.0, 6.1 \text{ Hz, 1 H), 3.29 - 3.78 (m, 6 H), 3.11 - 3.29 (m, 2 H), 2.70 - 2.90 (m, 1 H), 2.15 (d, } J=11.8 \text{ Hz, 1 H), 1.21 - 1.87 (m, 7 H), 0.94 (t, } J=7.2 \text{ Hz, 3 H), 0.67 - 0.82 (m, 2 H), 0.35 - 0.58 (m, 2 H). HPLC purity: 100%. MS [M+H]: 402.2.}
\]

Example 10
(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-butyloxymorphinan-6-one N-oxide hydrochloride (COOlO)

(i) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-(2'-butenyloxy)morphinan-6-one dimethyl ketal (2)

[000248] Compound 1 (713 mg, 1.60 mmol) was dissolved in anhydrous DMF (20 mL) and stirred under N₂. NaH (191 mg, 60% in mineral oil, 4.86 mmol) was added. After 20 min 2-butenyl bromide (0.25 mL, 2.40 mmol) was added. The resulting mixture was stirred at room temperature for 19 h. This was diluted with EtOAc (100 mL), washed with water (3X 70 mL) and brine (70 mL), dried over Na₂SO₄ and filtered. The filtrate was evaporated and the yellow gummy residue was purified by column (eluent: 20 - 100% EtOAc in hexanes) to give 2 (164 mg, 19%) as a yellow oil. MS [M+H]: 532.3.

(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-(2'-butenyloxy)morphinan-6-one (3)

[000249] Compound 2 (164 mg, 0.31 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. After cooled to room temperature the reaction solution was basified with aqueous Na₂CO₃ (10 mL, 2 M) and extracted with DCM (2X 30 mL). The DCM extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated to give 3 (136 mg, 90%) as a yellow gum.
(i) **17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-butyloxymorphinan-6-one** (4)

**[000250]** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.29 - 7.49 (m, 5 H), 6.70 (d, $J$=8.0 Hz, 1 H), 6.55 (d, $J$=8.3 Hz, 1 H), 5.66 - 5.87 (m, 2 H), 5.17 - 5.30 (m, 2 H), 4.71 (s, 1 H), 4.27 (dd, $J$=9.9, 5.5 Hz, 1 H), 3.82 - 3.91 (m, 1 H), 3.68 - 3.77 (m, 0 H), 3.53 - 3.63 (m, 2 H), 3.13 (d, $J$=18.7 Hz, 1 H), 2.81 - 2.95 (m, 1 H), 2.67 - 2.76 (m, 1 H), 2.02 - 2.42 (m, 5 H), 1.76 (d, 3 H), 1.40 - 1.65 (m, 3 H), 0.83 - 0.95 (m, 1 H), 0.49 - 0.58 (m, 2 H), 0.15 (dd, $J$=4.7, 1.4 Hz, 2 H). MS [M+H]: 486.3.

(ii) **17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-butyloxymorphinan-6-one N-oxide hydrochloride** (COOlO) (33 mg, HCl salt, 26%)

**[000251]** Compound 3 (136 mg, 0.28 mmol) was dissolved in MeOH (20 mL). Pd/C (144 mg, 10%, wet, 0.134 mmol) was added. The resulting mixture was stirred at room temperature under a H$_2$ balloon. Mass spectrometry after 110 min showed complete conversion of the starting material to the product. The reaction solution was filtered through a pad of Celite. The Celite was washed with MeOH (2×10 mL). The filtrate was evaporated to give 4 (112 mg, 100%) as a white foam.

**[000252]** $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 6.75 (d, $J$=8.3 Hz, 1 H), 6.65 (d, $J$=8.3 Hz, 1 H), 4.72 (s, 1 H), 4.32 (br. s., 1 H), 3.68 - 3.78 (m, 1 H), 3.48 - 3.63 (m, 1 H), 3.30 - 3.47 (m, 5 H), 2.88 - 3.10 (m, 2 H), 2.47 - 2.77 (m, 1 H), 2.27 (d, $J$=13.5 Hz, 1 H), 1.90 - 2.05 (m, 2 H), 1.26 - 1.69 (m, 5 H), 0.98 - 1.14 (m, 2 H), 0.94 (t, $J$=7.2 Hz, 3 H), 0.47 - 0.84 (m, 3 H). MS [M+H]: 398.2.

(iv) **(S)-17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-butyloxymorphinan-6-one N-oxide hydrochloride** (COOlO)

**[000253]** To a solution of compound 4 (156 mg, 0.28 mmol) in a mixture of DCM (5 mL) and MeOH (2 mL) cooled at 0 °C was added mCPBA (62 mg, 77%, 0.28 mmol). The resulting mixture was stirred at room temperature for 6 h. DCM was evaporated and the residue was purified by column (eluent: 5 - 10% MeOH in DCM). The purified product (38 mg yellowish foam) was dissolved in aqueous HCl (15 mL, 0.5 N) and was washed with Et$_2$O (2×20 mL). After residual Et$_2$O was removed by rotary evaporation the aqueous solution was lyophilized to give COOlO (33 mg, HCl salt, 26%) as a white foam.
\[ \text{H NMR (300 MHz, } D_2O) \delta \text{ ppm: 6.80 (d, } J=8.3 \text{ Hz, 1 H), 6.72 (d, } J=8.5 \text{ Hz, 1 H), 5.08 (s, 1 H), 4.86 (d, } J=4.7 \text{ Hz, 1 H), 3.61 - 4.05 (m, 4 H), 2.94 - 3.58 (m, 5 H), 2.59 - 2.77 (m, 1 H), 2.39 - 2.53 (m, 1 H), 2.25 (d, } J=15.1 \text{ Hz, 1 H), 1.80 - 1.94 (m, 1 H), 1.54 - 1.77 (m, 3 H), 1.21 - 1.52 (m, 3 H), 0.89 (t, } J=7.4 \text{ Hz, 3 H), 0.69 - 0.84 (m, 2 H), 0.37 - 0.61 (m, 2 H). \] HPLC purity: 100%. MS [M+H]: 414.1.

Example 11

(5)-17-Cyclopropylmethyl-4,5\(\alpha\)-epoxy-3-hydroxy-14-benzyloxyhiporphinan-6-one N-oxide hydrochloride (COOII)

(i) 17-Cyclopropylmethyl-4,5 \(\alpha\)-epoxy-3-benzyloxy-14-benzyloxymorphinan-6-one dimethyl ketal (2)

\[ \text{[000255] Compound 1 (839 mg, 1.88 mmol) was dissolved in anhydrous DMF (20 mL) and stirred under } N_2. \text{ NaH (191 mg, 60\% in mineral oil, 4.86 mmol) was added. After 20 min benzyl bromide (0.25 mL, 2.40 mmol) was added. The resulting mixture was stirred at room temperature for 19 h. The reaction solution was diluted with EtOAc (100 mL), washed with water (3X 70 mL) and brine (70 mL), dried over } Na_2SO_4 \text{ and filtered. The filtrate was evaporated. The yellow gummy residue was purified by column (eluent: 20 - 100 \% EtOAc in hexanes) to give 2 (450 mg, 45 \%) as a yellow oil. MS [M+H]: 568.3.} \]

(ii) 17-Cyclopropylmethyl-4,5 \(\alpha\)-epoxy-3-benzyloxy-14-benzyloxymorphinan-6-one (3)
Compound 2 (450 mg, 0.84 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. After cooled to room temperature the reaction solution was basified with aqueous Na₂CO₃ (10 mL, 2 M) and extracted with DCM (2X 30 mL). The DCM extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated to give 3 (404 mg, 92 %) as a yellow gum.

[000257] ³H NMR (300 MHz, CDCl₃) δ ppm 7.29 - 7.55 (m, 10 H), 6.72 (d, J=8.3 Hz, 1 H), 6.58 (d, J=8.3 Hz, 1 H), 5.26 (d, 2 H), 4.92 (d, J=9.9 Hz, 1 H), 4.70 (s, 1 H), 4.38 (d, J=9.9 Hz, 1 H), 3.71 (d, J=5.0 Hz, 2 H), 3.13 - 3.25 (m, 1 H), 2.73 - 2.97 (m, 2 H), 2.34 - 2.49 (m, 2 H), 2.11 - 2.29 (m, 2 H), 1.83 - 1.95 (m, 1 H), 1.44 - 1.80 (m, 3 H), 0.89 (d, J=7.7 Hz, 1 H), 0.48 - 0.56 (m, 2 H), 0.10 - 0.19 (m, 2 H). MS [M+H]: 522.3.

(iii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzyloxymorphinan-6-one (4)

[000258] Compound 3 (219 mg, 0.42 mmol) was dissolved in a mixture of MeOH (20 mL) and DCM (5 mL). Pd/C (144 mg, 10%, wet, 0.134 mmol) was added. The resulting mixture was stirred at room temperature under a H₂ balloon. Mass spectrometry after 35 min showed complete conversion of the starting material to the product. The reaction solution was filtered through a pad of Celite. The Celite was washed with MeOH (2X 10 mL). The filtrate was evaporated to give 4 (165 mg, 91 %) as a yellow gum. MS [M+H]: 432.2.

(iv) (S)-17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-benzyloxymorphinan-6-one N-oxide hydrochloride (COO11)

[000259] Compound 4 (165 mg, 0.38 mmol) was dissolved in a mixture of DCM (5 mL) and MeOH (1 mL) and stirred at 0 °C. mCPBA (85 mg, 77 %, 0.38 mmol) was added. The resulting mixture was stirred at room temperature 1 h. DCM was evaporated and the residue was purified by column (eluent: 5 - 10 % MeOH in DCM). The purified product (70 mg, off-white solid) was dissolved in a mixture of aqueous HCl (20 mL, 0.05 N) and MeOH (5 mL) and washed with Et₂O (2X30 mL). After residual Et₂O was removed by rotary evaporation the aqueous solution was lyophilized to give COO11 (76 mg, HCl salt, 46%) as a white foam.
[000260] ¹H NMR (301 MHz, D₂O) δ ppm 7.34 - 7.54 (m, 5 H), 6.81 (d, J=8.3 Hz, 1 H), 6.75 (d, J=8.3 Hz, 1 H), 5.06 (s, 1 H), 5.02 (d, J=5.0 Hz, 1 H), 4.89 (d, J=10.5 Hz, 1 H), 4.77 - 4.78 (m, 2 H), 2.74 - 3.08 (m, 2 H), 2.60 (d, J=15.1 Hz, 1 H), 2.30 (d, J=15.1 Hz, 1 H), 1.61 - 1.90 (m, 2 H), 1.22 - 1.40 (m, 1 H), 0.80 (dd, J=13.5, 4.1 Hz, 2 H), 0.38 - 0.62 (m, 2 H). HPLC purity: 100%. MS [M+H]: 448.1.

Example 12

(S)-17-Isobutyl-4,5 α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one N-oxide hydrochloride (COO12)

[000261] To a solution of compound 1 (142 mg, 0.414 mmol) in DCM (10 mL) cooled with an ice bath was added mCPBA (93.5 mg, 77%, 0.414 mmol). The resulting mixture was stirred at 0 °C for 40 min and then at room temperature for 2.5 h. The reaction solution was concentrated and the residue was purified by column (eluent: 1% MeOH in DCM) to give CO012 base plus mCBA (77 mg) as a white solid. This impure product was dissolved in water (10 mL). HCl (0.3 mL, 3N) was added. The resulting solution was washed with Et₂O (2X15 mL). After residual Et₂O was removed by rotary evaporation the aqueous solution was lyophilized to give pure CO012 (77.6 mg, HCl salt, 47%) as a white foam.

[000262] ¹H NMR (300 MHz, DMSO-d₆) δ ppm 9.63 (br. s., 1 H), 6.72 (d, J=8.3 Hz, 1 H), 6.66 (d, J=8.3 Hz, 1 H), 5.09 (s, 1 H), 4.41 (d, J=5.0 Hz, 1 H), 3.04 - 4.03 (m, 8 H), 2.71 - 2.98 (m, 2 H), 2.31 - 2.46 (m, 1 H), 2.09 - 2.26 (m, 2 H), 1.76 (d, J=12.1 Hz, 1 H), 1.46 - 1.64 (m, 1 H), 1.15 (d, J=6.6 Hz, 3 H), 1.04 (d, J=6.9 Hz, 3 H). HPLC purity: 100%. MS [M+H]: 360.1.
Example 13

(R)-4,5α-epoxy-3-hydroxy-(17,14-N, O-ethylene)morphinan-6-one N-oxide trifluoroacetic acid salt (C0013)

[000263] To a solution of compound 1 (81 mg, 0.189 mmol) in MeOH (10 mL) cooled at 0 °C was added mCPBA (34 mg, 77%, 0.152 mmol). The resulting mixture was stirred at room temperature for 5.5 h. MeOH was removed. The yellow solid residue was dissolved in water (10 mL) and washed with Et₂O (2X10 mL). After residual Et₂O was removed by rotary evaporation the aqueous solution was lyophilized to give white foam (56 mg). This impure product was purified by semi-prep HPLC to give pure C0013 (30 mg, TFA salt, 35%) as a white foam.

[000264] ¹H NMR (300 MHz, DMSO-d₆) δ ppm 9.57 (br. s., 1 H), 6.63 - 6.75 (m, 2 H), 5.07 (s, 1 H), 4.76 (d, J=6.3 Hz, 1 H), 4.56 - 4.70 (m, 1 H), 4.38 - 4.52 (m, 1 H), 4.06 - 4.30 (m, 2 H), 3.79 - 3.89 (m, 1 H), 3.73 (d, J=19.8 Hz, 1 H), 3.06 - 3.23 (m, 2 H), 2.74 - 2.98 (m, 2 H), 2.06 - 2.21 (m, 2 H), 1.76 (dd, J=14.3, 4.1 Hz, 1 H), 1.41 - 1.57 (m, 1 H), -1.65 (s, 1 H). HPLC purity: 100%, MS [M+H]: 330.1.

Example 14

(S)-17-Propargyl-4,5 α-epoxy-3,14-dihydroxymorphinan-6-one N-oxide trifluoroacetic acid salt (C0014)
Noroxymorphone 1 (600 mg, 3.09 mmol) was dissolved in anhydrous DMF (10 mL) and stirred under N₂. NaHCO₃ (519 mg, 6.18 mmol) was added, followed by propargyl bromide (0.40 mL, 3.51 mmol). The resulting mixture was stirred at room temperature 2 h. Aqueous Na₂CO₃ solution (40 mL, 2 M) was added. The resulting mixture was extracted with DCM (2X40 mL). The DCM extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated. The yellow solid was stirred with Et₂O overnight and filtered to give 2 (500 mg, 50%) as a tan solid.

**1H NMR** (300 MHz, DMSO-d₆) δ ppm 6.56 (d, J=8.0 Hz, 1 H), 6.51 (d, J=8.3 Hz, 1 H), 4.92 (s, 1 H), 4.76 (s, 1 H), 3.41 (d, J=2.5 Hz, 2 H), 3.24 (t, J=2.2 Hz, 1 H), 3.08 - 3.20 (m, 2 H), 2.83 - 2.98 (m, 1 H), 2.46 - 2.64 (m, 3 H), 2.29 - 2.43 (m, 1 H), 2.02 - 2.16 (m, 2 H), 1.67 - 1.81 (m, 1 H), 1.46 (t, J=12.4 Hz, 1 H), 1.25 - 1.37 (m, 1 H). MS [M+H]: 326.2.

To a solution of compound 2 (148 mg, 0.455 mmol) in a mixture of MeOH (1 mL) and DCM (5 mL) cooled at 0 °C was added mCPBA (101 mg, 77%, 0.455 mmol). The resulting mixture was stirred at room temperature for 4.0 h. Solvents were removed. The yellow solid residue was dissolved in aqueous HCl (0.7 N, 21 mL) and washed with Et₂O (2X10 mL). After residual Et₂O was removed by rotary evaporation the aqueous solution was lyophilized to give a yellow solid (173 mg). This impure product was purified on a 12 g C18 reverse phase column to give a white foam (99mg), which was purified again by semi-prep HPLC to give pure C0014 (90 mg, TFA salt, 43%) as a white foam.
[000268] $^1$H NMR (300 MHz, D$_2$O) δ ppm 6.80 (d, J = 8.3 Hz, 1 H), 6.73 (d, J = 8.3 Hz, 1 H), 5.08 (s, 1 H), 4.44 - 4.72 (m, 3 H), 3.65 - 3.78 (m, 1 H), 3.42 - 3.57 (m, 1 H), 3.25 - 3.42 (m, 2 H), 3.20 (t, J = 2.5 Hz, 1 H), 2.83 - 3.03 (m, 2 H), 2.10 - 2.34 (m, 2 H), 1.68 - 1.99 (m, 2 H). HPLC purity: 100%. MS [M+H]: 342.1.

Example 15

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-morphinan-6-one N-oxide (C0015)

The following reaction sequence was used for the preparation of target C0015.

![Chemical structure](image)

(i) 17-Methyl-4,5α-epoxy-3-hydroxy-morphinan-6-one N-oxide (2)

[000269] To a solution of 1 (1.83 g, 6.4 mmol) in DCM (100 ml) was added dropwise mCPBA (0.455 g (77% max), 7.04 mmol) in DCM (20 ml). After 1 hour the solvent was evaporated and the residue purified by column chromatography to provide 1.69 g (87%) of 2.

[000270] $^1$H NMR (300 MHz, CDCl$_3$): δ 10.16 (br. s., 1 H), 6.63 (d, J = 8.0 Hz, 1 H), 6.55 (d, J = 8.0, 1 H), 4.92 (s, 1 H), 4.03 (dt, J = 3.6, 13.0 Hz, 1 H), 3.36 - 3.43 (m, 1 H), 3.18 (s, 3H), 3.17 (d, 1H), 2.59 - 2.84 (m, 5 H), 2.17 (dt, J = 3.0, 8.0 Hz, 1 H), 1.63 - 1.74 (m, 1 H), 1.35 - 1.46 (m, 1 H), 1.21 - 1.27 (m, 1 H). (APCI +): 302 (M+1).
(H) 4,5α-epoxy-3-hydroxy-morphinan-6-one  (3)

[000271] FeSO₄·7H₂O (5 g, 17.9 mmol) was added portion-wise to a solution of 2 (1.6 g, 0.011 mmol) in MeOH (150 ml) and the reaction stirred for 1 h. The reaction mixture was directly absorbed on silica gel and purified by column chromatography to provide 0.530 g (38%) of compound 3.

[000272] ¹H NMR (300 MHz, DMSO-d₆): δ 9.13 (br. s., 1 H), 6.56 (d, J=8.0 Hz, 1 H), 6.50 (d, J=8.0 Hz, 1 H), 4.82 (s, 1 H), 3.31 - 3.42 (m, 1 H), 2.64 - 2.80 (m, 2 H), 2.38 - 2.48 (m, 2 H), 2.09 - 2.20 (m, 1 H), 1.85 - 2.03 (m, 2 H), 1.71 - 1.83 (m, 1 H), 1.45 - 1.57 (m, 1 H), 1.22 (m, 1 H), 0.84 - 1.01 (m, 2 H). (APCI⁺): 326 (M+1).

(iii) 17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-morphinan-6-one  (4)

[000273] A mixture of compound 3 (0.245 g, 0.9 mmol), cyclopropylmethyl bromide (0.122 g, 0.9 mmol) and NaHCO₃ (0.084 g, 1.0 mmol) in DMF (10 ml) was heated to 90 °C overnight under N₂. The solvent was evaporated to dryness and the residue purified by column chromatography to provide 0.130 g (45%) of compound 4.

[000274] ¹H NMR (300 MHz, CDCl₃): δ 7.8 (d, J=8.0 Hz, 1 H), 6.63 (d, J=8.3 Hz, 1 H), 4.74 (s, 1 H), 3.91 (br. s., 1 H), 3.19 (br. s., 1 H), 2.35 - 2.95 (m, 9 H), 1.84 - 2.00 (m, 2 H), 1.14 - 1.33 (m, 2 H), 0.63 - 0.75 (m, 2 H), 0.39 - 0.50 (m, 1 H), 0.32 (m, 1 H). (APCI⁺): 326 (M+1).

(iv) (S)-17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-morphinan-6-one  N-oxide (C0015):

[000275] To a solution of 4 (0.110 g, 0.34 mmol) in DCM (2 ml) was added dropwise mCPBA (0.076 g (77% max), 0.34 mmol) in DCM (4 ml). After 1 hour, the solvent was evaporated and the residue purified by column chromatography to provide 0.045 g (52%) of C0015. m.p. = 209-21 1°C.

[000276] ¹H NMR (300 MHz, CDCl₃): δ 6.80 (d, J=8.3 Hz, 1 H), 6.56 (d, J=8.0 Hz, 1 H), 4.75 (s, 1 H), 4.09 - 4.19 (m, 1 H), 3.98 - 4.07 (m, 1 H), 3.28 - 3.45 (m, 3 H), 2.81 - 3.05 (m, 4 H), 2.30 - 2.49 (m, 3 H), 1.78 - 1.91 (m, 1 H), 1.56 - 1.76 (m, 2 H), 1.04 - 1.21 (m, 1 H), 0.67 - 0.83 (m, 2 H), 0.31 - 0.50 (m, 2 H). (APCI⁺): 342 (M+1).
Example 16

(S)-17-(3,3,3-trifluoropropyl)-4,5 α-epoxy-3,14-dihydroxymorphinan-6-one N-oxide trifluoroacetic acid salt (C0016)

The following reaction sequence was followed for the preparation of COO 16.

(i) 17-(3,3,3-trifluoropropyl)-4,5 α-epoxy-3,14-dihydroxymorphinan-6-one (2)

[000277] The a mixture of oxymorphone (1) (0.574 g, 0.002 mole), 3,3,3-trifluoro-1-bromopropane (1.55 g, 0.009 mole) and NaHCO₃ (0.74 g, 0.009 mole) in DMF (4 ml) was heated to 90 °C for 32 h under N₂. The solvent was evaporated to dryness and the residue purified by column chromatography to provide 0.363 g (47%) of the compound 2.

[000278] ¹H NMR (300 MHz, CDCl₃): δ 6.74 (d, J=8.3 Hz, 1 H), 6.62 (d, J=8.0 Hz, 1 H), 4.86 (br. s., 1 H), 4.69 (s, 1 H), 2.95 - 3.14 (m, 3 H), 2.55 - 2.84 (m, 4 H), 2.20 - 2.48 (m, 5 H), 1.85 - 1.95 (m, 1 H), 1.64 (td, 2 H). (APCI+): 384 (M+1).

(ii) (S)-17-(3,3,3-trifluoropropyl)-4,5 βα-epoxy-3,14-dihydroxymorphinan-6-one N-oxide trifluoroacetic acid salt (C0016):

[000279] To a solution of 2 (0.3 g, 0.78 mmol) in DCM was added dropwise mCPBA (0.192 g (77% max), 0.86 mmol) in DCM. After 2 hours the solvent was evaporated and the residue purified by column chromatography to provide 140 mg (45%) of C0016. Final purification was achieved by semi-prep HPLC using MeOH/H₂O = 30/70 with 0.1% TFA to give the product as its TFA salt.
Example 17

17-Cyclopropylmethyl-4,5 α-epoxy-3, 14-hydroxy-6 α-methyl)morphinan N-oxide (C0017)

(i) 17-cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-hydroxy-6-methylene morphinan (2)

A mixture of Nalmefene hydrochloride (3.0 g, 8.0 mmol), benzyl bromide (1.43 g, 8.34 mmol) and K₂CO₃ (3.0 g, 21.7 mmol) in anhydrous DMF (30 mL)
was stirred at RT under N₂ overnight. The reaction mixture was poured onto water (500 mL), extracted with CH₂Cl₂, washed with water, brine and dried (Na₂SO₄). The solvent was evaporated under reduced pressure to obtain a residue which was dissolved in 2N HCl (200 mL) and extracted with ether to remove excess of BnBr (organic phase was discarded). The aqueous phase was made basic with c. NH₄OH, the precipitated white solid was extracted with CH₂Cl₂, washed with brine, dried (Na₂SO₄) and the solvent was removed under reduced pressure to obtain a white foam (2.40 g, 70%).

\[ 000281 \] ¹H NMR (300 MHz, DMSO-d₆): δ 7.3-7.43 (m, 5H), 6.77 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 5.18 (s, 1H, 14-OH), 5.13 (s, 2H), 4.90 (d, J = 14.3 Hz, 3H), 4.83 (s, 1H), 2.94-3.01 (m, 2H), 2.60-2.65 (m, 1H), 2.49-2.52 (m, 2H), 2.20-3.23 (m, 2H), 2.23 (dt, J = 8.5, 3.6 Hz, 1H), 2.05-2.09 (m, 1H), 1.96 (dt, J = 8.5, 3.6 Hz, 1H), 1.48-1.52 (m, 1H), 1.28-1.32 (m, 1H), 1.14-1.22 (m, 1H), 0.80-0.86 (m, 1H), 0.43-0.53 (m, 2H), 0.10-0.13 (m, 2H). APCI⁺ = 430.

(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-hydroxy-6 α-hydroxymethyl tnorphinan (3)

\[ 000283 \] To a solution of compound 2 (1.0 g, 2.33 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen was added BH₃ .THF (IM in THF, 0.4 g, 4.7 mmol) dropwise and the resulting mixture was stirred at RT overnight. The mixture was cooled to 0 °C, EtOH (8 mL) was added followed by 3M NaOH (2.2 mL) and H₂O₂ (35 wt %, 1.6 mL). After stirring the mixture for 1h at RT the solvents were removed under reduced pressure and the resulting residue was extracted with chloroform, washed with brine and dried (Na₂SO₄). Evaporation of the solvent provided the crude product, which was purified by flash chromatography using 2-4% MeOH / CHCl₃ + 1% NH₄OH as eluent to isolate the pure product (0.83 g, 80%) as a white solid.

\[ 000284 \] ¹H NMR (300 MHz, DMSO-d₆): δ 7.30-7.43 (m, 5H), 6.78 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.09 (s, 2H), 4.77 (s, 1H, 14-OH), 4.64 (d, J = 3.3 Hz, 1H), 4.53 (t, J = 5.3 Hz, 1H, 21-OH), 3.50-3.57 (m, 1H), 3.20-3.25 (m, 1H), 3.02 (d, J = 6.6 Hz, 1H), 2.95 (d, J = 18.7 Hz, 1H), 2.52-2.61 (m, 2H), 2.22-2.38 (m, 2H), 2.06-2.14 (m, 3H), 1.31-1.45 (m, 4H), 0.84-0.88 (m, 1H), 0.47-0.53 (m, 3H), 0.10-0.12 (m, 2H). APCI⁺ = 448.
(iii) n-Cyclopentylmethyl-4,5 \(\alpha\)-epoxy-3-benzyloxy-14-hydroxy-6\(\alpha\)-(p-toluenesulfonylmethyl) morphinan (4)

[000285] To a solution of 3 (300 mg, 0.67 mmol) and pyridine (0.7 mL) in anhydrous CH\(_2\)Cl\(_2\) (4 mL) under N\(_2\) at 0 °C was added p-toluenesulfonyl chloride (141 mg, 0.74 mmol), the mixture was warmed to RT and stirred overnight. The reaction mixture was diluted with EtOAc, washed with water, sat. NaHCO\(_3\), brine and dried (Na\(_2\)SO\(_4\)). The solvent was removed on a rotary evaporator to obtain the tosylate 4 as a yellow foam (384 mg, 96%).

[000286] \(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\) 7.80 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.3-7.43 (m, 5H), 6.78 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.09 (s, 2H), 4.77 (s, 1H, 14-OH), 4.55 (d, J = 3.3 Hz, 1H), 3.98-4.09 (m, 1H), 3.53-3.88 (m, 1H), 3.02 (d, J = 6.6 Hz, 2H), 2.95 (d, J = 18.7 Hz, 2H), 2.53-2.58 (m, 2H), 2.35 (s, 3H), 2.25-2.34 (m, 2H), 1.99-2.13 (m, 2H), 1.31-1.45 (m, 5H), 0.84-0.88 (m, 1H), 0.47-0.53 (m, 3H), 0.10-0.12 (m, 2H). APCI\(^+\) = 602.

(iv) 17-Cyclopropylmethyl-4,5 \(\alpha\)-epoxy-3-benzyloxy-14-hydroxy-6 \(\alpha\)-methyl morphinan (5)

[000287] To a slurry of LAH powder (0.42 g, 11.0 mmol) in anhydrous THF (8 mL) at 0 °C under N\(_2\) was added a solution of tosylate 4 (0.66 g, 1.1 mmol) in anhydrous THF (20 mL) dropwise over a period of 15 min. The mixture was warmed to RT and then heated to reflux for 1.5h. When the reaction was complete the reaction mixture was cooled to 0 °C and ~ 5 g of solid Na\(_2\)SO\(_4\),10H\(_2\)O was added to it portion-wise followed by EtOAc. After stirring the mixture for 1h the solids were filtered and washed with EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography using 10-60% EtOAc / hexanes as eluent to isolate the pure product 5 (0.18 g, 38%) as a white solid.

[000288] \(^1\)H NMR (300 MHz, MeOH-d3): \(\delta\) 7.30-7.43 (m, 5H), 6.78 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.13 (s, 2H), 4.55 (d, J = 3.3 Hz, 1H), 3.12 (d, J = 6.6 Hz, 1H), 3.10 (d, J = 18.7 Hz, 1H), 2.60-2.70 (m, 2H), 2.00-2.40 (m, 5H), 1.20-1.70 (m, 4H), 1.03 (d, J = 7.0 Hz, 3H), 0.84-0.88 (m, 1H), 0.47-0.53 (m, 3H), 0.10-0.12 (m, 2H). APCI\(^+\) = 432.
(v) 17-Cyclopropylmethyl-4,5 α-epoxy-3, 14-hydroxy-6α-methyl morphinan (6)

[000289] A solution of compound 6 (90 mg, 0.21 mmol) in a mixture of MeOH (2 mL) and EtOAc (1 mL) was hydrogenated with Pd(OH)_{2-C} (20 wt% Pd, wet, 30 mg) under atmospheric pressure for 1h. The black mixture was filtered through a pad of Celite, washed with MeOH and EtOAc. The filtrate was evaporated to obtain a residue that was co-evaporated with ether to isolate the desired product 6 (74 mg, quant.) as a white solid.

[000290] 1H NMR (300 MHz, MeOH-d3): δ 6.60 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.45 (d, J = 3.3 Hz, 1H), 3.13 (d, J = 19.0 Hz, 1H), 2.28-2.74 (m, 5H), 2.13-2.18 (m, 1H), 1.20-1.90 (m, 5H), 2.10-2.79-1.20 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H), 0.70-0.95 (m, 2H), 0.55-0.60 (m, 2H), 0.22 (m, 2H). APCf+ = 342.

(vi) 17-Cyclopropylmethyl-4,5 α-epoxy-3, 14-hydroxy-6α-methyl) morphinan N-oxide (C0017)

[000291] To a solution of compound 6 (71 mg, 0.208 mmol) in CHCl₃ (1 mL) and MeOH (3 drops) at 0 °C was added mCPBA (77%, 51 mg, 0.229 mmol) and the mixture was stirred for 1h. K₂CO₃ (~ 200 mg) was added to the solution and it was stirred for 10 min. The resulting solid was filtered, washed with CHCl₃ and the filtrate was evaporated to isolate the crude product. This material was purified by flash chromatography using 1-5% MeOH / CHCl₃ + 0.1-0.2% NH₄OH as eluent to obtain the pure product C0017 (42 mg, 57%) as a white solid.

[000292] 1H NMR (300 MHz, MeOH-d3): δ 6.66 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.58 (d, J = 3.3 Hz, 1H), 3.83 (d, J = 6.0 Hz, 1H), 3.57 (dd, J = 7.5, 5.7 Hz, 1H), 3.10-3.30 (m, 5H), 2.84-2.96 (m, 1H), 2.10-2.30 (m, 1H), 1.30-1.70 (m, 5H), 1.04 (d, J = 7.0 Hz, 3H), 0.70-0.82 (m, 3H), 0.48 (m, 2H). APCf= 358. HPLC = 100%.

Example 18

17-Cyclopropylmethyl-4, 5α-epoxy-3,14-dihydroxy-6 α-(1H-imidazoI-1-yl)methyl morphinan N-oxide (C0018)
(i) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-hydroxy-6α-(1H-imidazol-1-yl)methyl morphinan (7)

[000293] To a solution imidazole (45 mg, 0.66 mmol) in anhydrous DMF (6 mL) under N₂ was added NaH (60%, 27 mg, 0.66 mmol) and the solution stirred at RT for 1 h. The tosylate 4 (330 mg, 0.55 mmol) was then added and the reaction mixture was stirred at RT for 2 h and at 50 °C for 5 h. The contents of the flask were cooled to RT, poured onto water and extracted with EtOAc. The organic phase was washed with water, brine, dried (Na₂SO₄) and evaporated to isolate the crude product. This crude product was purified by flash chromatography with 100% EtOAc and 1-10% MeOH / EtOAc + 0.1 to 0.2% NH₄OH to isolate the pure product 7 (200 mg, 74%) as a white foam.

[000294] ¹H NMR (300 MHz, MeOH-d3): δ 7.62 (s, 1H), 7.28-7.45 (m, 5H), 7.16 (s, 1H), 6.98 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.19 (dd J = 12.4, 6.7 Hz, 2H), 4.27 (d, J = 3.3 Hz, 1H), 4.07 (dd, J = 8.0, 5.0 Hz, 1H), 3.88 (dd, J = 8.0, 5.0 Hz, 1H), 3.06-3.18 (m, 2H), 2.00-2.69 (m, 7H), 1.20-1.70 (m, 5H), 0.8-1.0 (m, 1H), 0.55 (m, 2H), 0.16 (m, 2H). APCI⁺ = 498.

(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-6α-(1H-imidazol-1-yl)methyl morphinan (8)

[000295] A solution of compound 7 (100 mg, 0.201 mmol) in MeOH (6 mL) was hydrogenated with Pd(OH)₂-C (20 wt% Pd, wet, 30 mg) under atmospheric pressure for 1 h. The black mixture was filtered through a pad of Celite, washed with MeOH and EtOAc. The filtrate was evaporated to obtain a white solid, which was triturated with ether to isolate the desired product 8 (62 mg, 76%) as a white solid.
1H NMR (300 MHz, MeOH-d3): δ 7.76 (s, 1H), 7.23 (s, 1H), 6.98 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 4.19 - 4.27 (ra, 2H), 4.00 (dd, J = 8.0 Hz, 1H), 3.16 (d, J = 18.7 Hz, 1H), 3.14 (d, J = 6.6 Hz, 1H), 2.0-2.69 (m, 7H), 1.7-1.2 (m, 4H), 0.80-1.08 (m, 2H), 0.52-0.54 (m, 2H), 0.14-0.16 (m, 2H). APCI⁺ = 408. HPLC = 100%.

(iii) 17-Cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxy-6α-(1H-imidazol-1-yl)methylmorphinan N-oxide (C0018)

[000297] To a solution of compound 8 (80 mg, 0.196 mmol) in CHCl₃ (3 mL) at 0 °C was added mCPBA (77%, 46.3 mg, 0.206 mmol) and the mixture was stirred for 1h. K₂CO₃ was added to the solution and it was stirred for 10 min. The solid was filtered, washed with CHCl₃ and the filtrate was evaporated to isolate the crude product. This material was purified by flash chromatography using 1-8% MeOH / CHCl₃ + 0.2-0.4% NH₃OH as eluent to obtain the pure product CO018 (74 mg, 89%) as a white solid.

[000298] 1H NMR (300 MHz, MeOH-d3): δ 7.80 (s, 1H), 7.25 (s, 1H), 7.01 (s, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 4.40 (d, J = 3.0 Hz, 1H), 4.24 (dd, J = 8.8, 4.7 Hz, 1H) 4.00 (dd, J = 8.0, 5.0 Hz, 1H), 3.83 (d, J = 6.4 Hz, 1H), 3.56 (dd, J = 7.4, 5.8 Hz, 1H), 3.20-3.31 (m, 5H), 2.80-2.93 (m, 1H), 2.51-2.63 (m, 1H), 1.33-1.74 (m, 5H), 0.8-1.00 (m, 3H), 0.40-0.50 (m, 2H). APCI⁺ = 424. HPLC = 100%.

Example 19

(S)-17-Cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxy-6,7-(2'-oxo-r,2'-dihydropyridine-3'-carboxylic acid methyl ester ) morphinan N-oxide (C0019)
A mixture of naltrexone hydrochloride (3.0 g, 7.94 mmol), benzyl bromide (1.43 g, 8.34 mmol) and K$_2$CO$_3$ (3.0 g, 21.7 mmol) in anhydrous DMF (30 mL) was stirred at RT under N$_2$ overnight. The reaction mixture was poured onto water (500 mL), extracted with CH$_2$Cl$_2$, washed with water, brine and dried (Na$_2$SO$_4$). The solvent was evaporated under reduced pressure to obtain a residue, which was dissolved in 2N HCl (200 mL) and extracted with ether (to remove excess BnBr). The organic phase was discarded and the aqueous phase was made basic with c. NH$_4$OH, the precipitated white solid was extracted with CHCl$_3$, washed with brine, dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure to obtain 2 (3.30 g, 96%) as a white foam.

$^1$H NMR (300 MHz, chloroform-d): $\delta$ 7.20-7.50 (m, 5H), 6.71 (d, J = 8.0 Hz, IH), 6.56 (d, J = 8.0 Hz, IH), 5.13 (dd, J = 13.5, 11.8 Hz, 2H), 4.70 (s, 1H), 4.83 (s, 1H), 3.00-3.18 (m, 3H), 2.28-2.74 (m, 6H), 2.13 (dt, J = 8.5, 3.6 Hz, 1H), 1.50-1.70 (m, 2H), 0.85 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H). APCI$^+$ - 432.
(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-hydroxy-7-(N,N-dimethylamino)methylene)-6-oxo morphinan (3)

[000301] A mixture of compound 2 and DMF-DMA was heated to reflux for 1.5h under N₂. Excess of DMF-DMA was removed on a rotary evaporator under reduced pressure and the residue was co-evaporated with EtOAc to isolate the crude product. This crude material was purified by flash chromatography with 1-5% MeOH / CHCl₃ to isolate the pure enamino 3 (1.71 g, 76%) as a yellow solid.

[000302] ¹H NMR (300 MHz, chloroform-d): δ 7.62 (s, 1H), 7.20-7.50 (m, 5H), 6.71 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.20 (dd, J = 13.5, 11.8 Hz, 2H), 4.94 (bs, 1H), 4.62 (s, 1H), 3.17 (d, J = 6.6 Hz, 1H), 3.05-3.12 (m, 1H), 3.02 (s, 6H), 2.56-2.70 (m, 3H), 2.2-2.43 (m, 5H), 1.60-1.63 (m, 1H), 0.84-0.88 (m, 1H), 0.53-0.56 (m, 2H), 0.13-0.16 (m, 2H). APCI⁺ = 487.

(iii) (S)-17-Cyclopropylmethyl-4,5α-epoxy-3-benzyloxy-14-hydroxy-6,7-(2'-oxo-1', 2'-dihydropyridine-3'-carboxylic acid methyl ester) morphinan (4)

[000303] A solution of compound 3 (500mg, 1.03 mmol) and methyl cyanoacetate (130 mg, 1.24 mmol) in anhydrous MeOH (5 mL) was heated to reflux in a sealed tube for 48h. The solvent was removed under reduced pressure to obtain a brown residue, which was purified by flash chromatography using 1-10% MeOH / CHCl₃ + 0.2-0.4% NH₄OH to isolate the desired pyridone 4 (120 mg, 22%) as a yellow solid.

[000304] ¹H NMR (300 MHz, DMSO-d6): δ 12.3 (bs, 1H), 7.73 (s, 1H), 7.27-7.35 (m, 5H), 6.80 (d, J = 8.2 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 5.17 (s, 1H), 5.07 (dd, J = 13.5, 11.8 Hz, 2H), 3.72 (s, 3H), 3.22 (m, 1H), 3.10 (d, J = 18.7 Hz, 1H), 2.60-2.80 (m, 2H), 2.10-2.40 (m, 6H), 1.49-1.54 (m, 1H), 0.84-0.88 (m, 1H), 0.53-0.56 (m, 2H), 0.13-0.16 (m, 2H). APCI⁺ = 541.

(iv) (S)-17-Cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxy-6,7-(2'-oxo-1', 2'-dihydropyridine-3'-carboxylic acid methyl ester) morphinan (5)

[000305] A solution of compound 4 (120 mg, 0.22 mmol) in MeOH (10 mL) was hydrogenated with Pd-C (10 wt% Pd, wet, 90 mg) under atmospheric pressure for 1h. The black mixture was filtered through a pad of Celite, washed with MeOH and EtOAc.
The filtrate was evaporated to obtain a residue, which was purified by flash chromatography with 1-10% MeOH / CHCl₃ + 0.2-0.4% NH₄OH to give the desired product 5 (73 mg, 73%) as a yellow solid.

\[ \text{NMR (300 MHz, CDCl}_3\]): \delta \ 7.90 \ (s, \ 1H), \ 6.67 \ (d, \ J = 8.0 \ Hz, \ 1H), \ 6.55 \ (d, \ J = 8.0 \ Hz, \ 1H), \ 5.34 \ (s, \ 1H), \ 3.86 \ (s, \ 3H), \ 3.25-3.27 \ (m, \ 1H), \ 3.13 \ (d, \ J = 18.7 \ Hz, \ 1H), \ 2.92 \ (s, \ 1H), \ 2.64-2.74 \ (m, \ 2H), \ 2.29-2.50 \ (m, \ 5H), \ 1.74-1.78 \ (m, \ 1H), \ 0.84-0.88 \ (m, \ 1H), \ 0.53-0.56 \ (m, \ 2H), \ 0.13-0.16 \ (m, \ 2H). \ APCI^+ = 451. \]

(v) (S)-17-Cyclopropylmethyl 1-4,5α-epoxy-3-hydroxy-14-ethoxy-6-oxo-morphinan N-oxide (C0020)

To a solution of compound 5 (48 mg, 0.107 mmol) in CHCl₃ (2 mL) at 0 °C was added mCPBA (77%, 27 mg, 0.118 mmol) and the mixture was stirred for 1h. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography using 1-10% MeOH / CHCl₃ + 0.2-0.4% NH₄OH as eluent to obtain the pure product C0019 (36 mg, 72%) as a white solid.

\[ \text{NMR (300 MHz, MeOH-d3):} \ \delta \ 7.97 \ (s, \ 1H), \ 6.67 \ (d, \ J = 8.0 \ Hz, \ 1H), \ 6.63 \ (d, \ J = 8.0 \ Hz, \ 1H), \ 5.37 \ (s, \ 1H), \ 4.01 \ (d, \ J = 6.3 \ Hz, \ 1H), \ 3.81 \ (s, \ 3H), \ 3.60 \ (dd, \ J = 7.14 \ Hz, \ 1H), \ 3.32-3.43 \ (m, \ 2H), \ 3.22-3.29 \ (m, \ 3H), \ 2.98-3.07 \ (m, \ 1H), \ 2.57 \ (d, \ J = 15.7 \ Hz, \ 1H), \ 2.46 \ (d, \ J = 15.7 \ Hz, \ 1H), \ 1.84-1.90 \ (m, \ 1H), \ 1.49-1.55 \ (m, \ 1H), \ 0.74-0.77 \ (m, \ 2H), \ 0.47-0.52 \ (m, \ 2H). \ APCI^+ = 467. \ HPLC = 100\%. \]

Example 20

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-ethoxy-6-oxo-morphinan N-oxide (C0020)
(i) 17-cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-hydroxy morphinan-6-one (2)

[000309] A mixture of naltrexone hydrochloride 1 (3.0 g, 7.94 mmol), benzyl bromide (1.43 g, 8.34 mmol) and K₂CO₃ (3.0 g, 21.7 mmol) in anhydrous DMF (30 mL) was stirred at RT under N₂ overnight. The reaction mixture was poured onto water (500 mL), extracted with CH₂Cl₂, washed with water, brine and dried (Na₂SO₄). The solvent was evaporated under reduced pressure to obtain a residue, which was dissolved in 2N HCl (200 mL) and extracted with ether (to remove excess BnBr). The organic phase was discarded and the aqueous phase was made basic with c. NH₄OH, the precipitated white solid was extracted with CH₂Cl₂, washed with brine, dried (Na₂SO₄) and the solvent was removed under reduced pressure to provide 2 (3.30 g, 96%) as a white foam.

[000310] ¹H NMR (300 MHz, chloroform-d): δ 7.20-7.50 (m, 5H), 6.71 (d, J = 8.0 Hz, IH), 6.56 (d, J = 8.0 Hz, IH), 5.13 (dd, J = 13.5, 11.8 Hz, 2H), 4.70 (s, 1H), 4.83
(s, 1H), 3.00-3.18 (m, 3H), 2.28-2.74 (m, 6H), 2.13 (dt, J = 8.5, 3.6 Hz, 1H), 1.50-1.70 (m, 2H), 0.85 (m, 1H), 0.53 (m, 5H), 6.70 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.22 (dd, J = 13.5, 1.8 Hz, 2H), 4.60 (s, 1H), 3.55-3.69 (m, 6H), 2.96-3.15 (m, 5H), 2.54-2.65 (m, 2H), 2.29-2.36 (m, 3H), 2.13 (dt, J = 8.5, 3.6 Hz, 1H), 1.91-2.05 (m, 1H), 1.30-1.70 (m, 5H), 0.85 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H). APCI⁺ = 432.

(ii) 17-Cyclopropylmethyl-4, 5α-epoxy-3-benzyloxy-14-hydroxy-6,6-dimethoxyniropbinan (3)

[000311] To a solution of the ketone 2 (2.63 g, 5.56 mmol) in anhydrous methanol (10 mL) was added trimethyl orthoformate (10 mL) and cone. sulfuric acid (2 mL). This mixture was heated to reflux for 4h under N₂. Volatiles were removed under reduced pressure to obtain a residue to which was added cone. NH₄OH and it was then extracted with chloroform. The organic phase was washed with water, brine and dried (NaSO₄). Evaporation of the solvent provided a yellow oil, which was purified by flash chromatography using 1-10% MeOH / CHCl₃ to isolate 3 (0.43 g) and a mixture of 3 and 3a (10:1) (2.0 g). Total yield = 94%.

[000312] ¹H NMR (300 MHz, chloroform-d): δ 7.20-7.50 (m, 5H), 6.71 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.27 (dd, J = 13.5, 11.8 Hz, 2H), 4.60 (s, 1H), 3.43 (s, 3H), 2.96-3.15 (m, 5H), 2.54-2.65 (m, 2H), 2.29-2.36 (m, 3H), 2.13 (dt, J = 8.5, 3.6 Hz, 1H), 1.91-2.05 (m, 1H), 1.30-1.70 (m, 5H), 0.85 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H). APCI⁺ = 478.

(iii) 17-Cyclopropylmethyl-4, 5α-epoxy-3-benzyloxy-14-ethoxy-6,6-dimethoxymorphinan (4)

[000313] To a solution of compound 3 (0.5 g, 1.05 mmol) in anhydrous DMF (6 mL) under N₂ was added NaH (60%, 0.2 g, 5.25 mmol) and it was stirred at RT for 1h. Diethyl sulfate (0.5 g, 3.15 mmol) was then added and the reaction mixture was stirred at RT for 48h. 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 (140 mg, 26%) as a colorless oil.

[000314] ¹H NMR (300 MHz, MeOH-d3): δ 7.20-7.50 (m, 5H), 6.70 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.22 (dd, J = 13.5, 11.8 Hz, 2H), 4.60 (s, 1H), 3.55-3.69
(m, 2H), 3.40 (s, 3H), 3.07-3.13 (m, 1H), 2.93 (s, 3H), 2.54-2.64 (m, 2H), 2.29-2.36 (m, 3H), 2.00-2.07 (m, 2H), 1.67-1.85 (m, 3H), 1.19-1.30 (m, 5H), 0.85 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H). APCI + = 506.

(iv) 17-Cyclopropylmethyl-4, 5α-epoxy-3-hydroxy-14-ethoxy-6-oxo-morphinan (5)

[000315] A solution of compound 4 (130 mg, 0.26 mmol) in TFA (2 mL) was heated to reflux for 45 min. The mixture was cooled to RT, poured onto sat. NaHCO₃ solution, extracted with EtOAc, washed with brine, dried (Na₂SO₄) and evaporated to isolate crude 5 as a white solid. The solid was triturated with ether to obtain pure product 5 (85 mg, 90%).

[000316] ¹H NMR (300 MHz, MeOH-d₃): δ 6.61 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 4.68 (s, 1H), 3.84-3.77 (m, 2H), 3.66 (d, J = 6.0 Hz, 1H), 3.45-3.50 (m, 1H), 3.15 (d, J = 18.4 Hz, 1H), 2.60-2.90 (m, 3H), 2.32-2.41 (m, 3H), 2.41-2.30 (m, 3H), 1.27-1.44 (m, 5H), 0.90 (m, 1H), 0.46-0.56 (m, 2H), 0.12-0.22 (m, 2H). APCI + = 370.

(v) 17-Cyclopropylmethyl-4, 5α-epoxy-3-hydroxy-14-ethoxy-6-oxo-morphinan N-oxide (CO020)

[000317] To a solution of compound 5 (84 mg, 0.23 mmol) in CHCl₃ (2 mL) and MeOH (3 drops) at 0 °C was added mCPBA (77%, 53 mg, 0.242 mmol) and the mixture was stirred for 1h. K₂CO₃ (~ 200 mg) was added to the solution and it was stirred for 10 min. The solid was filtered, washed with CHCl₃ and the filtrate was evaporated to isolate the crude product. This material was purified by flash chromatography using 1-8% MeOH / CHCl₃ + 0.2-0.4% NH₄OH as eluent to obtain the pure product CO020 (66 mg, 75%) as a white solid.

[000318] ¹H NMR (300 MHz, MeOH-d3): δ 6.69 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.80 (s, 1H), 3.99-4.04 (m, 2H), 3.61 (dd, J = 6.0 3.30 Hz, 2H), 3.40-3.50 (m, 2H), 3.22-3.29 (m, 1H), 2.70-3.10 (m, 4H), 2.28-2.34 (m, 1H), 2.10-2.16 (m, 1H), 1.40-1.64 (m, 3H), 1.30 (t, J = 6.90 Hz, 3H), 0.64 -0.72-(m, 2H), 0.32-0.42 (m, 2H). APCI + = 386. HPLC = 100%. 

Example 21

17-cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-6α-hydroxymethyl morphinan N-oxide (C0021)

(i) 17-Cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-6α-hydroxymethyl morphinan (2)

[000319] To a solution of Nalmefene (free base) 1 (0.3 g, 0.88 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen was added BH₃·THF (IM in THF, 0.15 g, 1.8 mL, 1.76 mmol) dropwise and the resulting mixture was stirred at RT overnight. The mixture was cooled to 0 °C, EtOH (3 mL) was added followed by 3M NaOH (0.8 mL) and H₂O₂ (35 wt %, 0.6 mL). After stirring the mixture for 1h at RT, saturated NH₄Cl was added until pH = 7. The reaction mixture was then extracted with chloroform, washed with brine and dried (Na₂SO₄). Evaporation of the solvent provided the crude product, which was purified by flash column chromatography using 2-4% MeOH / CHCl₃ + 1% NH₄OH as eluent to isolate the pure product (0.16 g, 51%) as a white solid.

[000320] ¹H NMR (300 MHz, DMSO-d₆): δ 8.87 (s, 1H, 3-OH), 6.54 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 4.77 (s, IH, 14-OH), 4.56 (d, J = 3.3 Hz, 1H), 4.45 (t, J = 5.3 Hz, IH, 21-OH), 3.52 (m, IH), 3.23 (m, IH), 3.02 (d, J = 6.6 Hz, IH), 2.95 (d, J = 18.7 Hz, IH), 2.58 (m, 2H), 2.31 (m, 2H), 2.11 (m, 3H), 1.33 (m, 4H), 0.86 (m, IH), 0.53 (m, 3H), 0.12 (m, 2H). APCI⁺ = 358.

(ii) (S)-17-Cyclopropylmethyl-4, 5α-epoxy-3,14-dihydroxy-6 α-hydroxymethyl morphinan N-oxide (C0021)

[000321] To a solution of compound 2 (32 mg, 0.089 mmol) in CHCl₃ (1 mL) at 0 °C was added mCPBA (77%, 21 mg, 0.094 mmol) and the mixture was stirred for 1h.
K$_2$CO$_3$ (~ 200 mg) was added to the solution and it was stirred for 10 min. The solid was filtered, washed with CHCl$_3$ and the filtrate was evaporated to isolate the crude product. This material was purified by flash chromatography using 2-10% MeOH / CHCl$_3$ + 1-3% NH$_3$OH as eluent to provide the pure product C0021 as a cream colored solid (16 mg, 49%)

[000322] $^1$H NMR (300 MHz, MeOH-d3): $\delta$ 6.64 (d, $J = 8.0$ Hz, 1H), 6.54 (d, $J = 8.0$ Hz, 1H), 4.82 (d, $J = 3.8$ Hz, 1H), 3.83 (d, $J = 6.1$ Hz, 1H), 3.72 (dd, $J = 8.0$, 2.8 Hz, 1H), 3.57 (dd, $J = 7.2$, 5.4 Hz, 2H), 3.45 (d, $J = 6.6$ Hz, 1H), 3.43 (d, $J = 6.6$ Hz, 1H), 3.20 (m, 3H), 2.95 (m, 1H), 2.35 (m, 1H), 1.68 (m, 2H), 1.51 (m, 3H), 0.76 (m, 3H), 0.46 (m, 2H). APCI$^+$ = 374, HPLC = 100%

**Example 22**

($S$)-17-Cyclopropylmethyl-4,5$\alpha$-epoxy-3-hydroxy-14-(3'-phenylpropyloxy)-6-methylene morphinan N-oxide trifluoroacetic acid salt (C0022)

The following reaction sequence was used for the preparation of C0022.

(i) 17-cyclopropylmethyl-4, 5$\alpha$-epoxy-3-benzyloxy-14-hydroxy-6-methylene morphinan (2):
[000323] A mixture of nalmefene hydrochloride (1) (3.0 g, 8.0 mmol), benzyl bromide (1.43 g, 8.34 mmol) and K$_2$CO$_3$ (3.0 g, 21.7 mmol) in anhydrous DMF (30 ml) was stirred at RT under N$_2$ overnight. The reaction mixture was poured onto water (500 ml), extracted with DCM, washed with water, brine and dried (Na$_2$SO$_4$). The solvent was evaporated under reduced pressure to provide a residue that was dissolved in 2N HCl (200 ml) and extracted with ether (organic phase was discarded). The aqueous phase was made basic with aqueous NH$_4$OH and extracted with DCM, washed with brine and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to provide a white foam (2.4 g, 70%).

[000324] $^1$H NMR (300 MHz, DMSO-d$_6$): 7.3-7.43 (m, 5H), 6.77 (d, $J$ = 8.0 Hz, 1H), 6.59 (d, $J$ = 8.0 Hz, 1H), 5.18 (s, 1H, 14-OH), 5.13 (s, 2H), 4.90 (d, $J$ = 14.3 Hz, 3H), 4.83 (s, 1H), 2.94-3.01 (m, 2H), 2.60-2.65 (m, 1H), 2.49-2.52 (m, 2H), 2.20-2.35 (m, 2H), 2.23 (dt, $J$ = 8.5 Hz, $J_2$ = 3.6 Hz, 1H), 2.05-2.09 (m, 1H). 1.96 (dt, $J$ = 8.5 Hz, $J_2$ = 3.6 Hz, 1H), 1.48-1.52 (m, 1H), 1.28-1.32 (m, 1H), 1.14-1.22 (m, 1H), 0.80-0.86 (m, 1H), 0.43-0.53 (m, 2H), 0.10-0.13 (m, 2H). (APCI$^+$): 430 (M+1).

(ii) 17-cyclopropylmethyl-4,5a-epoxy-3-benzyloxy-14-(3’phenylpropoxy)-6-methylene morphinan (3)

[000325] To DMSO (10 ml) was added NaH (60% emulsion) (0.81 g, 20.5 mmol) the mixture was stirred at RT under a nitrogen atmosphere. Benzylnalmefene (2) (1.75 g, 4.1 mmol) was then added to this solution. After stirring the mixture for 30 minutes 3-phenyl-1-bromopropane (1.85 ml, 12.2 mmol) was added dropwise and the reaction solution stirred for 18 days (reaction time not optimized). After diluting the reaction mixture with water (200 ml) it was extracted with ethyl acetate (3 X 50 ml). The combined organic phases were washed with water, brine and dried (Na$_2$SO$_4$). Evaporation of solvent followed by chromatographic purification using 10% ethyl acetate in hexane, 50% ethyl acetate in hexane and finally ethyl acetate gave 0.34 g (16%) of 3 and 1.3 g (74%) of starting material.

[000326] $^1$H NMR (300 MHz, CDCl$_3$): 7.11 - 7.50 (m, 10 H), 6.71 (d, $J$=8.0 Hz, 1H), 6.52 (d, $J$=8.3 Hz, 1H), 5.32 (d, $J$=1.9 Hz, 1H), 5.19 (s, 2H), 5.03 (s, 1H), 4.85 (d, $J$=1.9 Hz, 1H), 3.67 (q, $J$=8.0 Hz, 1H), 3.40 (d, $J$=5.0 Hz, 1H), 3.32 (q, $J$=6.1 Hz, 1
H), 3.06 (d, J=17.9 Hz, 1 H), 2.80 (t, J=7.4 Hz, 1 H), 2.46 - 2.74 (m, 3 H), 2.24 - 2.37 (m, 3 H), 1.89 - 2.12 (m, 4 H), 1.72 - 1.84 (m, 1 H), 1.33 - 1.44 (m, 1 H), 1.13 (dt, 1 H), 0.66 - 0.81 (m, 1 H), 0.38 - 0.51 (m, 2 H), 0.00 - 0.14 (m, 2 H). (APCI<sup>+</sup>): 548 (M+).

(iii) 17-cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3'-phenylpropoxy)-6-methylene morphinan (4)

[000327] A mixture of compound 3 (0.1 g) and TFA (4 ml) was refluxed for 1 h. AU volatiles were removed and the residue basified with 7M ammonia in methanol. It was then purified by column chromatography using 50% ethyl acetate in hexane to provide 0.05 g (60%) of 4.

[000328] <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 7.14 - 7.42 (m, 5 H), 6.67 (d, J=8.3 Hz, 1 H), 6.53 (d, J=8.3 Hz, 1 H), 5.23 (d, J=I. 9 Hz, 1 H), 5.04 (br. s., 1 H), 4.82 (d, J=I. 9 Hz, 1 H), 3.66 (q, J=6.3 Hz, 1 H), 3.41 (d, J=5.0 Hz, 1 H), 3.25 - 3.36 (m, 1 H), 3.07 (d, J=17.9 Hz, 1 H), 2.79 (t, J=7.4 Hz, 2 H), 2.47-2.70 (m, 3H), 2.25 - 2.37 (m, 3 H), 1.90 - 2.14 (m, 4 H), 1.78 (dt, j=3.3, 13.5 Hz, 1 H), 1.38 (dd, J=2.7, 10.7 Hz, 1 H), 1.12 (dt, j=3.8, 13.5 Hz, 1 H), 0.67 - 0.83 (m, 1 H), 0.40 - 0.50 (m, 2 H), -0.01 - 0.14 (m, 2 H) (APCI<sup>+</sup>): 458 (M+).

(iv) (S)-17-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(3'-phenylpropyloxy)-6-methylenemorphinan N-oxide trifluoroacetic acid salt (C0022)

[000329] To a solution of 4 (0.05 g, 0.1 mmol) in DCM (4 ml) was added dropwise mCPBA (0.027 g, 77% max, 0.86 mmol) in DCM (2 ml). After 1 hour the solvent was evaporated and the residue purified by column chromatography using 5-10% of MeOH in DCM as eluent to provide 30 mg of impure 5. Further purification was achieved by using semi-prep HPLC using MeOH/water = 60/40 mixture with 0.1% TFA as eluent to provide 22 mg (34%) of compound C0022 as a TFA salt. m.p. = 182 °C (decomposing).

[000330] <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): 7.15 - 7.37 (m, 5 H), 6.72 (d, J=8.0 Hz, 1 H), 6.66 (d, J=8.5 Hz, 1 H), 5.41 (br. s., 1 H), 5.06 (br. s., 1 H), 4.65 (d, J=4.4 Hz, 1 H), 4.03 (dd, J=13.5, 5.8 Hz, 1 H), 3.74 - 3.89 (m, 2 H), 3.58 - 3.70 (m, 1 H), 3.51 (d, J=20.1 Hz, 1 H), 3.07 - 3.44 (m, 3 H), 2.73 - 2.89 (m, 3 H), 2.00 - 2.29 (m, 5 H), 1.76 -
1.87 (m, 1 H), 1.18 - 1.43 (m, 2 H), 0.77 - 0.92 (m, 2 H), 0.47 - 0.66 (m, 2 H). (APCI+): 474 (M+1).

**General Experimental Procedure for the Synthesis of Compounds (C0023-C0026)**

**General procedure for the 3-O-benzylation of 17-cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxyomorphinan derivatives**

To a solution of the 3-hydroxy compound (1 eq.) in DMF (2mL/mmol) under N₂ was added K₂CO₃ (1.3 eq) followed by benzyl bromide (1.1 eq) and the resulting mixture stirred for 20 h. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organics were dried over MgSO₄ and concentrated to give the crude 3-O-benzyl derivative that was further treated as described in the individual cases.

**General procedure for the 14-O-alkylation of 3-Benzylxoy-17-cyclopropylmethyl-4,5α-epoxy-14-hydroxyomorphinan derivatives**

NaH (3 eq, 60% suspension in mineral oil) was added to a solution of 3-benzyloxy-17-cyclopropylmethyl-4,5α-epoxy-14-hydroxyomorphinan derivatives (1 eq.) in DMF under N₂. After 20 minutes the alkyl halide/alkyl sulfate was added (1.3 eq.) and the resulting mixture was stirred for 2-5 h 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 to provide the crude material that was purified whenever necessary or used as such further.

**General procedure for hydrogenation:**

10-50 Mol % of the palladium catalyst (10% Pd on carbon, 50% wet) was added to a solution of the compound in methanol or methanol-THF mixture (1:1) and hydrogenated at 1 atmosphere pressure for 2 to 3 h at room temperature. The catalyst was filtered off and the filtrate was evaporated to give the crude product which was used as such without further purification for the next step.

**General procedure for the N-oxidation using raCPBA:**
To a solution of the amine (1 eq.) in dichloromethane was added mCPBA (1.2 eq., 77%) and the reaction stirred at room temperature for 2 h. At the end of the reaction, as indicated by mass spec analysis, the reaction mixture was purified either by silica gel column chromatography or by semi-prep HPLC.

Example 23

17-Cyclopropylmethyl-4,5 α-epoxy-3, 14-dihydroxymorphinan- N-oxide (C0023)

The title compound was prepared from 17-Cyclopropylmethyl-4,5 α-epoxy-3, 14-dihydroxymorphinan using the general procedure for N-oxidation. At the end of the reaction the reaction mixture was diluted with dichloromethane and washed with saturated NaHCO₃ solution. The organic phase dried (MgSO₄), evaporated and the crude material was purified by preparative TLC (1 mm plate, eluent MeOH/DCM 5/95) to afford 65% of C0023 as a white solid.

1H NMR (301 MHz, CHLOROFORM-d) ppm 6.75 (d, J=8.3 Hz, 1 H), 6.54 (d, J=8.3 Hz, 1 H), 4.84 (t, J=8.0 Hz, 1 H), 3.73 (br. s., 1 H), 3.36 - 3.46 (m, 2 H), 3.04 - 3.17 (m, 2 H), 3.04 - 3.09 (m, 1 H), 2.91 - 3.03 (m, 2 H), 2.09 - 2.27 (m, 1 H), 1.79 - 2.01 (m, 1 H), 1.46 - 1.67 (m, 4 H), 1.15 - 1.43 (m, 4 H), 0.63 - 0.84 (m, 2 H), 0.26 - 0.53 (m, 2 H); APCI [M+H] 344.2; HPLC (70/30 Water/Methanol with 0.1% TFA, Rₜ = 7.08 min).

Example 24

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxymorphinan-N-oxide (C0024)

(i) S-Benzzyloxy-17-cyclopropylmethyl-4, 5α-epoxy-14-methoxymorphinan

The title compound was synthesised in 82% yield by treating 3-benzyloxy-17-cyclopropylmethyl-4,5 α-epoxy-14-hydroxymorphinan with dimethyl sulfate and NaH as described in the general procedure and was isolated as a light yellow oil.
(0003381) 1H NMR (301 MHz, CHLOROFORM-d) ppm 7.29 - 7.49 (m, 5 H), 6.74 (d, J=8.3 Hz, 1 H), 6.55 (d, J=8.0 Hz, 1 H), 5.17 (dd, J=15.7, 12.1 Hz, 2 H), 4.74 (t, J=7.7 Hz, 1 H), 3.51 (d, J=5.0 Hz, 1 H), 3.30 (s, 3H), 3.12 (d, J=18.2 Hz, 1 H), 2.64 (dd, J=11.3, 4.7 Hz, 1 H), 2.25 - 2.51 (m, 3 H), 2.02 - 2.23 (m, 2 H), 1.55 - 1.83 (m, 2 H), 1.15 - 1.45 (m, 1H), 0.80 - 0.96 (m, 5 H), 0.40 - 0.66 (m, 2 H), 0.15 (m, 2 H); APCI [M+H]^+ 432.3

(ii) n-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxymorphinan

[000339] A methanolic solution of 3-benzyloxy-17-cyclopropylmethyl-4,5 α-epoxy-14-methoxymorphinan was subjected to hydrogenation as described in the general procedure to afford the title compound in quantitative yield.

[000340] 1H NMR (301 MHz, METHANOL-di) ppm 6.67 - 6.75 (m, 2 H), 4.71 (t, J=8.5, 7.7 Hz, 1 H), 4.41 (d, J=5.8 Hz, 1 H), 3.35 - 3.55 (m, 4 H), 2.96 - 3.17 (m, 2 H), 2.67 - 2.90 (m, 2 H), 2.41 - 2.66 (m, 1 H), 2.12 - 2.33 (m, 1 H), 2.03 (d, J=14.6 Hz, 1 H), 1.41 - 1.68 (m, 2H), 1.04 - 1.26 (m, 3 H), 0.68 - 0.99 (m, 4 H), 0.43 - 0.63 (m, 2 H); APCI [M+H]^+ 342.3.

Example 25

n-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxymorphinan-N-oxide (C0025)

[000341] The title compound was prepared from 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxymorphinan according to the general procedure. A mixture of dichloromethane and methanol (5:1) was used as solvent. At the end of the reaction, as indicated by 1H NMR analysis, the solvents were removed in vacuum and the residue was re-dissolved in water and washed with ether (to remove the final traces of mCBA). The aqueous extracts were lyophyllized to get the crude material that was purified by semi-prep HPLC (water/methanol 70/30, with 0.1% TFA) to afford 31% of C0025 as a white solid.

[000342] 1H NMR (301 MHz, DEUTERIUM OXIDE) ppm 6.83 (d, J=8.3 Hz, 1 H), 6.72 (d, J=8.3 Hz, 1 H), 4.89 (t, J=8.0 Hz, 1 H), 4.67 (d, J=5.2 Hz, 1 H), 3.95 (dd,
A=I 3.5, 5.8 Hz, 1 H), 3.72 (dd, J =13.5, 4.1 Hz, 1 H), 3.49 (d, J=20.4 Hz, 1 H), 3.44 (s, 3 H), 3.16 - 3.40 (m, 3 H), 2.71 (dt, J=14.6, 4.7 Hz, 1 H), 2.12 - 2.30 (m, 1 H), 2.04 (d, J=14.9 Hz, 1 H), 1.76 (dd, J=14.9, 3.3 Hz, 1 H), 1.42 (d, J=9.4 Hz, 1 H), 1.12 - 1.37 (m, 4 H), 0.69 - 0.85 (m, 2 H), 0.38 - 0.60 (m, 2 H); APCI [M+H] 370.3.

Example 26

17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propyloxymorphinan-N-oxide
(C0026)

(i) M- Allyloxy-3-benzyloxy-17-cyclopropylmethyl-4,5 α-epoxymorphinan

[000343] The title compound was synthesised in 75 % by treating 3-benzyloxy-17-cyclopropylmethyl-4,5 α-epoxy-14-hydroxymorphinan with allyl bromide and NaH as described in the general procedure and was isolated as a colorless oil.

[000344] 1H NMR (301 MHz, CHLOROFORM-d) ppm 7.25 - 7.57 (m, 5 H), 6.72 (d, J=8.3 Hz, 1 H), 6.53 (d, J=8.0 Hz, 1 H), 5.88 - 6.17 (m, 1 H), 5.33 (dd, J=17.3, 1.7 Hz, 1 H), 4.75 (d, J=15.1 Hz, 1 H), 4.19 (dd, J=12.1, 4.7 Hz, 2 H), 3.82 (dd, J=12.1, 5.2 Hz, 1 H), 3.39 (d, J=5.0 Hz, 1 H), 3.09 (d, J=18.2 Hz, 1 H), 2.61 - 2.70 (m, 1 H), 2.44 - 2.58 (m, 1 H), 2.28 - 2.42 (m, 3 H), 1.97 - 2.20 (m, 2 H), 1.57 - 1.81 (m, 2 H), 1.23 - 1.43 (m, 2 H), 0.96 - 1.17 (m, 2 H), 0.76 - 0.94 (m, 2 H), 0.37 - 0.59 (m, 2 H), 0.11 (d, J=5.0 Hz, 2 H); APCI [M+H] 458.2.

(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxymorphinan

[000345] A methanolic solution of M-allyloxy-3-benzyloxy-17-cyclopropylmethyl-4,5 α-epoxymorphinan was subjected to hydrogenation as described in the general procedure to afford the title compound in quantitative yield.

[000346] 1H NMR (301 MHz, CHLOROFORM-d) ppm 6.68 (d, J=8.3 Hz, 1 H), 6.55 (d, J=8.3 Hz, 1 H), 4.66 (t, J=8.3, 7.7 Hz, 1 H), 4.10 (d, J=4.7 Hz, 1 H), 3.44 (d, J=6.3 Hz, 1 H), 3.38 (m, 3 H), 3.17 - 3.34 (m, 4 H), 2.87 - 3.16 (m, 2 H), 2.42 - 2.79 (m, 2 H), 2.05 - 2.22 (m, 1 H), 1.79 - 1.95 (m, 3 H), 1.42 - 1.71 (m, 2 H), 0.90 (t, J=7.4 Hz, 3 H), 0.71 - 0.82 (m, 3 H), 0.43 - 0.66 (m, 2 H); APCI [M+H] 370.3.
(iii) n-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propyloxymorphinan-N-oxide (C0026)

[000347] The title compound was prepared from 17-cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxymorphinan according to the general procedure. A mixture of dichloromethane and methanol (5:1) was used as solvent. At the end of the reaction the solvents were removed in vacuum and the residue was purified by column chromatography (methanol/dichloromethane 9/1) to afford 66% of C0026 as a white solid.

[000348] 1H NMR (301 MHz, DEUTERIUM OXIDE) ppm 6.80 (dd, J=8.3, 1.1 Hz, 1 H), 6.70 (d, /=8.3 Hz, 1 H), 4.91 (t, /=7.7 Hz, 1 H), 4.67 (d, /=4.4 Hz, 1 H), 3.91 (dd, /=13.5, 6.1 Hz, 1 H), 3.65 - 3.75 (m, 2 H), 3.53 - 3.63 (m, 1 H), 3.46 (d, J=20.4 Hz, 1 H), 3.34 (dd, /=13.5, 8.0 Hz, 1 H), 3.15 - 3.29 (m, 2 H), 2.75 (dt, /=14.0, 3.9 Hz, 1 H), 2.09 - 2.21 (m, 1 H), 2.04 (d, /=14.6 Hz, 1 H), 1.74 (dd, /=14.6, 3.3 Hz, 1 H), 1.54 - 1.68 (m, 1 H), 1.36 - 1.50 (m, 2 H), 1.10 - 1.34 (m, 3 H), 0.92 (s, 1 H), 0.92 (t, 3 H), 0.66 - 0.81 (m, 2 H), 0.38 - 0.57 (m, 2 H); APCI [M+H] 386.3; HPLC (60/40 Water/Methanol with 0.1 % TFA) R_T = 10.45 min.

Example 27

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-6-oxo-14-propyloxymorphinan-N-Oxide (C0027)
(i) S-Benzyloxy-17-cyclopropylmethyl-4,5α-epoxy-14-hydroxy-6,6-
dimethoxymorphin (3)

[000349] (a) To a solution of naltrexone hydrochloride (1.0 HCl, 2.2 g, 1 eq.) in methanol (30 mL) was added trimethylorthoformate (2.04 g, 3.3 eq.) and HCl in ether (2 M, 3.2 mL, 1.1 eq.) and the mixture was stirred at room temperature for 3 h. 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-
dimethoxymorphin (2) as a white foam.

[000350] 1H NMR (301 MHz, CHLOROFORM-d) 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=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.

[000351] (b) To a solution of 2 (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 3 (with small amount of DMF as impurity) as a highly viscous liquid.

[000352] 1H NMR (301 MHz, CHLOROFORM-d) 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=18.1, 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.

(ii) 14-Allyloxy-3-benzyloxy-17-cyclopropylmethyl-4,5α-epoxy-6,6-
dimethoxymorphin (4)
NaH (628 mg, 3 eq, 60% suspension in mineral oil) was added to a solution 3 (2.41 g, 1 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 4 as a viscous liquid.

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, /=21.2 Hz, 2 H), 5.13 (dd, /=10.5, 1.7 Hz, 1 H), 4.66 (s, 1 H), 4.15 - 4.25 (m, 1 H), 3.80 (dd, J=11.8, 5.2 Hz, 1 H), 3.43 (d, /=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), 0.11 (m, 2 H); APCI [M+H] 518.2.

To a methanolic (10 mL) solution of 4 was added IN HCl (20 mL) and stirred at room temperature for 3h. Saturated NaHC₃O₃ solution was added and the reaction extracted with dichloromethane. After evaporating the solvent crude 5 was obtained (1.06g, 91%) and was used for the next step without further purification.

1H NMR (301 MHz, CHLOROFORM-d) ppm 7.30 - 7.49 (m, 5 H), 6.71 (d, J=8.3 Hz, 1 H), 6.55 (d, J=8.3 Hz, 1 H), 5.96 - 6.21 (m, 1 H), 5.38 (dd, J=17.3, 1.7 Hz, 1 H), 5.16 - 5.32 (m, 3 H), 4.71 (s, 1 H), 4.29 - 4.45 (m, 1 H), 3.93 (dd, J=11.8, 5.5 Hz, 1 H), 3.57 (d, J=5.0 Hz, 1 H), 3.14 (d, 1 H), 2.80 - 2.94 (m, 1 H), 2.62 - 2.79 (m, 2 H), 2.38 (d, J=6.6 Hz, 2 H), 2.20 (dt, J=14.6, 3.0 Hz, 1 H), 2.02 - 2.12 (m, 2 H), 1.40 - 1.57 (m, 2 H), 0.77 - 0.98 (m, 1 H), 0.44 - 0.60 (m, 2 H), 0.05 - 0.21 (m, 2 H); APCI [M+H] 472.2
50 MoI % of palladium catalyst (10 % Pd on carbon, 50% wet) was added to a solution of 5 in methanol-THF mixture (20 mL, 1:1) and was hydrogenated at 1 atmosphere for 3 h at room temperature. The catalyst was filtered off and the filtrate was evaporated to get the crude 6 in quantitative yield, which was used as such without further purification for the next step.

1H NMR (301 MHz, CHLOROFORM-d) ppm 6.69 (d, J=8.3 Hz, 1 H), 6.56 (d, J=8.3 Hz, 1 H), 4.66 (s, 1 H), 3.69 (dd, J=14.3, 6.9 Hz, 1 H), 3.52 (d, J=5.0 Hz, 1 H), 3.28 (dd, J=14.3, 6.6 Hz, 1 H), 3.11 (d, /=18.2 Hz, 1 H), 2.84 (dt, J=14.3, 5.0 Hz, 1 H), 2.62 - 2.75 (m, 2 H), 2.32 - 2.43 (m, 2 H), 2.28 (d, J=5.5 Hz, 1 H), 2.13 - 2.23 (m, 1 H), 2.00 - 2.11 (m, 2 H), 1.84 - 1.93 (m, 1 H), 1.60 - 1.73 (m, 2 H), 1.35 - 1.50 (m, 2 H), 1.01 (t, J=7.4 Hz, 3 H), 0.78 - 0.94 (m, 1 H), 0.42 - 0.60 (m, 2 H), 0.09 - 0.18 (m, 2 H); APCI [M+H] 384.2.

17-Cyclopropylmethyl-4,15βε-epoxy-3-hydroxy-6-oxo-14-propyloxymorphiiian-N-oxide (7) (C0027)

To a solution of the amine 6 (800 mg leq.) in dichloromethane was added mCPBA (1.2 eq, 77 %) and the reaction stirred at room temperature for 2 h. At the end of the reaction, as indicated by mass spec analysis, it was purified by silica column to get 410 mg of (C0027) as a white solid.

1H NMR (301 MHz, METHANOLS) ppm 6.56 - 6.78 (m, 2 H), 4.82 (s, 1 H), 4.18 (d, J=3.9 Hz, 1 H), 3.89 - 4.11 (m, 1 H), 3.61 - 3.78 (m, 2 H), 3.47 (d, J=20.4 Hz, 2 H), 3.03 - 3.17 (m, 1 H), 2.86 - 3.03 (m, 1 H), 2.73 (dt, J=14.6, 5.0 Hz, 1 H), 2.26 - 2.45 (m, 1 H), 2.08 - 2.24 (m, 1 H), 1.68 - 1.81 (m, 2 H), 1.42 - 1.66 (m, 3 H), 1.02 (t, J=9.6, 7.7 Hz, 3 H), 0.64 - 0.85 (m, 2 H) 0.40-0.49 (m, 2H); APCI [M+H] 400.1; HPLC (65/35 Water/Methanol with 0.1 % TFA) R_τ = 6.32 min; Elemental analysis calcd for C_{23}H_{29}NO_{5}·1.9H_2O C 63.69, H 7.62, N 3.23; found C 63.70, H 7.32, N 3.32 [ _\text{D}]_{D}=-157\degree (c =1, \text{ methanol}).

Example 28

Naltriben-N-oxide (C0028)
To a solution of Naltriben (50 mg, 1 eq., received as methanesulfonic acid salt) in dichloromethane (2 mL) at room temperature was added mCPBA (1.1 eq.) and the solution stirred for 2 h. The solvent was evaporated and purified by silica column. A chloroform solution of the material isolated after column purification, which was contaminated with mCBA was treated with K₂CO₃. The potassium carbonate was filtered off and the filtrate concentrated to afford 31 mg (52%) of the N-oxide (C0028) as a white solid.

1H NMR (301 MHz, METHANOLS) ppm 7.41-7.51 (m, 2 H), 7.29 (ddd, J = 15.4, 1.4 Hz, 1 H), 7.13-7.24 (m, 1 H), 6.64 (m, 2 H), 5.70 (s, 1 H), 4.09 (br. s., 1 H), 3.65 (dd, J = 12.9, 7.2 Hz, 1 H), 3.33-3.48 (m, 3 H), 3.20-3.30 (m, 2 H), 3.08 (ddd, J = 13.2, 4.4 Hz, 1 H), 2.90 (d, J = 16.0 Hz, 1 H), 2.64 (dd, J = 15.7, 1.1 Hz, 1 H), 1.95 (d, J = 13.5 Hz, 1 H), 1.545-1.63 (m, 1 H), 0.65-0.93 (m, 2 H), 0.39-0.64 (m, 2 H); APCI [M+H] 432.1; HPLC (55/45 Water/Methanol with 0.1% TFA) Rₜ = 8.61 min.

Example 29

(S)-17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-methoxy-morphinao-6-one N-oxide (C0029)
[000363] Compound 1 (2.03 g, 4.25 mmol) was dissolved in anhydrous DMF (30 mL) and stirred under N₂. NaH (60% in mineral oil, 0.34 g, 8.49 mmol) was added. After 20 min dimethyl sulfate (0.48 mL, 5.07 mmol) was added. The resulting mixture was stirred at room temperature for 2 h. EtOAc (150 mL) was added. The solution was washed with water (3 X 100 mL) and brine (100 mL), dried over Na₂SO₄ and filtered. The filtrate was evaporated. The yellow oil was purified by column (eluent: 0.5% MeOH and 50 % EtOAc in hexanes) to give 2 (0.50 g, 24 %) as a yellow foam. ¹H NMR (300 MHz, CDCl₃) ppm 7.41 - 7.49 (m, 2 H), 7.28 - 7.39 (m, 3 H), 6.70 (d, J=8.3 Hz, 1 H), 6.52 (d, J=8.3 Hz, 1 H), 5.15 - 5.23 (m, 2 H), 4.91 (s, 1 H), 3.63 (d, J=5.8 Hz, 1 H), 3.32 (s, 6 H), 3.13 (d, J=18.2 Hz, 1 H), 2.98 (s, 3 H), 2.08 - 2.72 (m, 8 H), 1.47 - 1.85 (m, 3 H), 0.83 - 0.98 (m, 1 H), 0.44 - 0.63 (m, 2 H), 0.16 (d, J=1.4 Hz, 2 H). MS [M+H]: 492.3.

(ii) 17-Cyclopropylmethyl-4,5 α-epoxy-3-benzyloxy-14-methoxymorphinan-6-one dimethyl ketal (2)

[000364] Compound 2 (0.5 g, 1.31 mmol) was dissolved in THF (10 mL) and aqueous HCl (3 mL, 3 N) was added. The resulting solution was stirred at room temperature for 3 h and then 60 °C for 2 h. Aqueous Na₂CO₃ (10 mL, 2 M) was added. THF was removed and the aqueous residue was extracted with DCM (2X 50 mL). The DCM extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was evaporated
to give 3 (0.46 g, 100%) as a brown foam. This was used in the next reaction without purification. \(^1\)H NMR (300 MHz, CDCl\(_3\)) ppm 7.43 - 7.51 (m, 2 H), 7.28 - 7.40 (m, 3 H), 6.71 (d, \(J=8.0\) Hz, 1 H), 6.56 (d, \(J=8.3\) Hz, 1 H), 5.17 - 5.33 (m, 2 H), 4.68 (s, 1 H), 3.66 (d, \(J=5.2\) Hz, 2 H), 3.60 (t, \(J=6.6\) Hz, 1 H), 3.40 (s, 3 H), 3.14 (d, \(J=18.2\) Hz, 1 H), 2.58 - 2.87 (m, 2 H), 2.50 (dd, \(J=12.7, 6.1\) Hz, 1 H), 2.28 - 2.41 (m, 1 H), 2.03 - 2.27 (m, 2 H), 1.69 - 1.79 (m, 1 H), 1.39 - 1.54 (m, 2 H), 0.84 - 0.99 (m, 1 H), 0.46 - 0.63 (m, 2 H), 0.17 (dd, \(J=5.0, 1.4\) Hz, 2 H). MS [M+H]: 446.3.

(iii) \( \alpha \)-Cyclopropylmethyl-4,5 \( \alpha \)-epoxy-3-hydroxy-14-methoxymorphinan-6-one (4)

[000365] Morphinan 3 (0.46 g, 1.0 mmol) was dissolved in MeOH (60 mL). Pd/C (10%, wet, 0.24 g, 0.224 mmol) was added. The resulting mixture was stirred at room temperature under a H\(_2\) balloon. Mass spectrometry after 1 h indicated complete conversion of the starting material to the product. The reaction solution was filtered and the residue was dissolved in DCM (25 mL) and washed with aqueous NaHCO\(_3\) (10 mL, 2M). The DCM layer was separated and the aqueous layer was extracted with DCM (25 mL). The DCM extract was combined with the above DCM layer. This was dried over Na\(_2\)SO\(_4\) and filtered. The filtrate was evaporated to give 4 (0.256 g, 71 %) as a yellow foam. This was used in the next reaction without purification.

[000366] \(^1\)H NMR (300 MHz, CDCl\(_3\)) ppm 6.71 (d, \(J=8.0\) Hz, 1 H), 6.59 (d, \(J=8.3\) Hz, 1 H), 4.66 (s, 1 H), 3.66 (d, \(J=5.2\) Hz, 1 H), 3.60 (d, \(J=6.6\) Hz, 1 H), 3.40 (s, 3 H), 3.15 (d, \(J=18.2\) Hz, 1 H), 2.56 - 2.88 (m, 2 H), 2.46 - 2.56 (m, 1 H), 2.04 - 2.40 (m, 5 H), 1.68 - 1.82 (m, 1 H), 1.38 - 1.55 (m, 2 H), 0.81 - 1.01 (m, 1 H), 0.52 (d, 2 H), 0.17 (d, \(J=5.0\) Hz, 2 H). MS [M+H]: 356.2.

(iv) \( \alpha \)-Cyclopropyl methyl-4,5 \( \alpha \)-epoxy-3-hydroxy-14-methoxy-morphinan-6-one N-oxide (C0029)

[000367] To a solution of compound 4 (256 mg, 0.72 mmol) in DCM (36 mL) stirred at room temperature was added mCPBA (161 mg, 77 %, 0.72 mmol), followed by MeOH (10 mL) to dissolve the gel-like mixture. The resulting mixture was stirred for 20 min. Solvents were removed and the residue was dissolved in aqueous HCl (20 mL, 0.5 N). This was washed with Et\(_2\)O (2X50 mL), basified with aqueous NaHCO\(_3\) (saturated) and extracted with 10% MeOH in DCM (2X20 mL). The DCM extracts were combined,
dried over NaISO₄ and filtered. The filtrate was evaporated and the residue was purified by semi-prep HPLC to give C0029 (40 mg, 15%) as a white foam.

\[\text{H}NMR\ (300\ MHz,\ D_{2}O)\ \text{ppm}\ 6.76\ (d,\ J=8.3\ Hz,\ 1\ H),\ 6.68\ (d,\ J=8.3\ Hz,\ 1\ H),\ 5.01\ (s,\ 1\ H),\ 4.82\ (d,\ J=5.0\ Hz,\ 1\ H),\ 3.90 - 4.03\ (m,\ 1\ H),\ 3.69 - 3.82\ (m,\ 1\ H),\ 3.51\ (s,\ 3\ H),\ 3.09 - 3.47\ (m,\ 5\ H),\ 2.86 - 3.03\ (m,\ 1\ H),\ 2.58 - 2.77\ (m,\ 1\ H),\ 2.33 - 2.47\ (m,\ 1\ H),\ 2.21\ (d,\ J=15.1\ Hz,\ 1\ H),\ 1.79 - 1.90\ (m,\ 1\ H),\ 1.50 - 1.65\ (m,\ 1\ H),\ 1.23 - 1.38\ (m,\ 1\ H),\ 0.63 - 0.82\ (m,\ 2\ H),\ 0.35 - 0.57\ (m,\ 2\ H).\ \text{HPLC purity:}\ 100\%.\ \text{MS}\ [\text{M}+\text{H}]:\ 372.2.\n
**Example 30**

(S)-17-Cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxy-7-methyl-morphinan-6-one N-oxide (C0030)

![Chemical Structure](image)

(i) (S)-17-Cyclopropylmethyl-4,5α-epoxy-S-benzyloxy-14-hydroxy-T-methyl-morphinan-6-one (2)

[000369] Compound 1 (0.6 g, 1.39 mmol, prepared as described previously) was dissolved in anhydrous DMF (10 mL) and stirred under N₂. NaH (60% in mineral oil, 67 mg, 1.67 mmol) was added, followed by MeI (0.16 mL, 1.67 mmol). The resulting mixture was stirred at room temperature for 2.5 h. Water (20 mL) was added and the mixture was extracted with DCM (2X25 mL). The DCM extracts were combined, dried
over Na₂SO₄ and filtered. The filtrate was evaporated. The yellow oil was purified by column (eluent: 0.1-0.5 % MeOH in DCM) to give 2 (150 mg, 24 %) as a yellow gum.

[000370] ¹H NMR (300 MHz, CDCl₃) ppm 7.22 - 7.53 (m, 5 H), 6.72 (d, 6.20 Hz, 1 H), 5.65 (d, 6.30 Hz, 1 H), 5.16 - 5.40 (m, 3 H), 4.75 (s, 1 H), 2.87 - 3.29 (m, 4 H), 2.45 - 2.87 (m, 3 H), 2.06 - 2.22 (m, 1 H), 1.85 (dd, 6.95 Hz, 1 H), 1.51 - 1.75 (m, 2 H), 1.27 (d, 6.95 Hz, 3 H), 1.00 (d, 6.65 Hz, 3 H), 0.47 - 0.66 (m, 2 H), 20.07 - 0.24 (m, 2 H). MS [M+H]: 446.3.

(ii) (S)-17-Cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-7-methyl-morphinan-6-one (3)

[000371] Compound 2 (150 mg, 0.34 mmol) was dissolved in MeOH (15 mL). Pd/C (10%, wet, 80 mg, 0.075 mmol) was added. The resulting mixture was stirred at room temperature under a H₂ balloon. Mass spectrometry after 2.5 h showed complete conversion of the starting material to the product. The reaction solution was filtered and the filtrate was evaporated to give 3 (140 mg, 100 %) as a yellow foam.

[000372] ¹H NMR (300 MHz, CDCl₃) ppm 6.71 (d, 6.0 Hz, 1 H), 6.59 (d, 6.0 Hz, 1 H), 5.25 - 5.38 (m, 1 H), 4.71 (s, 1 H), 3.18 (d, 6.0 Hz, 2 H), 3.04 (d, 6.0 Hz, 1 H), 2.71 (d, 6.0 Hz, 1 H), 2.56 (d, 6.0 Hz, 1 H), 2.35 - 2.48 (m, 4 H), 2.18 (d, 6.0 Hz, 1 H), 1.45 (s, 1 H), 1.23 - 1.36 (m, 1 H), 1.00 (d, 6.0 Hz, 3 H), 0.80 - 0.93 (m, 1 H), 0.50 - 0.66 (m, 3 H), 0.11 - 0.21 (m, 2 H). MS [M+H]: 356.2.

(iii) (S)-17-Cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-7-methyl-morphinan-6-one N-oxide (C0030)

[000373] To a solution of compound 3 (166 mg, 0.47 mmol) in a mixture of DCM (50 mL) and MeOH (5 mL) stirred at room temperature was added mCPBA (77 %, 310 mg, 1.37 mmol). The resulting mixture was stirred for 4 h. The reaction solution was concentrated and the residue was purified by column (5-10 % MeOH in DCM) to give 90 mg of product, which was then purified by semi-prep HPLC twice to give C0030 (44 mg, TFA salt, 26 %) as a white foam.

[000374] ¹H NMR (300 MHz, METHANOL-δ) ppm 6.67 - 6.81 (m, 2 H), 5.03 (s, 1 H), 4.39 (d, 5.2 Hz, 1 H), 3.99 - 4.10 (m, 1 H), 3.76 - 3.87 (m, 1 H), 3.38 -
3.62 (m, 3 H), 3.18 - 3.27 (m, 1 H), 2.93 - 3.14 (m, 2 H), 2.18 (dd, J=14.0, 4.4 Hz, 1 H), 1.85 - 1.98 (m, 1 H), 1.57 (d, J=13.8 Hz, 1 H), 1.36 - 1.50 (m, 1 H), 0.97 (d, J=6.6 Hz, 3 H), 0.76 - 0.92 (m, 2 H), 0.47 - 0.72 (m, 2 H). HPLC purity: 100%. MS [M+H]: 372.2.

**Example 31**

[000375] A short novel route was developed for the synthesis of, 17-cyclopropylmethyl-4,5 α-epoxy-3-methoxy-14-amino morphinan-6-one, amine 4, and is described in the following scheme. Amine 4 is a synthetic intermediate en route to 14-amido substituted morphinanans such as (S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-acetamido-morphinan-6-one N-oxide trifluoroacetic acid salt.

Amine 4, 17-cyclopropylmethyl-4,5 α-epoxy-3-methoxy-14-amino morphinan-6-one, provides a convergent route to 14-amino morphinan derivatives.

(i) **Preparation of cycloadduct (3)**

[000376] 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, benzyl N-hydroxycarbamate (2) (0.715 g, 0.0043 mole). The mixture was stirred at the same temperature for additional 1 hour 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 (Na$_2$SO$_4$). 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).

**[000377]** $^1$H NMR (300 MHz, CDCl$_3$): δ 7.22-7.43 (m, 5H), 6.67 (d, J = 8.26 Hz, 1H), 6.53 (d, J = 8.26 Hz, 1H), 6.01-6.06 (m, 2H), 5.40-5.48 (m, 2H), 4.55 (s, 1H), 3.79 (s, 3H), 3.47 (s, 3H), 3.24 (d, J = 18.71 Hz, 1H), 2.79 (td, J = 12.38, 4.13 Hz, 2H), 2.37-2.54 (m, 3H), 2.01-2.12 (m, 1H), 1.9 (d, J = 10.18 Hz, 1H), 1.64-1.72 (m, 1H), 0.92-0.94 (m, 1H), 0.42-0.47 (m, 2H), 0.07-0.09 (m, 2H). (APCI$^+$): 517 (M$^+$).

**ii) Preparation of 17-cyclopropymethyl-4,5 $\alpha$-epoxy-3-methoxy-14-amino morphinan-6-one (4)**

**[000378]** 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.

**[000379]** $^1$H NMR (300 MHz, CDCl$_3$): δ 6.68 (d, J = 8.26 Hz, 1H), 6.60 (d, J = 8.26 Hz, 1H), 4.71 (s, 1H), 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, 12.11 Hz, 1H), 2.04 (s, 1H), 1.66-1.79 (m, 2H), 1.54 (dd, J = 2.19, 12.9 Hz, 1H), 0.82-0.88 (m, 1H), 0.49-0.56 (m, 2H), 0.11-0.15 (m, 2H). (APCI$^+$): 355 (M$^+$)

**Example 32**

**[000380]** A synthetic route was developed for the synthesis of 17-Cyclopropymethyl-4, 5$\alpha$-epoxy-3-hydroxy-14-allyloxy-6-oxo-morphinan N-oxide (C0031)
(i) Preparation of 3-\(O\)-benzyl naltrexone (2)

A mixture of naltrexone hydrochloride 1 (3.0 g, 7.94 mmol), benzyl bromide (1.43 g, 8.34 mmol) and \(K_2CO_3\) (3.0 g, 21.7 mmol) in anhydrous DMF (30 mL) was stirred at RT under \(N_2\) overnight. The reaction mixture was poured onto water (500 mL), extracted with \(CH_2Cl_2\), washed with water, brine and dried (\(Na_2SO_4\)). The solvent was evaporated under reduced pressure to give a residue, which was dissolved in 2N \(HCl\) (200 mL) and extracted with ether (to remove excess BnBr). The organic phase was discarded and the aqueous phase was made basic with c. \(NH\_2OH\), precipitated white solid was extracted with \(CH_2Cl_2\), washed with brine, dried (\(Na_2SO_4\)) and the solvent was removed under reduced pressure to obtain 2 (3.30 g, 96%) as a white foam.

\(^1\)H NMR (300 MHz, chloroform-d): \(\delta\) 7.20-7.50 (m, 5H), 6.71 (d, \(J = 8.0\) Hz, \(IH\)), 6.56 (d, \(J = 8.0\) Hz, \(IH\)), 5.13 (dd, \(J = 13.5, 11.8\) Hz, 2H), 4.70 (s, 1H), 4.83
(s, 1H), 3.00-3.18 (m, 3H), 2.28-2.74 (m, 6H), 2.13 (dt, J = 8.5, 3.6 Hz, 1H), 1.50-1.70 (m, 2H), 0.85 (m, 1H), 0.53 (m, 5H), 6.70 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.95-6.05 (m, 1H), 5.24-5.37 (m, 2H), 5.13-5.17 (m, 2H). APCI⁺ = 432.

(ii) Preparation 17-Cyclopropylmethyl-4, 5α-epoxy-3-benzyloxy-14-hydroxy-6,6-dimethoxy morphinan (3)

[000383] To a solution of the ketone 2 (2.63 g, 5.56 mmol) in anhydrous methanol (10 mL) was added trimethyl orthoformate (10 mL) and cone. sulfuric acid (2 mL). This mixture was heated to reflux for 4h under N₂. Volatiles were removed under reduced pressure to give a residue, to which was added cone. NH₄OH and extracted with chloroform. The organic phase was washed with water, brine and dried (Na₂SO₄). Evaporation of the solvent provided a yellow oil, which was purified by flash chromatography using 1-10% MeOH / CHCl₃ to isolate 3 (0.43 g) and a mixture of 3 and 3a (10:1) (2.0 g). Total yield = 94%.

[000384] ¹H NMR (300 MHz, chloroform-d): δ 7.20-7.50 (m, 5H), 6.71 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.27 (dd, J = 13.5, 11.8 Hz, 2H), 4.60 (s, 1H), 3.43 (s, 3H), 2.96-3.15 (m, 5H), 2.54-2.64 (m, 2H), 2.29-2.36 (m, 3H), 2.13 (dt, J = 8.5, 3.6 Hz, 1H), 1.90-2.10 (m, 1H), 1.30-1.70 (m, 5H), 0.85 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H). APCI⁺ = 478.

(ii) Preparation of 17-Cyclopropylmethyl-4, 5α-epoxy-3-benzyloxy-14-allyloxy-6,6-dimethoxymorphinan (4)

[000385] To a solution of compound 3 (0.2 g, 0.42 mmol) in anhydrous DMF (2 mL) under N₂ was added NaH (60%, 20 mg, 0.5 mmol) and the reaction stirred at RT for 1h. Allyl bromide ( 61 mg, 0.5 mmol) was then added and the reaction mixture was stirred at RT for 48h. 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 (80 mg, 37%) as a colorless oil.

[000386] ¹H NMR (300 MHz, MeOH-d3): δ 7.20-7.50 (m, 5H), 6.70 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.95-6.05 (m, 1H), 5.24-5.37 (m, 2H), 5.13-5.17 (m,
(iv) Preparation of 17-Cyclopropylmethyl-4, 5α-epoxy-3-hydroxy-14-allyloxy-6-oxomorphinan (5)

[000387] A solution of compound 4 (260 mg, 0.50 mmol) in TFA (2 mL) was heated to reflux for 1h. The mixture was cooled to RT, poured onto sat. NaHCO₃ solution, extracted with EtOAc, washed with brine, dried (Na₂SO₄) and evaporated to isolate crude 5, which was purified by flash chromatography using 1-2% MeOH / CHCl₃ as eluent to obtain 5 (135 mg, 60%) as a white solid.

[000388] ¹H NMR (300 MHz, MeOH-d3): δ 6.61 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 6.04-612 (m, 1H), 5.40 (d, J = 17.3 Hz, 1H), 5.17 (d, J = 17.3 Hz, 1H), 4.70 (s, 1H), 4.32-4.38 (m, 1H), 3.99-4.05 (m, 1H), 3.69 (m, 1H), 3.15 (d, J = 17.9 Hz, 1H), 2.67-2.91 (m, 3H), 2.54-2.64 (m, 2H), 2.35-2.41 (m, 3H), 1.35- 2.22 (m, 2H), 0.89 (m, 1H), 0.53 (m, 2H), 0.15 (m, 2H). APCI⁺ = 382.

(v) Preparation of n-Cyclopropylmethyl-4, 5α-epoxy-3-hydroxy-14-allyloxy-6-oxomorphinan N-oxide (C0031)

[000389] To a solution of compound 5 (100 mg, 0.26 mmol) in CHCl₃ (2 mL) at 0 °C was added mCPBA (77%, 60 mg, 0.265 mmol) and the mixture was stirred for 1h. K₂CO₃ (~ 200 mg) was added to the solution and it was stirred for 10 min. The resulting solid was filtered, washed with CHCl₃ and the filtrate was evaporated to isolate the crude product. This material was purified by flash chromatography using 1-8% MeOH / CHCl₃ + 0.1-0.2% NH₄OH as eluent to obtain the pure product C0031 (73 mg, 70%) as a white solid.

[000390] ¹H NMR (300 MHz, MeOH-d3): δ 6.70 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.04-6.22 (m, 1H), 5.30 (d, J = 17.3 Hz, 1H), 5.17 (d, J = 17.3 Hz, 1H), 4.82 (s, 1H), 4.62-4.66 (m, 1H), 4.05 (d, J = 4.1 Hz, 1H), 3.90- 4.05 (m, 1H), 3.60-3.64
Pharmacology Data.

Evaluation for agonist and antagonist activities at the µ-opioid receptors in the guinea pig ileum.

[000391] Agonist/antagonist activity at the µ-opioid receptor was determined using the well known guinea pig ileum test. Briefly, a section of ileum was placed in a stabilizing solution in a tensed state. Transducers were used to measure changes in tension upon electrical stimulation to the tissue before and after challenge with a potential agonist/antagonist. Using a control, constriction inhibition, and constriction inhibition cancellation, may be measured.

In the first exemplary case, agonistic activity of the test compound naltrexone N-oxide, COO01, was measured versus the µ-selective agonist DAMGO (D-Ala²-N-Me-Phe⁴,Gly⁵-ol-enkephalin) are shown in Table 1. No agonistic activity was observed at a concentration of 1.0 x 10⁻⁴ M.

Table 1. Evaluation of agonist activity

<table>
<thead>
<tr>
<th>Compounds</th>
<th>% Control response to DAMGO (1.0E⁻⁷ M)</th>
<th>Responses to increasing concentrations of the compounds (M)</th>
<th>Naloxone (1.0E⁻⁷ M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Conc., M)</td>
<td>1.0E⁻⁸</td>
<td>3.0E⁻⁸</td>
<td>1.0E⁻⁷</td>
</tr>
<tr>
<td>COO01</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(Conc., M)</td>
<td>1.0E⁻⁹</td>
<td>1.0E⁻⁸</td>
<td>1.0E⁻⁷</td>
</tr>
<tr>
<td>DAMGO</td>
<td>100</td>
<td>9</td>
<td>57</td>
</tr>
</tbody>
</table>
In Table 2, in an exemplary case demonstrating antagonistic activity, test compounds were compared to the µ-selective antagonist naloxone, the results of which are expressed as a percent of the control response to DAMGO (decrease in twitch contract amplitude). The responses to DAMGO are decreased with increasing amounts of the compounds, indicating antagonistic activity.

The following Table 3 shows results from testing exemplary morphinan-N-oxides of the disclosure, the results obtained in a human µ-receptor model (Ki) and a tissue model (IC50) for antagonist activity. % Inhibition at 1x10⁻⁵ M, relative binding constants (Ki), and effective concentrations (IC50) are shown.

<table>
<thead>
<tr>
<th>Test Compound</th>
<th>%Inhibition at 1x10⁻⁵ M</th>
<th>Ki (10⁻⁹ M)</th>
<th>IC50 (10⁻⁹ M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0001</td>
<td>96</td>
<td>+++</td>
<td>560</td>
</tr>
<tr>
<td>C0023</td>
<td>101</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>C0002</td>
<td>94</td>
<td>-</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>C0003</td>
<td>100</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1 shows a competition binding curve of the human mu-receptor as a function of concentration for exemplary compound C0020 (O-5720).

This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings or examples. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

Having thus described several embodiments of this invention, it is to be appreciated various alterations, modifications, and improvements will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and are intended to be within the spirit and scope of the invention. Accordingly, the foregoing description and drawings are by way of example only.

STATEMENT REGARDING EMBODIMENTS

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.
WHAT IS CLAIMED IS:

1. An axial-0 configured N-oxide compound of the Formula (Ic),

   \[
   \text{(Ic)}
   \]

or a pharmaceutically acceptable salt form, polymorph, or prodrug thereof, wherein:

- \( R_1 \) and \( R_2 \) are independently H, OH, OR, aryl, halide, silyl;
- \((C_{1-8})\) alkyl substituted with 0-3 \( R_{19} \);
- \((C_{2-8})\) alkenyl substituted with 0-3 \( R_{19} \);
- \((C_{2-8})\) alkynyl substituted with 0-3 \( R_{19} \);
- \((C_{3-10})\) cycloalkyl substituted with 0-3 \( R_{20} \);
- \((C_{3-10})\) carbocycle substituted with 0-3 \( R_{20} \);
- aryl substituted with 0-3 \( R_{20} \);

or \( R_1 \) and \( R_2 \) are combined to form a C3-C6 carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring;

- \( R_3 \) is H, cyano, OH, OR, halide, silyl, CO\(_2\)R, SO\(_2\)R, B(OR)\(_2\);
- \((C_{1-8})\) alkyl substituted with 0-3 \( R_{19} \);
- \((C_{2-8})\) alkenyl substituted with 0-3 \( R_{19} \);
(C₂-C₈) alkynyl substituted with 0-3 R₁₉;

(C₃-C₁₀) cycloalkyl substituted with O-3R₂₀;

(C₃-C₁₀) carbocycle substituted with O-3R₂₀;

aryl substituted with 0-3R₂₀;

R₅ is H, OH, OR₂₀,

(C₁-C₈) alkyl substituted with 0-3 R₁₉;

(C₂-C₈) alkenyl substituted with 0-3 R₁₉;

(C₂-C₈) alkynyl substituted with 0-3 R₁₉;

(C₁-C₁₀) cycloalkyl substituted with 0-3R₂₀;

(C₃-C₁₀) carbocycle substituted with O-3R₂₀;

aryl substituted with 0-3R₂₀;

R₆ is H, =O, OH, OR₂₉, NR₂₂R₂₃, =(R₁₉) (R₁₉) , =(heterocycle substituted with 0-3R₂₀),
=(C₃-7 cycle substituted with O-3R₂₀);

(C₁-C₈) alkyl substituted with 0-3 R₁₉;

(C₂-C₈) alkenyl substituted with 0-3 R₁₉;

(C₂-C₈) alkynyl substituted with 0-3 R₁₉;

(C₁-C₁₀) cycloalkyl substituted with 0-3R₂₀;

(C₃-C₁₀) carbocycle substituted with O-3R₂₀;

aryl substituted with 0-3R₂₀;

amine, amide, sulfonamide, ester, heterocycle, cyclic carbohydride, aryl;

R₇ is H, OH, OR₂₉,
(C<sub>1</sub>-C<sub>20</sub>) alkyl substituted with 0-3 R<sub>1</sub>; 
(C<sub>2</sub>-C<sub>20</sub>) alkenyl substituted with 0-3 R<sub>19</sub>; 
(C<sub>2</sub>-C<sub>20</sub>) alkynyl substituted with 0-3 R<sub>19</sub>; 
(C<sub>3</sub>-C<sub>10</sub>) cycloalkyl substituted with 0-3R<sub>20</sub>; 
(C<sub>3</sub>-C<sub>10</sub>) carbocycle substituted with 0-3R<sub>20</sub>; 
aryl substituted with 0-3R<sub>20</sub>;

or R<sub>b</sub> and R<sub>7</sub> are combined to form an O-fused ring, a C<sub>3</sub>-C<sub>6</sub> carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring or a bicyclic combination thereof, a 5-, 6-, 5-6-membered aryl with O-3R<sub>20</sub>;

R<sub>8</sub> is H, OH, OR<sub>29</sub>, heterocycle with O-3R<sub>20</sub>, alkylaryl with 0-3 R<sub>20</sub>, arylalkyl with O-3R<sub>20</sub>,

wherein X is bond, =O, O, S, N(R<sub>29</sub>), SO, SO<sub>2</sub>, SO<sub>2</sub>N(R<sub>29</sub>), CON(R<sub>29</sub>), N(R<sub>29</sub>)CON(R<sub>29</sub>), N(R<sub>29</sub>)C(=NR<sub>29</sub>ON(R<sub>29</sub>), COO;

(C<sub>1</sub>-C<sub>8</sub>) alkyl substituted with 0-3 R<sub>19</sub>; 
(C<sub>2</sub>-C<sub>8</sub>) alkenyl substituted with 0-3 R<sub>19</sub>; 
(C<sub>2</sub>-C<sub>8</sub>) alkynyl substituted with 0-3 R<sub>19</sub>; 
(C<sub>3</sub>-C<sub>10</sub>) cycloalkyl substituted with O-3R<sub>20</sub>; 
(C<sub>3</sub>-C<sub>10</sub>) carbocycle substituted with 0-3R<sub>20</sub>; 
arly substituted with 0-3R<sub>20</sub>;

R<sub>14</sub> is H, OH, OR<sub>29</sub>, NHR<sub>29</sub>, heterocycle with 0-3R<sub>20</sub>, alkylaryl with 0-3R<sub>20</sub>, arylalkyl with 0-3R<sub>20</sub>,
wherein $X$ is bond, =O, O, S, N(R$_{29}$), SO, SO$_2$, SO$_2$N(R$_{29}$), CON(R$_{29}$), N(R$_{29}$)CON(R$_{29}$), N(R$_{29}$)C(=NR$_{29}$)N(R$_{29}$)$_2$, COO;

(C$_1$-C$_8$) alkyl substituted with 0-3 R$_p$;

(C$_2$-C$_8$) alkenyl substituted with 0-3 R$_p$;

(C$_2$-C$_8$) alkynyl substituted with 0-3 R$_p$;

(C$_3$-C$_9$) cycloalkyl substituted with 0-3 R$_{20}$;

(C$_3$-C$_9$) carbocycle substituted with 0-3 R$_{20}$;

aryl substituted with 0-3 R$_{25}$; aryloxy, acyloxy,

or R$_{14}$ is combined with R$_{18}$ to form an O-fused ring, or a C$_3$-C$_6$ carbocycle fused ring;

R$_{17}$ is OR$_{25}$, heterocycle with 0-3 R$_{20}$, aUcylarly with 0-3 R$_{20}$, aUcylarly with 0-3 R$_{20}$;

(C$_4$-C$_{20}$) alkyl substituted with 0-3 R$_{25}$;

(C$_4$-C$_{20}$) alkenyl substituted with 0-3 R$_{25}$;

(C$_4$-C$_{20}$) alkynyl substituted with 0-3 R$_{25}$;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂⁶;

(C₃-C₁₀) carbocycle substituted with 0-3R₂⁶;

aryl substituted with 0-3R₂⁶; or allyl;

R₉ is at each occurrence is independently selected from:

H, C₁-C₆ alkyl, CF₃, OR₂₅, Cl, F, Br, I, =O, CN, NO₂, NR₂₂R₂₃; acyl(C₁-C₆)alkyl;

acylaryl substituted with 0-3R₂₃;

C₃-C₁₀ carbocycle substituted with 0-3R₂₁;

aralkyl substituted with 0-3R₂₁;

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3R₂₁; or

aryl substituted with 0-3R₂₀;

R₂₀ at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO₂;

NR₂₂R₂₃, acetyl, OR₂₅, XR₂₅,

wherein X is bond, =O, O, S, N(R₂₉), SO, SO₂, SO₂N(R₂₉), CON(R₂₉),
N(R₂₉)CON(R₂₉⁻), N(R₂₉Q=NR₂₉⁻)N(R₂₉⁻'), COO;

C₁-C₆ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl,

C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl-S⁻;

R₂₁ at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO₂;

NR₂₂R₂₃, CF₃, acetyl, OR₂₅, XR₂₅,

wherein X is bond, =0, O, S, N(R₂₉), SO, SO₂, SO₂N(R₂₉), CON(R₂₉),
N(R₂₉)CON(R₂₉⁻), N(R₂₉C(=NR₂₉⁻)N(R₂₉⁻'), COO;
C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, and C<sub>1</sub>-C<sub>4</sub> haloalkyl-S-; or

NR<sub>22</sub>R<sub>23</sub> may be a heterocyclic ring selected from the group piperidinyl, homopiperidinyl, and morpholinyl;

<sup>R<sub>22</sub></sup>, at each occurrence, is independently selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl,

(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-, and (C<sub>1</sub>-C<sub>6</sub> alkyl)-S(=O)<sub>2</sub>-.

<sup>R<sub>23</sub></sup>, at each occurrence, is independently selected from:

H, (C<sub>1</sub>-C<sub>6</sub>) alkyl, heteroaryl, heterocycle, alkylaryl, arylalkyl, C6-10 aryl, heteroaryl, heterocycle, haloalkyl, arylalkyl,

(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-, and (C<sub>1</sub>-C<sub>6</sub> alkyl)-S(=O)<sub>2</sub>-;

or R<sub>22</sub> and R<sub>23</sub> are combined to form a 5-, 6-, or 5-6-membered cycle with O-2Ria;

<sup>R<sub>24</sub></sup>, at each occurrence, is independently selected from H, phenyl, benzyl, (C<sub>1</sub>-C<sub>6</sub>) alkyl, haloalkyl and (C<sub>1</sub>-C<sub>6</sub>) alkoxyalkyl;

<sup>R<sub>25</sub></sup>, at each occurrence, is independently selected from:

H, C<sub>1</sub>-C<sub>6</sub> alkyl, haloalkyl, OR<sub>24</sub>, Cl, F, Br, =O, CN, NO<sub>2</sub>, NR<sub>27</sub>R<sub>28</sub>;

C<sub>5</sub>-C<sub>10</sub> carbocycle substituted with 0-3 R<sub>27</sub>;

aryl substituted with 0-3 R<sub>27</sub>; or

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R<sub>27</sub>;
R_{26}, at each occurrence, is independently selected from: H, (C_{1}-C_{6})alkyl, benzyl, phenethyl, (C_{1}-C_{6} alkyl)-C(=O)-, halide;

R_{27}, at each occurrence, is independently selected from:

H, OH, C_{1}-C_{6} alkyl, C_{1}-C_{4} alkoxy;

R_{28}, at each occurrence, is independently selected from:

H, C_{1}-C_{6} alkyl;

R_{29} is at each occurrence is independently selected from:

H, C_{1}-C_{6} alkyl, CF_{3}, acyl(C_{1}-C_{6})alkyl;

acylaryl substituted with 0-3 R_{21};

C_{3}-C_{10} carbocycle substituted with 0-3 R_{21};

aralkyl substituted with 0-3 R_{21};

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R_{21}; or

aryl substituted with 0-3 R_{20}; and

wherein, when R_{24} is OH, and R_{8} is selected from the group consisting of =O and =CH_{2}, then R_{3} is not OH.


3. An axial-0 configured N-oxide compound of the Formula (I),
or a pharmaceutically acceptable salt form or prodrug thereof, wherein:

$R_1$ and $R_2$ are independently $H$, $OH$, $OR_2$, aryl, halide, silyl;

- $(C_1-C_8)$ alkyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkenyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkynyl substituted with 0-3 $R_{19}$;
- $(C_3-C_{10})$ cycloalkyl substituted with 0-3 $R_{20}$;
- $(C_3-C_{10})$ carbocycle substituted with 0-3 $R_{20}$;
- aryl substituted with 0-3 $R_{20}$;

or $R_1$ and $R_2$ are combined to form a $C_3-C_6$ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring;

$R_3$ is $H$, cyano, $OH$, $OR_{29}$, halide, silyl;

- $(C_1-C_v)$ alkyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkenyl substituted with 0-3 $R_{19}$;
- $(C_2-C_8)$ alkynyl substituted with 0-3 $R_{19}$;
- $(C_{1-C_{19}})$ cycloalkyl substituted with 0-3 $R_{29}$;
(C₃-C₁₀) carbocycle substituted with O-3R₂₀;
aryl substituted with 0-3R₂₀;

R₅ is H, OH, OR₂ₓ,

(C₁-C₈) alkyl substituted with 0-3 R₁₉;
(C₂-C₆) alkenyl substituted with 0-3 R₁₉;
(C₂-C₆) alkynyl substituted with 0-3 R₁₉;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with O-3R₂₀;

R₆ is H, =0, OH, OR₂₉; NR₂₂R₂₃;

(C₁-C₈) alkyl substituted with 0-3 R₁₉;
(C₂-C₈) alkenyl substituted with 0-3 R₁₉;
(C₂-C₈) alkynyl substituted with 0-3 R₁₉;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with O-3R₂₀;
aryl substituted with O-3R₂₀;

amine, amide, sulfonamide, ester, heterocycle, cyclic carbohydride, aryl;

R₇ is H, OH, OR₂₉,

(C₁-C₂₀) alkyl substituted with 0-3 R₁₉;
(C₂-C₂₀) alkenyl substituted with 0-3 R₁₉;
(C₂-C₂₀) alkynyl substituted with 0-3 R₁₉;
(C₃₋C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃₋C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

or R₈ and R₁₄ are combined to form an O-fused ring, a C₁₋C₅ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring or a bicyclic combination thereof;

R₈ is H, OH, OR₂₉

(C₁₋C₈) alkyl substituted with 0-3R₁₉;
(C₂₋C₈) alkenyl substituted with 0-3R₁₉;
(C₂₋C₈) alkynyl substituted with 0-3R₁₉;
(C₃₋C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃₋C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

R₁₄ is H, OH, OR₂₉, NHR₂₉

(C₁₋C₈) alkyl substituted with 0-3R₁₉;
(C₂₋C₈) alkenyl substituted with 0-3R₁₉;
(C₂₋C₈) alkynyl substituted with 0-3R₁₉;
(C₃₋C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃₋C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀; aryloxy, acyloxy,

or R₁₄ is combined with R₈ to form an O-fused ring, or a C₃₋C₅ carbocycle fused ring;
$R_{17}$ is $OR_{25}$,

$(C_4\text{-}C_{20})$ alkyl substituted with 0-3 $R_{25}$;

$(C_4\text{-}C_{20})$ alkenyl substituted with 0-3 $R_{25}$;

$(C_4\text{-}C_{20})$ alkynyl substituted with 0-3 $R_{25}$;

$(C_3\text{-}Q0)$ cycloalkyl substituted with 0-3$R_{26}$;

$(C_3\text{-}C_{10})$ carbocycle substituted with 0-3$R_{26}$;

aryl substituted with 0-3$R_{26}$; or allyl;

$R_{19}$ is at each occurrence is independently selected from:

H, $C_1\text{-}C_6$ alkyl, $C_F_3$, OR$_{24}$, Cl, F, Br, I, =O, CN, NO$_2$, NR$_{22}$R$_{23}$; acyl($C_1\text{-}C_6$)alkyl;

acylaryl substituted with 0-3 $R_{24}$;

$C_3\text{-}C_{10}$ carbocycle substituted with 0-3 $R_{24}$;

aralkyl substituted with 0-3 $R_{24}$; or

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 $R_{24}$;

$R_{20}$ at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO$_2$,

NR$_{22}$, R$_{23}$, acetyl,

$C_1\text{-}C_6$ alkyl, $C_1\text{-}C_4$ alkoxy, $C_1\text{-}C_4$ haloalkyl,

$C_1\text{-}C_4$ haloalkoxy, and $C_1\text{-}C_4$ haloalkyl-$S$;

$R_{21}$, at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO$_2$,

NR$_{22}$, R$_{23}$, CF$_3$, acetyl,

$C_1\text{-}C_6$ alkyl, $C_1\text{-}C_4$ alkoxy, $C_1\text{-}C_4$ haloalkyl,
C<sub>1</sub>-C<sub>4</sub> haloalkoxy, and C<sub>1</sub>-C<sub>4</sub> haloalkyl-S-; or

NR-, R<sub>23</sub> may be a heterocyclic ring selected from the group piperidinyl, homopiperidinyl, and morpholinyl;

R<sub>22</sub>, at each occurrence, is independently selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl,

(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-, and (C<sub>1</sub>-C<sub>6</sub> alkyl)-S(=O)<sub>r</sub>;

R<sub>23</sub>, at each occurrence, is independently selected from:

H, (C<sub>1</sub>-C<sub>6</sub>) alkyl,

(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-, and (C<sub>1</sub>-C<sub>6</sub> alkyl)-S(=O)<sub>2</sub>;

R<sub>24</sub>, at each occurrence, is independently selected from H, phenyl, benzyl, (C<sub>1</sub>-C<sub>6</sub>) alkyl, and (C<sub>2</sub>-C<sub>6</sub>) alkoxyalkyl;

R<sub>25</sub>, at each occurrence, is independently selected from:

H, C<sub>1</sub>-C<sub>6</sub> alkyl, OR<sub>24</sub>, Cl, F, Br, =0, CN, NO<sub>2</sub>, NR<sub>27</sub>R<sub>28</sub>;

C<sub>3</sub>-C<sub>10</sub> carbocycle substituted with 0-3 R<sub>27</sub>;

aryl substituted with 0-3 R<sub>27</sub>; or

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R<sub>27</sub>;

R<sub>26</sub>, at each occurrence, is independently selected from: H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, benzyl, phenethyl, (C<sub>1</sub>-C<sub>6</sub> alkyl)-C(=O)-, halide;

R<sub>27</sub>, at each occurrence, is independently selected from:

H, OH, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy;

R<sub>28</sub>, at each occurrence, is independently selected from:
H, C₁₋₆ alkyl;

R₂⁹ is at each occurrence is independently selected from:

H, C₁₋₆ alkyl, CF₃, acyl(C₁₋₆)alkyl;

acylaryl substituted with 0-3 R₂₁;

C₃₋₁₀ carbocycle substituted with 0-3 R₂₁;

aralkyl substituted with 0-3 R₂₁;

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂₁; or

aryl substituted with 0-3R₂⁹i and

wherein, when R₁₄ is OH, and R₆ is selected from the group consisting of =O and =CH₂, then R₃ is not OH.; and

wherein, when R₁₄ is OH, and R₆ is selected from the group consisting of =O and =CH₂, then R₃ is not OH.

4. An axial-0 configured N-oxide compound of the Formula (Ia):

or a pharmaceutically acceptable salt form, polymorph, or prodrug thereof, wherein:
R₁ and R₂ are independently H, OH, OR₂⁹, halide, silyl;

(C₁⁻C₈) alkyl substituted with 0-3 R₁;

(C₂⁻C₈) alkenyl substituted with 0-3 R₂;

(C₂⁻C₈) alkynyl substituted with 0-3 R₂;

(C₃⁻C₁₀) cycloalkyl substituted with 0-3R₂⁹;

(C₃⁻C₁₀) carbocycle substituted with 0-3R₂⁰;

aryl substituted with 0-3R₂⁰;

or R₁ and R₂ can also be combined to form a C₃-C₆ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring;

R₃ is H, cyano, OH, OR₂⁹, halide, silyl;

(C₁⁻C₈) alkyl substituted with 0-3 R₃;

(C₂⁻C₈) alkenyl substituted with 0-3 R₃;

(C₂⁻C₈) alkynyl substituted with 0-3 R₃;

(C₃⁻C₁₀) cycloalkyl substituted with 0-3R₂⁰;

(C₃⁻C₁₀) carbocycle substituted with 0-3R₂⁰;

aryl substituted with 0-3R₂⁰;

R₅ is H, OH, OR₂⁹,

(C₁⁻C₄) alkyl substituted with 0-3 R₅;

(C₂⁻C₈) alkenyl substituted with 0-3 R₅;

(C₂⁻C₈) alkynyl substituted with 0-3 R₅;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

R₆ is H, =0, OH, OR₂₉;

(C₁-C₈) alkyl substituted with 0-3R₁₉;
(C₂-C₈) alkenyl substituted with 0-3R₁₉;
(C₂-C₈) alkynyl substituted with 0-3R₁₉;
(C₃-C₇)O cycloalkyl substituted with 0-3R₇₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

amine, amide, sulfonamide, ester, heterocycle, cyclic carbohydride, aryl;

R₇ is H, OH, OR₂₉,

(C₁-C₈) alkyl substituted with 0-3R₁₉;
(C₂-C₈) alkenyl substituted with 0-3R₁₉;
(C₂-C₈) alkynyl substituted with 0-3R₁₉;
(C₃-C₁₀) cycloalkyl substituted with 0-3R₂₀;
(C₃-C₁₀) carbocycle substituted with 0-3R₂₀;
aryl substituted with 0-3R₂₀;

or R₆ and R₇ can also be combined to form an O-fused ring, a C₃-C₆ carbocycle fused ring, a benzo fused ring, or a 5-6 membered heteroaryl fused ring, or a combination thereof;
$R_8$ is H, OH, OR$_{29}$

(\(C_1\)-\(C_8\)) alkyl substituted with 0-3 $R_{19}$;

(\(C_{21}\)-\(C_3\)) alkenyl substituted with 0-3 $R_{19}$;

(\(C_{21}\)-\(C_8\)) alkynyl substituted with 0-3 $R_{19}$;

(\(C_{31}\)-\(C_{61}\)) cycloalkyl substituted with 0-3$R_{20}$;

(\(C_{31}\)-\(C_{61}\)) carbocycle substituted with 0-3$R_{20}$;

aryl substituted with 0-3$R_{20}$;

$R_{34}$ is H, OH, OR$_{29}$,

(\(C_1\)-\(C_8\)) alkyl substituted with 0-3 $R_{19}$;

(\(C_{21}\)-\(C_{6}\)) alkenyl substituted with 0-3 $R_{19}$;

(\(C_{21}\)-\(C_{6}\)) alkynyl substituted with 0-3 $R_{19}$;

(\(C_{31}\)-\(C_{61}\)) cycloalkyl substituted with 0-3$R_{20}$;

(\(C_{31}\)-\(C_{61}\)) carbocycle substituted with 0-3$R_{20}$;

aryl substituted with 0-3$R_{20}$; aryl, acyloxy,

or $R_{14}$ is combined with $R_{18}$ to form an O-fused ring, or a \(C_{31}\)-\(C_{6}\) carbocycle fused ring;

$R_{17}$ is (\(C_4\)-\(C_{10}\)) alkyl substituted with 0-3 $R_{25}$;

(\(C_4\)-\(C_{10}\)) alkenyl substituted with 0-3 $R_{25}$;

(\(C_4\)-\(C_{10}\)) alkynyl substituted with 0-3 $R_{25}$;

(\(C_{31}\)-\(C_{61}\)) cycloalkyl substituted with 0-3$R_{26}$;
(C₃₋C₁₀) carbocycle substituted with 0-3 R₂₆;

aryl substituted with 0-3 R₂₆; or allyl;

R₉₉ is at each occurrence is independently selected from:

H, C₁₋C₆ alkyl, CF₃, OR₂₄, C₁₋F, Br, I, =O, CN, NO₂, NR₂₂R₂₃;

acyl(C₁₋C₆)alkyl, acylaryl substituted with 0-3 R₂₁;

C₃₋C₁₀ carbocycle substituted with 0-3 R₂₁;

aralkyl substituted with 0-3 R₂₁; or

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂₁;

R₂₀ is at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO₂,

NR₂₂R₂₃, acetyl,

C₁₋C₆ alkyl, C₁₋C₄ alkoxy, C₁₋C₄ haloalkyl,

C₁₋C₄ haloalkoxy, and C₁₋C₄ haloalkyl-S-;

R₂₁, at each occurrence, is independently selected from H, OH, Cl, F, Br, I, CN, NO₂,

NR₂₂R₂₃, CF₃, acetyl,

C₁₋C₆ alkyl, C₁₋C₄ alkoxy, C₁₋C₄ haloalkyl,

C₁₋C₄ haloalkoxy, and C₁₋C₄ haloalkyl-S-;

R₂₂, at each occurrence, is independently selected from H, C₁₋C₆ alkyl, (C₁₋C₆ alkyl)-C(=O)-, and (C₁₋C₆ alkyl)-S(=O)₂-;

R₂₃, at each occurrence, is independently selected from:

H, (C₁₋C₆) alkyl,
(C₁-C₆ alkyl)-C(=O)-, and (C₁-C₆ alkyl)-S(=O)₂⁻;

R₂₄, at each occurrence, is independently selected from H, phenyl, benzyl, (C₁-C₆) alkyl, and (C₂-C₆) alkoxyalkyl;

R₂₅, at each occurrence, is independently selected from:

H, C₁-C₆ alkyl, OR₂₄, =0, CN, NO₂, NR₂₇ R₂₈;

C₃-C₁₀ carbocycle substituted with 0-3 R₂₇;

aryl substituted with 0-3 R₂₇; or

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂₇;

R₂₆, at each occurrence, is independently selected from:

H, (C₁-C₆) alkyl, benzyl, phenethyl, (C₁-C₆ alkyl)-C(=O)-, halide;

R₂₇, at each occurrence, is independently selected from:

H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy;

R₂₈, at each occurrence, is independently selected from:

H, C₁-C₆ alkyl;

R₂₉ is at each occurrence is independently selected from:

H, C₁-C₆ alkyl, CF₃, acyl(C₁-C₆)alkyl;

acylaryl substituted with 0-3 R₂₁;

C₃-C₃₀ carbocycle substituted with 0-3 R₂₁;

aralkyl substituted with 0-3 R₂₁;
5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R_{14}; or aryl substituted with 0-3R_{20}; and

wherein when R_{14} is selected from the group consisting of =0 and =CH_{2}, then R_1 is not OH.

5. A composition comprising a compound of claim 4, wherein the compound present in the composition is greater than 90% in an axial configuration with respect to nitrogen.

6. The composition comprising a compound of claim 4, wherein the compound present in the composition is greater than 95% in an axial configuration with respect to nitrogen.

7. The composition comprising a compound of claim 4 wherein the compound present in the composition is greater than 98% in an axial configuration with respect to nitrogen.

8. The composition comprising a compound of claim 4 wherein the composition is free of HPLC detectable O-N equatorial stereoisomer at a detection limit of 0.02% and at a quantitation limit of 0.05%.

9. The composition comprising a compound of claim 4 wherein the compound present in the composition is greater than 99% in an axial configuration with respect to nitrogen.

10. The pharmaceutical composition comprising a compound of claim 4, further comprising a pharmacological agent other than an axial-0 configured N-oxide compound.

11. The pharmaceutical composition of claim 10, wherein the pharmacological agent is an opioid agonist.
12. The pharmaceutical composition of claim 11, wherein the opioid agonist is selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levorphanol, metazocine, propiram, propoxyphene, remifentanil, sufentanil, ticlidine, tramadol, and combinations thereof.

13. The pharmaceutical composition of claim 10, further comprising at least one pharmacological agent that is not an opioid agonist or an opioid antagonist.

14. The pharmaceutical composition of claim 10, wherein at least one pharmaceutical agent is a non-opioid analgesic/anti-pyretic, an antiviral agent, an antifungal agent, an anticancer agent, an antispasmodic agent, an anti-muscarinic agent, an anti-inflammatory agent, a pro-motility agent, a 5HTi 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.

15. The pharmaceutical composition of claim 14, 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.

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

17. A pharmaceutical composition comprising the compound of claim 3 enterically coated for oral administration.

18. A pharmaceutical composition comprising the compound of claim 3 in a lyophilized formulation.
19. A pharmaceutical composition comprising the compound of claim 3 in a sustained release formulation or an immediate release formulation.

20. The pharmaceutical composition of claim 19, further comprising an opioid.

21. The pharmaceutical composition of claim 20, wherein the opioid is selected from the group consisting of alfentanil, anileridine, asimodiline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenyloxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanil, sufentanil, tilidine, tramadol, and combinations thereof.

22. The pharmaceutical composition of claim 21, further comprising at least one pharmacological agent that is not an opioid or an opioid antagonist.

23. The pharmaceutical composition of claim 22, wherein at least one pharmacological 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 5HT₁ agonist, a 5HT₃ antagonist, a 5HT₄ antagonist, 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.

24. The composition of claim 23, 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, azathioprine, tacrolimus, steroids, sulfasalazine, olsalazine, mesalamine, and combinations thereof.

25. A method for treating or preventing opioid-induced side effects comprising administering to a patient in need of such treatment the compound of claim 4 in an amount effective to treat or prevent the side effect.
26. A method for preventing or treating opioid-induced side effect in a patient chronically administered opioids, the method comprising administering a compound of claim 4 in an amount sufficient to prevent or treat the side effect in the patient.

27. A method of claim 25, wherein the side effect is selected from a group consisting of constipation, immune suppression, inhibition of gastrointestinal motility, inhibition of gastric emptying, nausea, emesis, incomplete evacuation, bloating, abdominal distension, increased gastroesophageal reflux, hypotension, bradycardia, gastrointestinal dysfunction, pruritus, dysphoria, and urinary retention.

28. A method for treating a patient receiving an opioid for pain resulting from surgery comprising administering to the patient a compound of claim 4 in an amount effective to promote gastrointestinal motility, gastric emptying or relief of constipation.

29. A method for treating or preventing endogenous opioid-induced dysfunction, comprising administering to a patient in need of such treatment the compound of claim 4 in an effective amount to treat the endogenous opioid-induced dysfunction.

30. The method of claim 29, wherein the dysfunction is selected from a group consisting of gastrointestinal dysfunction, obesity, hypertension and addictions.

31. A method for preventing or treating idiopathic constipation comprising administering to a patient a compound of claim 4 in an amount effective to prevent or treat the idiopathic constipation.

32. A method for treating irritable bowel syndrome comprising administering to a patient in need of such treatment the compound of claim 4 in an amount effective to ameliorate at least one symptom of the irritable bowel syndrome.

33. The method of claim 32 further comprising administration of at least one irritable bowel syndrome therapeutic agent to the patient.

34. The method of claim 33 wherein the irritable bowel syndrome therapeutic is selected from the groups consisting of an antispasmodic agent, an anti-muscarinic agent, a non-steroidal or steroidal anti-inflammatory agent, a pro-motility agent, a 5HTi agonist,
a 5HTj antagonist, a 5HT3 antagonist, a 5HT6 agonist, a bile salt sequestering agent, a bulk-forming agent, an alpha2-adrenergic agonist, a mineral oil, an antidepressant, an herbal medicine, an anti-diarrheal agent and combinations thereof.

35. The method of claim 34 wherein the irritable bowel syndrome therapeutic is an antispasmodic agent.

36. A method for inducing taxation in a patient in need of laxation comprising administering to a patient in need of such treatment the compound of claim 4 in an amount effective to induce laxation.

37. A method for preventing or treating post-operative ileus comprising administering to a patient in need of such prevention or treatment the compound claim 4 in an amount effective to prevent or ameliorate at least one symptom of post-operative ileus.

38. The method of claim 37 wherein, the amount is effective to shorten the time to first laxation post-operatively.

39. A method for treating or preventing opioid-induced side effects comprising administering to a patient in need of such treatment the compound of claim 3 in an amount effective to treat or prevent the side effect.

40. The method according to claim 39, wherein the patient is receiving opioids acutely or chronically.

41. A method of 40, wherein the side effect is selected from a group consisting of constipation, immune suppression, inhibition of gastrointestinal motility, inhibition of gastric emptying, nausea, emesis, incomplete evacuation, bloating, abdominal distension, increased gastroesophageal reflux, hypotension, bradycardia, gastrointestinal dysfunction, pruritus, dysphoria, and urinary retention.

42. The method of claim 41, wherein the opioid-induced side effect is constipation.

43. The method of claim 42, wherein the opioid-induced side effect is inhibition of gastrointestinal motility or inhibition of gastric emptying.
44. The method of claim 41, wherein the opioid-induced side effect is nausea or emesis.

45. The method of claim 41, wherein the opioid-induced side effect is pruritus.

46. The method of claim 41, wherein the opioid-induced side effect is dysphoria.

47. The method of claim 41, wherein the opioid-induced side effect is urinary retention.

48. A method for treating a patient receiving an opioid for pain resulting from surgery comprising administering to the patient a compound of claim 3 in an amount effective to promote gastrointestinal motility, gastric emptying or relief of constipation.

49. A method for treating or preventing endogenous opioid-induced dysfunction, comprising administering to a patient in need of such treatment the compound of claim 3 in an effective amount to treat the endogenous opioid-induced dysfunction.

50. The method of claim 49, wherein the dysfunction is selected from a group consisting of gastrointestinal dysfunction, obesity, hypertension and addictions.

51. A method for preventing or treating idiopathic constipation comprising administering to a patient a compound of claim 3 in an amount effective to prevent or treat the idiopathic constipation.

52. A method for treating irritable bowel syndrome comprising administering to a patient in need of such treatment a compound of claim 3 in an amount effective to ameliorate at least one symptom of the irritable bowel syndrome.

53. The method of claim 52, further comprising administration of at least one irritable bowel syndrome therapeutic agent to the patient.

54. The method of claim 53, wherein the irritable bowel syndrome therapeutic is selected from the groups consisting of an antispasmodic agent, an anti-muscarinic agent, a non-steroidal or steroidal anti-inflammatory agent, a pro-motility agent, a 5HT\textsubscript{1} 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, an herbal medicine, an anti-diarrheal agent and combinations thereof.

55. An axial-0 configured N-Oxide compound of the Formula (Ib):

```
  axial 
  O'  
  R₁₇ 

   equatorial

   R₁⁴  R₁₅  R₆  R₇

   10  16  0  6  5

   R₂⁹  R₂₈

   R₂  R₁

   R₁⁵  R₂₅

   R₄  R₃

   R₇  R₆
```

(lb)

or a pharmaceutically acceptable salt form, polymorph, or prodrug thereof, wherein:

R₁ and R₂₉ are independently H, OH, OR₂₉, halide, silyl;

wherein R₂₉ is at each occurrence is independently selected from:

H, C₁-C₆ alkyl, CF₃, acyl(C₁-C₆)alkyl;

acylaryl substituted with 0-3 R₂₁;

C₃-C₅ carbocycle substituted with 0-3 R₂₁;

aralkyl substituted with 0-3 R₂₁;

5 to 10 membered heterocycle containing 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein said 5 to 10 membered heterocycle is substituted with 0-3 R₂₁; or
aryl substituted with 0-3R₂₀;

R₁₇ is a substituted or unsubstituted C₂ - C₆ alkyl, C₂-C₆ alkenyl, C₃-C₆ alkylnyl, or, substituted or unsubstituted C₄ - C₁₀ (cycloalkyl)alkyl, C₄-C₁₀ (cycloalkenyl)alkyl, (C₄-C₁₀)cycloheteroalkyl, or (C₂-C₆₅) arylalkyl, alkoxy, C₄-C₅O carbocyclohalide;

R₆ is =0, =CH₂, H, alkylhydroxy, C₁-C₆ alkyl, N-dialkyl, C₄ - C₆₅ alkylene, QR₁₉R₂₀ (wherein Q=C, O, N, CO, CO₂, or CON), NR₂₉COR₂₀, none, a cyclic ring, or forms a cyclic ring with R₁⁷, and R₁⁹ and R₂₀ are independently H, alkyl, aryl;

R₇ and R₅ are independently H or alkyl;

R₁₄ is H, OH, halide, substituted or unsubstituted -O-alkyl, -O-alkylaryl, -O-alkenyl, -O-acylalkyl, -O-acylaryl, amidoaryl, or forms a cyclic ring with R₁₇, arloxy;

R₁ and R₂ are independently H, halide, alkoxy, alkyl, alkenylene, alkynyl or aryl;

R₃ is H, cyano, C=ONH₂, OH, C₁ - C₃ alkyl, C₄-C₁₀ ary1 or C₁ - C₃ acyl; and

R₅ is H, OH, alkyl, alkoxy, or arlyoxy; and

wherein when R₁₄ is OH and R₆ is selected from the group consisting of =O and =CH₂, then R₃ is not OH.

56. A compound according to Formula (II) or a pharmaceutically acceptable salt form, polymorph, or prodrug thereof,
wherein:

R₁₇ is a substituted or unsubstituted C₂-C₆ alkyl, C₄-C₁₀ alkoxy, C₄-C₁₀ haloalkyl, C₂-C₆ alkenyl, C₃-C₆ alkynyl, or substituted or unsubstituted C₄-C₁₀ (cycloalkyl)alkyl, C₄-C₁₀ (cycloalkylene)alkyl, C₄-C₁₀ (heterocyclo)alkyl or arylalkyl;

R₆ is =O, N-dialkyl, C₂-C₆ alkyne, QR₁₉R₂₀ (wherein Q is C, O, N, CO, CO₂, CON, or none), and R₁₉ and R₂₀ are independently H, alkyl, aryl, none, or form a carbocycle fused ring), a carbocycle, or R₆ forms a forms a carbocycle ring with R₇.

R₇ and R₈ are independently H or alkyl;

R₃ is H, C₁-C₃ alkyl, C₁-C₃ acyl, C₄-C₁₀ aryl;

R₁ and R₂ are independently H, halide, alkoxy, alkyl, alkyne, alkynyl or aryl; and

R₅ is H, OH, alkyl, alkyne, alkynyl, alkoxy, and aryloxy; and

M is SO₂WO, SOWO, COWO, WO, WS, W is C₁-C₃ substituted with 0-3 R₁₉.

57. A method of treatment comprising administering to a subject with a disorder characterized by unwanted migration or proliferation of endothelial cells an effective amount of a compound of claim 56.

58. A compound, polymorph, or stereoisomer selected from the group consisting of:

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxymorphinan N-oxide;

(S)-17-Cyclopropylmethyl-4,5-epoxy-morphinan-3,6 α,14-triol N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propyloxy morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-(3'-phenylpropyloxy) morphinan-6-one N-oxide;
(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-7-methyl-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxy-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-methoxy-morphinan N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propyloxy-morphinan N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-(3′-phenylpropyloxy) morphinan-3,6 α-diol N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzamido-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzamido-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzylamido-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-morphinan N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3,14-dihydroxy-6 α-hydroxymethyl morphinan N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-propyloxy-morphinan N-oxide hydrochloride;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-carbamoyl-14-hydroxy-morphinan N-oxide hydrochloride;
(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-Q'-phenylpropyloxy morphinan-3,6 β-diol N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-6α-methyl morphinan-3,14-diol N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-6α-(1H-imidazol-1-yl)methyl morphinan-3,14-diol N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-phenethylamido -morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-14-propyloxy morphinan-3,6 β-diol N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-butyloxymorphinan-6-one N-oxide hydrochloride;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-benzyloxymorphinan-6-one N-oxide hydrochloride;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-ethoxymorphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-acetoxy morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-allyloxymorphinan-6-one N-oxide;

(S)-Naltrindole-N-Oxide;
4,5α-epoxy-3-hydroxy-(17,14-N, O-ethylene) morphinan-6-one N-oxide trifluoroacetic acid salt;

(S)-17-Propargyl-4,5 α-epoxy-3,14-dihydroxy-morphinan-6-one N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-cyclopropylmethyloxy-morphinan-6-one N-oxide;

(S)-Naltriben N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3'-phenylpropyloxy)-6-methylenemorphinan N-oxide trifluoroacetic acid salt;

(S)-17-(3,3,3-Trifluoropropyl)-4,5α-epoxy-3,14-dihydroxy-morphinan-6-one N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14-acetamido-morphinan-6-one N-oxide trifluoroacetic acid salt;

(S)-SDM25N N-oxide (4bS,8R,8aS,14bR)-5,6,7,8,14,14b-Hexahydro-7-(2-methyl-2-propenyl)-4,8-methanobenzofuro[2,3-a]pyrido[4,3-b]carbazole-1,8a(9H)-diol N-oxide);

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-(3'-trifluoromethyl)benzyloxy-morphinan-6-one N-oxide;

(S)-17-Cyclopropylmethyl-4,5 α-epoxy-3-hydroxy-14-propoxy-6-methylenemorphinan N-oxide;

(S)-17-Cyclopropylmethyl-4,5a-epoxy-3,14-dihydroxy-6,7-(4'5'-1H-pyrazole ) morphinan N-oxide trifluoroacetic acid salt;

(S)-17-Cyclopropylmethyl-4,5a-epoxy-3,14-dihydroxy-6,7-(2'-oxo-τ, 2'-dihydropyridine-3'-carboxylic acid methyl ester ) morphinan N-oxide; and
(S)-17-Cyclopropylmethyl-4,5α-epoxy-3-cyano-14-hydroxy-morphinan-6-one N-oxide;

59. An equatorial-0 configured N-oxide compound according to Formula (III),

![Chemical Structure](image)

(III)

wherein:

- $R_6$ is =0, N-dialkyl, C$_2$-C$_6$ alkyne, QR$_9$R$_{20}$ (wherein Q is C, O, N, CO, CO$_2$, C=ON, or none), and R$_9$ and R$_{20}$ are independently H, alkyl, aryl, none, or form a carbocycle fused ring, a carbocycle, or $R_6$ forms a carbocycle ring with $R_7$,

- $R_3$ and $R_5$ are independently H, alkyl, aryl;

- $R_7$ and $R_8$ are independently H or alkyl; and

- M is O, S, NR$_{29}$, SO$_2$, SO, or CO.

60. A convergent method for synthesizing 17-cyclopropylmethyl-4,5α-epoxy-3-methoxy-14-amino morphinan-6-one comprising the steps of:

   adding N-(cyclopropylmethyl)northebaine in ethyl acetate to a suspension of sodium periodate and sodium acetate in water at about 0°C to form a two phase solution; and

   adding benzyl N-hydroxycarbamate to said two phase solution
61. A convergent method for synthesizing 17-cyclopropylmethyl-4,5α-epoxy-3-methoxy-14-amino morphinan-6-one comprising the steps of:

adding N-(cyclopropylmethyl)northebaine in ethyl acetate to a suspension of sodium periodate and sodium acetate in water at about 0 °C to form a two phase solution;

adding benzyl N-hydroxycarbamate portionwise to said two phase solution, and mixing to form a second solution;

stirring said second solution at about 0 °C for about 1 hour;

making said stirred second solution alkaline by the addition of saturated aqueous sodium hydrogen carbonate;

separating the ethyl acetate phase and extracting the aqueous phase with ethyl acetate (about 2 x 20 ml);

combining the ethyl acetate phases and washing with about 5% aqueous sodium thiosulphate, brine, and drying with anhydrous Na₂SO₄;

evaporating any residual solvent to give a crude cycloadduct between N-(cyclopropylmethyl)northebaine and said benzyl N-hydroxycarbamate;

purifying said crude cycloadduct by column chromatography using about 50% ethyl acetate in hexane and evaporating the ethyl acetate and hexane;

isolating the cycloadduct of N-(cyclopropylmethyl)northebaine and benzyl N-hydroxycarbamate;

hydrogenating the cycloadduct of N-(cyclopropylmethyl)northebaine and benzyl N-hydroxycarbamate with Pd/C (10%) in MeOH at about 30 psi hydrogen for about 3 hours;

filtering the Pd/C catalyst and evaporating the methanol solvent to give crude product;
purifying the hydrogenated cycloadduct of N-(cyclopropylmethyl)northebaine and benzyl N-hydroxycarbamate by column chromatography using 5% MeOH in dichloromethane; and

evaporating the 5% MeOH in dichloromethane solvent to isolate 17-cyclopropylmethyl-4,5-α-epoxy-3-methoxy-14-amino morphinan-6-one.

62. A compound, or a pharmaceutically acceptable salt form, polymorph, or prodrug thereof selected from the group consisting of:
and
63. A pharmaceutical composition comprising a compound of claim 61.
COMPETITION CURVE OBTAINED WITH COMPOUND O-5720
AT THE HUMAN MU RECEPTOR

IC50 = 6.1E-09 M
nH = 0.9
A. CLASSIFICATION OF SUBJECT MATTER

C07D 221/26(2006.01)i, C07D 487/08(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 8 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKIPASS(KIPO internal), Delphion (axial<and>N-oxide<and>configuration<and>morphi*)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<td>See page 8 &amp; claim 28</td>
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<tr>
<td>Y/A</td>
<td>US 4722928A (E I Du Pont de Nemours and Company) 2 February 1988</td>
<td>1-24, 58, 62/60, 61</td>
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<td>Y/A</td>
<td>Mandava et al, Configuration of the ring nitrogen in N-oxides and the conformation of tropanes Part XVIII Canadian Journal of Chemistry 46(17) 2761-2765 (1 September 1968)</td>
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<td>See Scheme 1</td>
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* Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 04 DECEMBER 2008 (04.12.2008)

Date of mailing of the international search report 04 DECEMBER 2008 (04.12.2008)

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 139 Seomsa-ro, Seogu, Daejeon 302-701, Republic of Korea

Authorized officer

CHO, Kyung Joo

Facsimile No 82-42-472-7140

Telephone No 82-42-481-8287

Form PCT/ISA/210 (second sheet) (My 2008)
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **IV** Claims Nos. 25, 54, 57
   - because they relate to subject matter not required to be searched by this Authority, namely
     - Claims 25 to 54, 57 pertain to methods for treatment of the human or animal body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the Regulations under the PCT, to search.

2. **X** Claims Nos. 28, 55, 56, 59, 63
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically
     - Claims 55, 56, & 59 are not clear since the substituents of their formula are not correctly defined as described in corresponding written opinion, and claims 28 & 63 are unclear, since “the compound of claim or claim 61” is not clear.

3. **☐** Claims Nos.
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6-4(a).

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This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.

**Remark on Protest**

- The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2008)
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<td>27.08.1992</td>
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